FOURTH EDITION



Clinical Medicine of the Dog and Cat

edited by
Michael Schaer
Frédéric Gaschen
Stuart Walton

CRC Press
Taylor & Francis Group

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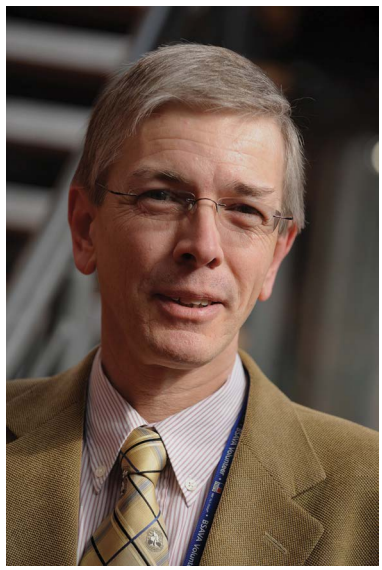
Preface to the Fourth Edition

Before the first edition of *Clinical Medicine of the Dog and Cat* was published, no other comprehensive small animal veterinary medicine textbook was available with a comparable amount and quality of relevant illustrated materials. The information in the first, second, and third editions was carefully selected so that it would be a one-stop resource offering clinically applicable information for the veterinary student, the small animal intern, and the general practitioner. It complemented our belief that clinical observation and the cognitive sense of the clinician are essential professional qualities that contribute to our clinical acumen. In the previous edition, Editors Michael Schaer and Frédéric Gaschen carefully selected experienced specialists from North America, Europe, and Australasia with the distinctive objective of providing the book with quality material that would have a truly international appeal. For this fourth edition, they welcome Stuart Walton to the editorial team. Dr. Walton received his veterinary degree and initial residency training in Australia. He then completed a second small animal internal residency at Louisiana State University. Dr. Walton is an ACVIM Diplomate in Small Animal Internal Medicine and is currently a faculty member at the University of Florida College of Veterinary Medicine. This new team of editors has brought forth fresh ideas, which include new chapter topics, a new five-part organization, and several new outstanding authors.

Like the third edition, this new textbook is composed of two main sections. The first elaborates on the medical approach to solving common medical problems. These additional short topics, written by experts, include medical history taking, polydipsia and polyuria, pigmenturia, vomiting, diarrhea, dyspnea, cough, fever of unknown origin, epistaxis, and pallor, with brand new sections on abdominal distension, peripheral edema, proteinuria, regurgitation, and seizures. The practical application of the information in these sections is presented with text, tables, and algorithms. The objective of this clinical problems section is to emphasize the logical clinical approach to the selected clinical signs.

The second section contains detailed medical information covering most organ systems, with selected clinical case material integrated throughout, applying some of the principles of medicine discussed. A number of new authors who are experienced specialists in their fields have contributed to this fourth edition: Steven Holloway, Claire Sharp, Samantha Wigglesworth, Amber Vitalo, Leonel Londoño, Laura Rayhel, Roman Husnik, Gabriel Garcia, Andrea Johnston, Matthew Johnson, Mitchell Gillick, Claire Cannon, Alex Lynch, Domenico Santoro, Amelia White, Ralph Hamor, Tina Wismer, Sophie Keyte, Severine Tasker, Beatriz Monteiro, Brad Simon, and, of course, Stuart Walton, whose biography you can find on page IX. In several instances, they provide a completely rewritten approach to chapters included in previous editions of the book. We would like to take this opportunity to thank our previous authors for their contributions to this textbook. Other chapters from the third edition have been revised by their authors with the inclusion of additional text and images (exception, the obesity chapter has no additions from the third edition). Chapters on thoracic and abdominal radiographs are now included in a new part on Diagnostic Techniques, for ease of reference.

In May 2020, during the writing of this update, the Editors received the devastating news that author Emeritus Professor Michael J. Day had passed away after a battle with cancer. His excellent chapter in Section IV on Immunologic Disorders is preserved from the third edition as a tribute to his immense contribution to the field. Professor Day championed a One Health approach and was awarded the WSAVA's prestigious Award for Global Meritorious Service. He was also renowned for his ability to teach immunology to veterinary undergraduates and postgraduates by making the complex seem accessible. Not just a highly respected colleague, Michael Day was a much-loved friend to many of us in the global veterinary community. We are honored to include his chapter in the fourth edition.



In this update, the Editors adhered to the original organizational plan of *Clinical Medicine of the Dog and Cat*, which was to cover the primary disorders of all organ systems as well as the associated subspecialties of veterinary internal medicine. However, in order to make this a practical text for our projected audience,

we omitted certain valuable topics such as genetics, preventive medicine, and coverage of the reproductive system. These areas, in addition to oncology, are instead included as a part of the organ systems chapters where indicated. Ophthalmology and dermatology certainly have enough information to fill books in their own right. Therefore, the Editors requested that the information provided be restricted to what would most likely impact on internal medicine.

As in the first three editions, each chapter of this text is arranged to provide the definition of each disorder, its clinical features, the differential diagnoses, the diagnostic methodology, and the treatment and prognosis. The aim remains to achieve brevity and clarity in order to provide the practicing veterinarian with a readily available resource of important clinical information. The numerous illustrations fulfill the main philosophy of this textbook, namely that "a picture is worth a thousand words," which is especially useful in the practice of veterinary medicine. Each author was requested to restrict his or her content to the more commonly seen clinical disorders but was allowed to exercise as much freedom of choice as possible. A limited list of recommended references is offered in this latest edition. The Editors elected to be flexible with the number of references included by the authors. With today's readily available access to literature search engines, we feel that the reader can easily find unlimited information for further detailed reading.

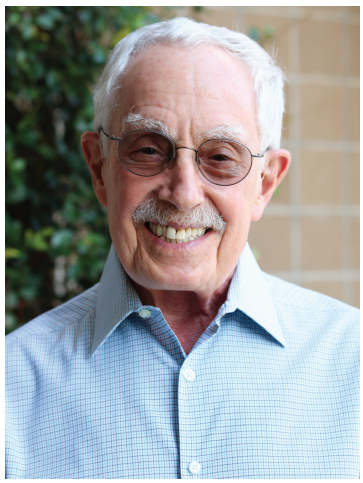
We would like to take this opportunity to thank our publisher's project leader Ms. Alice Oven and her editorial assistant Ms. Shikha Garg for their expertise in assembling all the information provided in this valuable learning tool. We would have never been able to complete this project without their patience and guidance. We are also grateful to Ms. Kalie Koscielak and Ms. Linda Leggio for their work on the copyediting, typesetting, and proofreading of the book, a heroic endeavour given they had almost 1000 pages to work with! Thirdly, we would like to thank Mr. Jim Wilson, who is a local wildlife artist in Gainesville, Florida, and whose artwork appears on the front cover.

The Editors are most appreciative to all our authors for taking time out of their very busy days to provide their valuable contributions. We thank you very much.

Lastly, but not least, we thank our families and our work colleagues for tolerating our frustrating moments brought about by long work hours, personal sacrifices, and all the other obstacles that confront editors who assume a major project such as this.

We hope that you, the readers, will truly enjoy using this textbook and that the information provided will be of assistance in your day-to-day practice of veterinary medicine.







Editor Biographies

Dr. Michael Schaer received his DVM degree from the University of Illinois in 1970. He then went to the Animal Medical Center (AMC) in New York City where he served as an intern and then as a medicine resident between 1970 and 1973. After the residency, he remained at the AMC as a staff member in the department of medicine until 1977. He then joined a private small animal practice in New Jersey until late 1978 at which time he joined the faculty at the University of Florida, College of Veterinary Medicine where he has remained until the present time. He has published numerous papers and book chapters, and he has lectured nationally and internationally. Dr. Schaer is also the author of five textbooks: *Clinical Medicine of the Dog and Cat* first, second, and third editions and *Clinical Signs in Small Animal Medicine* first and second editions. At the University of Florida, Dr. Schaer functions mainly as a clinician and a teacher. His previous UF professional duties included: Professor and Associate Chairman-Department of Small Animal Clinical Sciences, Associate Chief of Staff-Small Animal Hospital, and Service Chief—Small Animal Medicine. Dr. Schaer served as Interim Chair, Department of Comparative, Diagnostic, and Population Medicine from February 2017 until September 2018. He is currently Professor Emeritus and Adjunct Professor in Emergency and Critical Care Medicine, while still doing active teaching in the classroom and in the critical care unit. Dr. Schaer is board certified in internal medicine (ACVIM) and emergency and critical care (ACVECC), and is on the board of directors for the North American Society of Toxinology. He is also an Associate Member of the American College of Physicians.

Dr. Frédéric Gaschen is a graduate of the University of Bern, Switzerland. After a few years in mixed practice, he trained as a veterinary internist in North America (Ontario Veterinary College, Canada, and University of Florida, United States). He is a specialist in small animal internal medicine and a diplomate of both the American and the European Colleges of Veterinary Internal Medicine (ACVIM and ECVIM-CA). After teaching for 15 years at his alma mater, he joined the Louisiana State University (LSU) School of Veterinary Medicine 16 years ago where he is currently a professor of small animal medicine. Dr. Gaschen has a passion for canine and feline gastroenterology and recently became a Fellow of the American Gastroenterology Association. He has directed and published research on chronic enteropathies, digestive motility, and the impact of antibiotics on the gut microbiota in dogs and cats and has authored numerous book chapters on small animal gastroenterology topics. Dr. Gaschen loves to share his passion with his students, interns, and residents at LSU and with colleagues at congresses worldwide. He has been actively involved in professional associations for many years and is currently co-chair of the scientific committee of the World Small Animal Veterinary Association (WSAVA). He has been a member of the editorial team of *Clinical Medicine of the Dog and Cat* since the third edition.

Dr. Stuart Walton is a graduate of the University of Queensland, Australia. Dr. Walton initially worked in mixed practice for several years before transitioning into emergency medicine and critical care. He trained as a veterinary internist initially in Brisbane, Australia (Veterinary Specialist Services) before traveling to North America where he completed his residency training in small animal internal medicine at Louisiana State University (LSU) in Baton Rouge, Louisiana. He is a specialist in small animal internal medicine and a diplomate of the American College of Veterinary Internal Medicine (ACVIM). After his residency, Dr. Walton joined the University of Florida (UF) College of Veterinary Medicine where he is currently a clinical assistant professor of small animal medicine. He has a broad range of interests, including infectious and inflammatory diseases, immune-mediated disease, respiratory disease, and extracorporeal blood purification techniques. He has directed and published research on therapeutic plasma exchange, oomycete infections, and pancreatitis. He is passionate about the profession and is very involved in the education of students, interns, and residents at UF. Dr. Walton is the newest addition to the editorial team of *Clinical Medicine of the Dog and Cat*.

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Uncle Mikey's Maxims

A guiding philosophical path through the challenges of emergency medicine and critical care medicine.
—Michael Schaer, DVM

1. Treat for the treatable.
2. Assumptions lead to trouble; therefore, don't assume.
3. Always interpret clinical information within the context of the patient's presentation.
4. Avoid tunnel vision.
5. Treat your patient, not just his/her disease.
6. Avoid overmedicating.
7. Be honest with yourself.
8. Don't postpone today's urgencies until tomorrow.
9. Think that common things occur commonly.
10. Look closely at your patient; he/she will usually tell you what's wrong.
11. Never let your patient die without the benefit of the silver bullet.
12. When you hear hoofbeats, look for horses but don't forget about the zebras.
13. Never sell the basics short—they are still the best buy in town.
14. If you don't think it, you won't find it.
15. Never let a biological specimen go to waste.
16. Disaster lurks whenever a patient's problem is routine.
17. If he/she is not getting worse, give him/her a chance to get better.
18. Don't stray too far from the patient; the diagnosis will appear eventually.
19. Don't give your patient a disease he/she doesn't deserve to have.
20. Don't let technology make you decerebrate.
21. The necropsy is the clinician's trial by jury.
22. The wisdom of experience should never be ignored.
23. The diagnostician should always ask him/herself these two questions: Where am I with this patient and where am I going?
24. If the patient isn't going where you expect him/her to be going, then go back to square one.
25. In order to successfully treat a cat, you must think like a cat.
26. Avoid the pitfalls of the red herring.
27. If they can't afford a Caddy, then offer them a Chevy.
28. Know thy patient.
29. Nobody wants to pay for a big bill and a dead animal.
30. What matters is not so much what you say to a concerned client but how they perceive what you said.
31. Diagnostic cloudiness will soon be replaced by clear skies.
32. Better that the dying patient expire in the hospital than during the car ride home.
33. You must have cognition to be a competent diagnostician.
34. To prognose you must first be able to diagnose.
35. The toaster effect will occur when your patient reaches the turning point toward recovery.
36. To cut is to see; to see is to do; to do is to cure.



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SECTION

I

GENERAL APPROACH



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CHAPTER 1

Client Communication

Bobbi J. Conner

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Diversity, Equity, and Inclusion 3
Types of Medical Communication Styles 4
The Client Encounter 5
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INTRODUCTION

Effective communication is one of the most important aspects of providing veterinary care. No matter how good a veterinarian's clinical skills may be, if they cannot establish trust and a good working relationship with their clients, those skills may very well be wasted. The past few decades have seen a huge increase in awareness around the importance of developing good communication skills in both human and veterinary medicine. As such, there are many ways to approach client communication, and no one way will likely work for everyone in all situations. Indeed, veterinarians with excellent communication skills are often able to comfortably transition between different approaches to accommodate the diverse needs of their clientele. Though there are exceptions, nearly all patients a veterinarian will treat in their career will be attached to a human client; it is reasonable to occasionally remind oneself that the Veterinarian's Oath includes, in addition to the protection of animal health and welfare, the "promotion of public health," and part of public health necessarily includes human emotional and mental well-being. We as veterinary health professionals will be able to better achieve our goals of preventing and relieving animal suffering if we form a partnership with our patients' families and engage them as active participants in the health care of their pets. Finally, it is important to recognize that communication is a skill, and like all skills, it requires training and practice to develop, improve, and maintain skills. The following is an overview of some of the major components that should be considered when developing communication skills. There are also many excellent training programs, books, articles, podcasts, webinars, and more to help veterinary professionals continue the lifelong work of improving their communication.

DIVERSITY, EQUITY, AND INCLUSION

Although it has been rightly pointed out that veterinary medicine is among the least diverse of all the professions in the United States for which data is available, the clientele of veterinarians will be made up of a richly diverse group of people with respect to race, ethnicity, age, class, gender, sexual identity, religion, health, physical and mental ability, education, and a myriad of other differences. The common denominator of virtually any veterinary encounter is the shared responsibility of caring for an animal. In order to maximize the success of the veterinary–patient–client relationship, veterinary health professionals must be able to develop relationships with people from all backgrounds. This means actively trying to create an inclusive environment where all people (staff and clients alike) feel safe and welcome. Acknowledging the inequities that exist in our society and actively working to ameliorate the effect those inequities have on our clients' abilities to care for their pets may be one small way that veterinarians can have a positive impact on society.

Implicit Bias

Implicit bias refers to our unconscious attitudes and stereotypes that we hold that affect our decisions and actions – without us being aware of them. Implicit biases are deeply held biases that start to develop at a very early age and are influenced by many factors, including family, local environment, the media, and our collective experiences. Of particular importance are the implicit biases we hold that are in direct conflict with our declared beliefs. Also important is understanding that our biases are not set in stone. We can work to change our biases. We can work to identify these biases and work to reduce the impact they have on our behavior.

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Implicit bias can cause a veterinarian to behave differently with one client versus another. The way a client dresses for an appointment may impact the options given to a client because of subconscious beliefs about the clients' financial means. The effects of implicit bias on the inequities in human medicine are well documented. It is fair to assume that similar biases exist in veterinary medicine and may very well impact the care that pets are given. Although our implicit biases often develop to favor a group to which we belong, this is not always the case. There are many resources available to help individuals identify and understand their own implicit biases. When we acknowledge the biases we hold, we can begin to recognize when they might influence our behaviors and can actively work to reject the unfair biases we hold. Readers are encouraged to learn more about implicit bias. One excellent resource is *Biased: Uncovering the Hidden Prejudice That Shapes What We See, Think, and Do* by Jennifer L. Eberhardt, PhD. Readers might also consider exploring the website implicit.harvard.edu for information about implicit biases as well as a test you can take to help identify some of your own specific biases.

Acknowledging the presence of our implicit biases (even if we don't know what they are) is necessary to addressing any impact our biases may have on our ability to communicate with clients. Additional references to strategies aimed at reducing the effect of implicit bias will be referenced throughout this chapter.

TYPES OF MEDICAL COMMUNICATION STYLES

There are many ways to describe or categorize various approaches to medical communication. For this chapter, we will focus on the following three: Veterinarian (doctor)-centered, client (patient)-centered, and relationship-centered (see Table 1.1). In 1994, the Pew-Fetzer Task Force published a report describing the relationship-centered approach to medical care, adding to the previously dichotomous description of doctor-centered versus patient-centered. We will explore what each of these approaches means and some of the advantages and disadvantages of each approach.

Veterinarian-Centered Communication

This style of communication puts the evidence first. The emphasis is on evidence-based medicine, and, in general, the doctor approaches cases in a rational way, and provides information to the client about the best medical recommendations they have for the patient. Veterinarians who primarily use this approach will focus on getting as much information about the patient's clinical signs and pertinent history as possible. They also focus on the conveyance of facts and data to the client to help explain their pet's condition. The veterinarian makes recommendations based on what is best for the patient.

Client-Centered Communication

Client-centered communication prioritizes the client's feelings and concerns when making recommendations for the patient's care. How a pet's condition affects the client's well-being would be explored in a client-centered approach. Veterinarians who use a client-centered communication style will typically ask how a pet's condition is affecting the clients. When discussing care for the patient, the veterinarian will often present options, leaving the treatment decision up to the client, based on their specific situation and needs.

Relationship-Centered Communication

For this style of communication, the veterinarian and the client form a partnership. Both parties are stakeholders and take responsibility for the pet's care. In a relationship-centered approach, the veterinarian still provides information regarding options for the patient and will also clearly indicate their opinions for the best care; however, the veterinarian will also actively seek to understand the specific needs, concerns, and preferences of the client, and together the client and the veterinarian will determine a plan of action for the patient.

TABLE 1.1 Communication styles – Summary

	Veterinarian-centered	Client-centered	Relationship-centered
Options provided	Veterinarian provides only options which are considered appropriate by veterinarian	Veterinarian provides all options without providing preferences or weight to each option	Veterinarian provides all options and includes recommendations; client preferences also discussed
Decision-making	Primarily veterinarian	Primarily client	Shared responsibility between veterinarian and client
Pros	Theoretically, best medical care is provided; indecision by client avoided	Client's needs are considered, and responsibility for outcome falls with client	Client and veterinarian share responsibility for outcome of care; all parties opinions are considered
Cons	Client does not share responsibility for outcomes; may not be able to follow-through with care plan	Veterinarian may be upset when "best" treatment option not selected; patient care may be compromised	Small additional investment of time; not all clients will engage in this approach

Although relationship-centered communication is generally considered the ideal approach, some clients and some situations may call for different approaches. Some clients become paralyzed at the thought of making a decision for their pet's care; it is not uncommon for clients to say, "please do whatever you think is best." Keep in mind that cultural differences between the veterinarian and the client may necessitate adjusting one's "typical" communication style to accommodate the needs of the other person. In most cases, though, it is advisable to query the client about their particular situation and their ability to perform certain tasks or adhere to treatment plans. For example, sling-walking a lame 50 kg Saint Bernard may not be realistic for the single client who lives on a third-floor apartment. Thrice daily levetiracetam administration for a dog with idiopathic epilepsy may not be realistic for the firefighter who works 18-hour shifts at the fire station. Clients and veterinarians will often be more satisfied with the patient care if time is taken to get the full picture from the client at the outset.

THE CLIENT ENCOUNTER

Building Trust

A prerequisite for a successful veterinary–client relationship is establishing trust. You might think, "I can't *make* my clients trust me, especially if I've only just met them!" But you're likely benefitting from a general sense of trust in the veterinary profession; that is, your clients will likely give you the benefit of the doubt initially, and there are ways that you can enhance your ability to build trust with your clients. Two of the biggest things you can do to build trust are having an awareness of your nonverbal communication and expressing empathy.

Nonverbal Communication

You are likely aware that the majority of communication between two people is actually through nonverbal communication or your body language. We have likely evolved to pick up on one another's physical cues because they may be more reflective of our true thoughts than our words. By some estimates, the actual words we say make up as little as 7% of what we communicate. The remainder of our verbal communication is the character of our voice (tone, pace, inflection, etc.). Of particular importance is when our words don't match the other 93% of what we are trying to communicate. Most of us have some experience with our words being misinterpreted. A classic example is when our written words don't effectively convey the subtext that our voice and body language are so adept at. If you've ever sent or received an email or text message that was badly misinterpreted, you've experienced this.

Maintaining and awareness of what your body language and voice tone are communicating can be incredibly important when building trust with clients. Certain body positions can convey openness, such as keeping your arms uncrossed and your body angled slightly toward the client. Making eye contact with the client, particularly when important or potentially upsetting information is being delivered, is important for establishing trust. Looking away can be interpreted as a sign of dishonesty or a lack of confidence, causing a client to second-guess you. Avoid creating a power dynamic. It is often best to mirror the client's position. If they are seated, you should also take a seat or squat nearby, if possible. Try to remove any physical barriers between you and the client, such as an exam table. While it might be reasonable to take notes during a discussion, if you are only looking at the screen or pad of paper, you may lose the opportunity to make a connection with the client. Ensure you are looking up and making eye contact regularly or make use of a voice recorder or assistant to take notes.

It is also important to be aware of distractors that may seep into your body language without your awareness. If you are stressed about the full surgery schedule you have that day, you may inadvertently display to the client that you are in a rush, leaving them to wonder if you care about their concerns. Before entering the conversation, try to attend to urgent tasks (or delegate them to other staff) so that the focus can be on the client and their concerns.

Paying attention to the client's nonverbal communication cues is also important for building trust in the relationship. If you notice the client becoming anxious (tapping their feet, clenching and unclenching their fists), perhaps take a moment to check in with them to see how they are handling the information you're providing.

Expressing Empathy

The ability to understand and share the feelings of others is empathy. As people, we have an innate capacity for empathy; however, it can and should be developed. Here, we will discuss ways to express empathy as a method for building trust with your clients. A good "trick" for finding your empathy is to think of every client as a loved one or a close friend. How would you want your mother/sister/son/grandfather, etc., treated in this situation? Try looking for opportunities to express empathy either in real life or simulated client encounters. This can help improve your ability to express empathy naturally.

Opportunities to express empathy are frequent – "it must be exciting and also a lot of work to have a new puppy at home" or "I can see how much it terrified you to see Jasper breathing like that." Sometimes clients will share a personal situation they are going through, and these can be great opportunities to express empathy and build trust. For example, if a client is running late for an appointment (which can then seem to disrupt your whole day!), saying something like "It seems like you've got a lot on your plate right now" might be a good, nonjudgmental way to acknowledge the client's circumstances. Expressions of empathy don't tell the client how to feel, and they are often expressions of our assumptions or interpretations of the situation.

Many expressions of empathy start with phrases such as: "It seems like…" "I'm sensing that…" "It sounds like…" Leaving a pause after an expression of empathy is also important to convey the feeling behind your words. Even though the statement may not have been a question, empathic statements frequently invite the client to share more about how they are feeling: "We are definitely having fun with this new puppy, but he's a ball of energy, and we are all exhausted!" or "I didn't get any sleep at all last night because I was so worried about Jasper."

Remember that expressing empathy isn't about solving a problem. It's about acknowledging the situation, and it gives us an opportunity to bond over shared human experiences – the good and the bad ones. It's also not a good idea to tell the client that you understand exactly how they feel. Although you can start an empathic statement with the words "I understand…" I find it's often better to avoid those words altogether, lest we fall into the trap of minimizing the client's experiences.

Having a few phrases that you're comfortable with is a good place to start if you find expressing empathy to be a challenge. We want to ensure we are genuine when we empathize with clients, so taking a moment to really think about what the client must be going through is paramount to expressing empathy. Simple phrases like, "This must be really difficult for you" or "This must be really exciting for you" might be good starting points to incorporate more empathy into your client communication.

Getting a History

Establishing trust with a client occurs throughout all phases of the client encounter, so being aware of your nonverbal communication and finding opportunities to express empathy are often part of the history-taking portion a client visit. Getting an accurate medical history about the patient is crucial for diagnostic accuracy.

A more specific approach to take is the 4Es method: Engage, empathize, educate, and enlist (Figure 1.1). These can parallel the 2Fs for the biomedical tasks: Find it and fix it. Engaging and empathizing with the client can help us find the problem, while educating and enlisting the client in the fixing it process can help enhance the veterinarian–client relationship. Getting the medical history is the first, and arguably most important, part of the finding the problem – engage and empathize with the client to ensure you get the whole story.

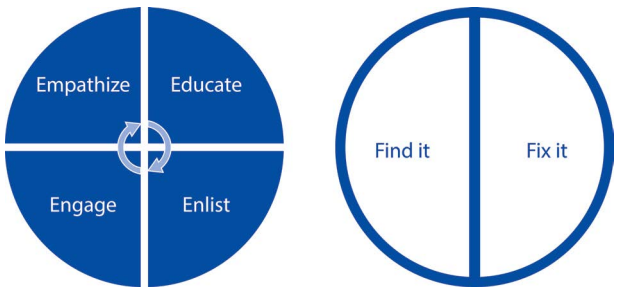


FIGURE 1.1 The 4Es of client communication versus the 2Fs representing the medical tasks for a patient's care.

Engaging the client is part of making a connection with them. At its most basic, it often starts with the introduction. Use the client's name during the introduction. It can be tempting to default to the pet's name ("You must be Scruffy's mom"); however, making an effort to engage with the client will help build the relationship, and ultimately, you depend on the client to provide care for the patient. Veterinarians may find the introduction challenging if the client's name is difficult to pronounce or they have different cultural norms. Making an effort to pronounce someone's name, without making a joke about it, can be a great icebreaker. "Did I pronounce your name correctly? I want to make sure I get it right" can be a sign of respect, or, "Could you say your name for me? I don't want to mispronounce it." If you suspect your offer to shake hands made the client uncomfortable, you could ask them if they prefer a different type of greeting: "I typically shake hands when I meet new people. Is there another greeting that you use?"

Telling the client your name and role is also important for engaging the client. Your title and anticipated role in their pet's care are helpful for creating realistic expectations for the client:

> I'm Patricia and I'm a veterinary technician here. I'm going to start by getting some information from you before Dr. Gonzales comes in to do her examination. Later, I'll be part of helping to collect any samples we need from Baxter and will help make sure you know what you need to do for him at home.

Remember to be aware of your nonverbal communication – smile, meet the client at their level (e.g., sit if they are sitting). Remember to use your expressions of empathy during this phase.

Organization of the History

Using a funneling technique (Figure 1.2) when gathering the history can help ensure that both the client's and veterinary team's needs are met. The client gets to

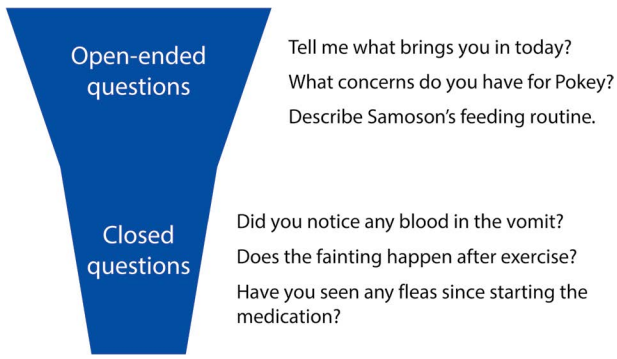


FIGURE 1.2 When getting a history from the client, start with open-ended questions and then funnel the conversation by asking follow-up, directed, and closed questions to get more detail as needed.

TABLE 1.2 Closed versus open-ended questions

Examples of closed questions and how to make them open-ended		
Information sought	**Closed question example**	**Open-ended example**
Vaccination status	Is your pet vaccinated?	Tell me about your pet's vaccination history.
Exercise routine	How often do you walk your dog?	What's a normal day like for your dog?
Indoor/outdoor status	Is your cat primarily indoor or outdoor?	Tell me about your cat's weekly routine.
Medication history	Is your cat on any medications?	What medications or treatments are you giving your cat?

tell their story, and the veterinary team gets the needed information to create a problem list and differentials.

Funneling is about starting with open-ended questions and then following up with directed, closed questions to address anything not covered by the open-ended questions. Some veterinary professionals like to use a checklist to ensure important questions don't get missed. Checklists can be helpful if used *in conjunction with*, not in place of, open-ended questions. Some options for getting the conversation going are: "Tell me what brings you in with Rufus today" or "What are your goals for today's appointment?" Examples of closed questions and how they can be converted to open-ended questions is provided in Table 1.2. A good guideline to help you is that it is difficult to start a closed question with the word "What."

Specific Elements of the History

It can be helpful to have some themes in mind when taking a history to ensure all necessary information is obtained. Much of the information may be covered during the open-ended portion of the conversation when the client is sharing their story. The veterinarian or other veterinary health care team member may take some notes as a reminder to follow up for any areas that need further exploration or anything that wasn't covered during the initial story. Depending on the chief complaint of the client and the physical examination findings, the veterinarian may need to spend more or less time on each of the areas discussed later. Remember, too, that any information that is forgotten or missed during the first chat is generally available with a follow-up conversation.

1. *Chief complaint:* Ensuring you understand the client's chief complaint or their most pressing concern is important. Sometimes their top concern will mirror your own, but at other times, the major medical issue for the pet may not be what the client is most concerned about. For example, if a client brings their pet in for "bloody urine," and the veterinarian identifies severe thrombocytopenia, the veterinarian will rightly focus on the platelets as a primary concern. The client, on the other hand, may not understand why the veterinarian doesn't seem to care about the urine problems and may feel that their concerns are being dismissed. Asking the client to identify their top concerns can help ensure that the right information can be relayed to address their needs. Taking a moment to explain the likely link between the platelets and the discolored urine may be all that is needed for the client to feel assured the pet's problems are being addressed.
2. *Diet and appetite:* In all pet encounters, it is important to elicit information about the pet's current appetite and any recent changes in the pet's eating habits. Increases or decreases in appetite are important to note and necessitate further exploration. What the pet is being offered (and what they are consuming) are also important details to obtain from the history. Recent changes to the diet being offered to the pet (and what prompted the change) should be documented in the history. As with the history overall, starting with open-ended questions ("Tell me about George's eating habits."), followed by specific, directed questions ("How much of the dry kibble are you giving George each day?") can help the veterinarian gather all the relevant information.
3. *Thirst and eliminations:* Drinking habits, urination, and defecation are all important details from the history and can be part of the chief complaint or may provide useful information in other diseases. If the client can quantify or estimate how much (or how little) a pet is drinking, that may provide insight into overall health or clue the veterinarian in to certain disease states. Thirst is a powerful stimulus in pets that become dehydrated or hypovolemic. Pets that have stopped drinking may be quite sick, and this should warrant investigation, although it may not indicate a specific condition. Polydipsia, on the other hand, can be a sign of many different diseases or syndromes. Excessive drinking is often accompanied by polyuria. Clients may not readily recognize the difference between polyuria (increased urine production) and pollakiuria (increased frequency to void urine), so asking specific questions about an animal that is reportedly urinating more can help. If the client has observed the pet urinating, ask if the pet appears to be straining or if it is urinating frequently but only small amounts rather than simply asking to go outside or using the litterbox more often than usual. Asking about the pet's bowel movements is also necessary for a complete history. Whether the stools appear normal in color or consistency or if the pet has any changes to their defecation habits (straining, increased frequency) will all be helpful details to sort out.
4. *Travel history:* It may not always be immediately obvious whether and how recent travel history will become important during a case investigation, and, therefore, it's a good idea to include questions about the pet's geographic history into the routine conversation. Differences in exposure to infectious diseases by region can greatly impact how differential diagnoses are prioritized. Further, asking about a pet's

exposure to other environments (even locally) can divulge important information about other exposures. Has the pet been around other domestic animals, wild animals, or people that it usually isn't around? Was the pet purchased from a breeder in another county, state, or country?

5. *Local environment:* Similar to travel history, a thorough understanding of the pet's local environment can reveal information that is crucial to making an accurate list of differential diagnoses; however, mundane facts may seem irrelevant to the client. Starting with a general question: "Tell me what Sasha's normal environment is like" and following up with more directed, specific questions can help the veterinarian determine what the routine exposures are and risks the pet may have.
6. *Progression of the condition:* It can be difficult at times for clients to keep track of what's been going on with their pet. Worry about the pet's condition can affect memory and distort what the client recalls. It can be helpful to direct the client by asking questions such as "When was the last time you remember that Sassy was completely normal?" Summarizing your understanding of the chronology for the client is also a great opportunity to reflect back to them, confirm you are both on the same page, and creates an opportunity for the client to fill in any gaps they've forgotten.
7. *Treatments attempted and responses to therapy:* In many cases when signs come on gradually, clients may forget things they've tried at home (switching the food for a pet with a reduced appetite, trying an over-the-counter pain medication). It can be important to avoid judgment when asking the client about treatments they have tried, and if the client feels like they may have done something wrong, they might avoid divulging important information. One approach could be, "You must have been worried about how Beanie was doing at home. What things have you tried so far to help her feel better?" Following up with questions about specific treatments they might have tried but didn't consider a treatment could be useful, too. For each treatment the client tried, clarify whether they perceived any response. Whether the pet improved with certain approaches can help narrow or prioritize the differential diagnoses and might even help guide the treatment plan.
8. *Current or recent medications and vaccination history:* Asking the client, "What other medications has Joey been getting?" rather than, "Is Joey taking any other medications?" will for some clients challenge them to really think about what other medications they have forgotten. In the former question, you are assuming there are other medications, and the client will often try to think what they could be. The latter closed question is more easily dismissed with a simple, "no." Also, asking "What is Joey vaccinated for?" might provide more information than simply asking if the pet is up to date. Admittedly, many clients won't remember the details, but for many, they will be able to recall at least some information about their pet's vaccination status. Again, funneling to more narrow questions after the initial query can help you gather the necessary detail.

When you think you've got all the information you need, it's a good idea to check back in with the client to ensure all their needs have been addressed. Rather than asking, "Do you have any other concerns?" you could switch it up to "What other concerns do you have for Boomer that we haven't yet covered?" Although a relatively slight change in the wording of the question, the second phrasing suggests that you have time for more discussion, rather than implying the end of the conversation. If the client was holding anything back, this might be their chance to bring up one more concern. Veterinarians might be rightly concerned that this could extend the time spent during the history-taking portion of the client visit; however, remember you could be saving time by addressing any concerns about the pet sooner rather than later, and that could lead to an improved outcome for the pet, which is everyone's ultimate goal!

Making a Plan

Once the veterinarian has a prioritized list of differential diagnoses, a diagnostic and preliminary therapeutic plan is created. In most situations, there are a variety of options available that can range from the gold standard or best recommendations to the most conservative plan. This is where employing a relationship-centered communication approach can be helpful.

In order for the client to be an equal partner in the decision-making process, as the veterinary professional, you'll likely need to educate them on their pet's condition or the diagnostic approach you would like to take. It's tempting to want to give the client a lot of information about the disease you've diagnosed or are suspecting. After all, the goal is for the client to be able to make an informed decision, right? Keep in mind, veterinarians have a minimum of 4 years of veterinary school plus experience gained before and since. It's not practical to expect the client to become an expert during the span of a single visit. It might be helpful to start by asking the client what they think might be going on with their pet, or, if you've made a diagnosis, what do they already know about the disease. This is a great opportunity for you to build them up, "Wow, I'm impressed with how knowledgeable you are about pancreatitis" or identify areas of confusion. "I can understand why you'd be confused about the signs of kidney disease versus a bladder infection. Let me see if I can clarify the differences."

When educating the client about their pet's condition, pay extra attention to the words you are using. It can be easy to fall into the trap of using medical jargon ("stifle" instead of "knee" or "radiographs" instead of "X-rays"). In human healthcare visits, physicians use an average of four un-clarified technical terms *per visit*. Veterinarians likely do this too without realizing it. If you let the client tell you what they know about the disease first, you can mirror the language they have used to avoid this situation. It's also useful to follow up with, "Have I used any technical language that was unclear to you?" or, more broadly, "I know you're planning to discuss this with your family. Could you summarize your understanding of the options so that we can ensure we're all on the same page?"

Once the education phase is complete (for now), it's time to enlist the client. Enlisting means you're inviting the client to share in the decision-making process. By collaborating with the client, you are validating their specific needs and preferences. This can be particularly important when we are trying to avoid making assumptions and different recommendations because of our implicit biases. By actively and intentionally involving the client from the beginning, you can reduce the likelihood that you are making (or withholding) recommendations based on the client's age, ability, race, ethnicity, gender, or other differences. Enlisting clients to be part of their pet's healthcare team can lead to reduced confusion, reduced anxiety, increased motivation and adherence to treatment plans, and greater satisfaction for both the client and the veterinary team.

It would be helpful to be clear that you want to form a partnership with the client in order to create the best plan moving forward for them and their pet. You could make your goals explicit by saying something like, "I certainly have my own opinions about what might be best for Charlie, and I want to hear from you about what your priorities and expectations for his care might be. Together, we can create a plan that works for you and Charlie."

The Medical Discharge

In human medicine, physicians tend to overestimate their patients' understanding of their discharge instructions and ongoing treatment plan. This has been recognized for decades without clear guidance on a resolution to the problem. There is some evidence that standardized verbal or written instructions can improve patient recall of important discharge information, though there is not clear evidence if verbal or written is superior. Both methods can be adversely affected by the client's comfort in the language communicated in and their overall literacy (for written), and veterinary health professionals must also take steps to minimize the effect their own biases may have on the communication that occurs at the end of a patient visit. Keeping in mind accessibility as an important barrier to overcome when considering client information is crucial. Multiple options to provide the same information is ideal. A variety of media may be a helpful way to provide clients with multiple options to obtain necessary information.

Having standardized handouts or pamphlets, trusted websites with informational videos, or even a phone number or two for them to call if they have questions (remind them of your clinic's contact information and, if appropriate, the nearest trusted emergency clinic's contact information). Consider having handouts in multiple languages, depending on the demographics in your region. Websites with videos should be closed-captioned for clients with hearing difficulties. Remember, too, that not all clients will have easy access to the internet, a reliable phone, or know who to call if your clinic is closed. Having this information (if not the method of delivery) standardized will also help ensure that all clients are given the same information about resources – don't assume the client wearing scrubs already knows what to do – and avoids the perception of judgment or criticism if you provide clients with standardized verbal, written, or a combination of instructions.

Remember, too, that all client instructions and information should be free of unclarified medical jargon. It generally should also be relatively brief and concise but may provide additional resources for the client who wants more information from trusted sources. The most important components of discharge instructions for clients typically includes three key components: (1) Medication instructions, (2) signs of improvement, and (3) worrisome signs/indications to seek medical advice.

At discharge, clients should be encouraged to ask questions about their instructions. A staff member knowledgeable about the patient should be available to spend time with the client to try to ensure they understand and are comfortable with the plan. Asking, "What questions do you have about Mickey's home care?" will likely yield more questions than the typical, "Do you have any questions?" It's also reasonable to ask the client to reiterate the instructions back to you before leaving: "Ms. Green, I've just gone over a lot of information about Bailey. Could you summarize for me your understanding of her at-home care to make sure we don't have a misunderstanding?"

Discharge instructions of any format should also be flexible to account for the back-and-forth that occurs during the discussion of at-home care that is unique to each case. Written instructions may have a space for annotation that is specific to the client's situation or questions. An audio or audiovisual recording of the discharge discussion might be a relatively easy way (with the ubiquity of smart phones or other recording devices) to provide documentation of the discharge instructions that both the client and the veterinary team can keep for reference.

Discussing Euthanasia and Making End-of-Life Decisions

One of the most important and impactful things a veterinarian will do in their career is to help clients through the difficult scenario surrounding the end of a pet's life. Although it is always difficult, it can actually help bring closure and a sense of well-being to both the client and the veterinarian when it is approached with compassion, patience, and understanding. Generally, the same concepts that have been discussed throughout this chapter apply to the discussion of end-of-life care and euthanasia, and we'll reinforce those concepts through this section.

Because end-of-life scenarios are necessarily fraught with intense emotions in many cases, conflict can arise under even the best of veterinarian–client relationships. Both clients and veterinarians bring their personal beliefs and wishes to these discussions, and veterinarians must acknowledge both the clients' and their own needs during these challenging scenarios. End-of-life communication, like all communication, involves a set of skills that can be learned, practiced, and reinforced. It can sometimes be helpful to break the topic up into separate components. There are numerous ways to do this, and the approach discussed here is simply one option of many.

Delivering Bad News

Veterinarians frequently must share difficult information about a client's pet to them, and the resultant reaction by the client can be emotionally jarring for both the client and the veterinarian. Clients may respond with anger, guilt, frustration, disbelief, sadness, or they may appear stoic or unaffected. Veterinarians should prepare for the unpredictability of a client's emotions, and there are techniques that can make the process easier for everyone involved.

One of the first things to do before delivering bad news to a client is to prepare. Ensure there is appropriate space, privacy, and time to have this conversation. Avoid situations that will make it difficult for the client to focus on what you need to share with them. If they are at work, can they take a break? If they have young children, can arrangements be made for someone to keep an eye on the kids for a while? If the news can be delivered in person, which might be preferred, if possible, having a designated comfort room at your clinic is ideal.

Depending on what has been discussed previously and recently about the pet's condition, it may be helpful in some situations to gather information from the client about how their pet is doing. This way, you can get a sense for how shocking this news will be for the client, and you can adjust your conversation accordingly. "Tell me what you're thinking about Buster's condition." You might learn the client is already anticipating the bad news, or you might learn they have no idea what's coming. You want to then ensure that the client is prepared to have this conversation. It's a great idea to ask permission: "I have new information about Buster's condition; is now a good time for you discuss things?" or "Would it be okay for me to share with you what we've learned about Buster?" If the owner isn't able to talk, arrange a better time to have the conversation.

If the client agrees to have the conversation, it's best to give them a warning about the content of the conversation: "Unfortunately, I don't have good news to share with you about Buster" or "As you suspected, Buster's condition is quite poor," or, if they weren't expecting the news: "This may come as a shock; however, I have some difficult information to share with you about Buster."

After the initial warning, it may be tempting to provide a lot of medical information about the case in an effort to explain the situation logically. Clients that are hearing bad news about their pet may be unable to process much information at a time. Try to be kind and empathetic and avoid using euphemisms that can be confusing. A direct approach is often most effective: "Buster's kidney values have continued to worsen and are causing him to feel so poorly. This progression will continue and eventually cause Buster's death." Some clients will have questions and want to know more. Others will need time to process what you've told them. You can ask, "I can tell how difficult this is for you. Would you like to know more about Buster's condition, or would you prefer to talk more later? Perhaps it would be helpful to have your partner here for the discussion." In this way, you can show you empathize with the client and that you can be flexible depending on their needs. Remember, too, that periods of silence might be needed. It can be difficult to let the silence linger, but your nonverbal communication may be more powerful and more appropriate in many cases.

Humane Euthanasia

Euthanasia, or good death, is a commonly performed medical procedure in veterinary medicine. As such, many veterinarians are relatively comfortable with humane euthanasia. That comfort often does not extend to the families of a pet that is terminally ill and may be suffering. Using some of the guidance described previously for delivering bad news also applies to initiating discussions about euthanasia. Depending on the communication style that has been used prior to this discussion, the veterinarian may choose to continue with the same approach or may need to switch up their communication style to be more appropriate. Again, as before, a relationship-centered approach may be best and lead to better outcomes for the client and the veterinarian. Sharing responsibility and reaching a consensus can help ensure that everyone's voice and perspective was considered.

Bringing up humane euthanasia for the first time can be difficult for the veterinarian. It is important to note that the majority of clients believe it is the veterinarian's responsibility to first broach the subject, so even if you mention it first, the client may have already been considering it for their pet. Bringing up euthanasia gives the client permission to start considering it if they haven't yet, and it validates their own concerns if they were wondering about it already. "We've been discussing the various treatment options for Jack, and another option we should consider is humane euthanasia" or "Given the severity of Jack's condition, would you be open to discussing humane euthanasia and whether and when it might be the right choice for you and Jack?" Avoid using euphemisms that can lead to miscommunication. Phrases like "putting to sleep" or "ending suffering" can mean different things to different people. Suggesting a plan for a "peaceful passing" could suggest to the client you mean hospice care. The pain caused by a misunderstanding would be far worse than the unavoidable pain caused when a beloved pet is declining.

Remember that clients will have different feelings about euthanasia, and for some, they may not consider it to ever be an option. Although this can be challenging for veterinarians in some cases, trying to explore the client's needs and wishes can help you continue to work together to ease the suffering of the pet: "If I'm understanding you correctly, electing humane euthanasia wouldn't be right for you and Jack. Would it be okay if we discuss options, including palliative care and hospice?" For veterinarians who have little experience or comfort with hospice care for pets, there may be resources in your area to refer pets for in-home or in-hospital hospice or palliative care. The International Association for Animal Hospice and Palliative Care (community.iaahpc.org) is a good resource to start with. Some areas have dedicated clinics where terminally ill pets can be referred for hospice

care. Having this information ready before you need it can reduce stress and anxiety for both the client and the veterinary healthcare team.

Once the decision to humanely euthanize a pet has been made, the veterinarian or other veterinary professional will need to discuss what will happen next. "If it's okay with you, I'd like to talk you through the process of humane euthanasia that we do here." Discussing the procedure, care of remains, and finances all should happen before the euthanasia is performed, whenever possible, so that the client can immediately continue the grieving process afterward. You can also discuss options for memorializing the pet, such as with a special urn for pets that will be cremated, or a clay paw impression. Make sure that clients understand not all decisions need to be made immediately. Allow them the opportunity to think about it or discuss options with family and friends if needed.

Once the client is ready, if the situation allows, it can be best to perform the euthanasia in a quiet, comfortable room that is free of distractions and, if possible, has a separate exit from the building. Check with the client to see if they want to spend some time with the pet. Let them know you'll check on them frequently but not to feel rushed. Sometimes it's helpful to ask the client if they've been through euthanasia for a pet before. Regardless of their previous experience, it's a good idea to remind them of the process:

> We are first going to place an IV catheter in Sassy's arm, which is how we'll deliver the medication. We will give her an overdose of an anesthetic drug, so at first, she'll go to sleep, as if she were having a procedure. As we continue to give the medication, her heart and brain function will stop. The procedure is painless, however you may notice some twitching or even some agonal or gasping-like breaths, which can occur even after death. I'll be right here with you the whole time if you have any questions or concerns, and you just need to hold Sassy and remind her how much you love her. The entire process takes between 30 and 90 seconds. Although it will be difficult for you, it will be painless for Sassy.

Offer the client an opportunity to ask questions, if needed, or to see if that process seems appropriate. If they comment that it seems quick or might be disturbing, discuss alternatives with them. Intraperitoneal sodium pentobarbital is an excellent alternative for clients who wish privacy during their pet's passing or don't want the death to be quite as quick as with intravenous administration. It's also a good alternative in situations where IV access has proven difficult. The sodium pentobarbital can be administered away from the client, and the pet can then be brought to the client to visit while the medication takes effect, generally after 10–20 minutes. If a client is uncomfortable being present for the euthanasia, ensure them that their pet will not be alone and will be made as comfortable as possible.

Once the pet has been euthanized, again expressing empathy is helpful: "I can see that this was difficult for you. I know how much you loved Gus and that you made this decision out of love for him. If you'd like, I'll give you some time with him, and I'll be back to check on you shortly." Having resources at the ready to give to clients to aid them with the grieving process can also be helpful. There are a number of potential resources, including hotlines, websites, or, if you're lucky, you might have access to a veterinary counselor or veterinary social worker to refer clients to.

Client communication doesn't end after the pet has died or been euthanized. Calling a client after a few days to check in to see how they are coping, if they have any questions, or if they need help with anything is a powerful way to show the client you care about them and to maintain the relationship. Sending a sympathy card with a handwritten message can also be very meaningful for clients. Expressing sympathy for their grief and maybe sharing a special memory of their pet can also help. Again, empathizing with the client's loss is important. Becoming adept at end-of-life discussions is an attainable and important goal for veterinarians to achieve. We are responsible for promoting the well-being of animals and to prevent their suffering. In doing so, we can also promote the well-being of our clients and ourselves.

SUMMARY

Communication is an integral part of a veterinarian's professional career, and fortunately, it is a skill that everyone can and should continually work to improve. Being able to communicate effectively with clients in all types of situations and from all kinds of backgrounds can help ensure that the veterinarian provides the best possible outcomes for the animals under our care and will also help ensure the mental health and well-being of veterinarians as well. Ensuring effective communication can increase adherence to medical advice, improve client satisfaction, and reduce complaints. Veterinarians can be leaders in their practice when it comes to seeking opportunities to practice and model effective communication, prioritize communication-based continuing education for themselves and their staff, and being open to feedback on their own communication.

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CHAPTER 2

Common Clinical Problems
CHAPTER 2.1 Abdominal Distension

Steven Holloway

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INTRODUCTION

Abdominal distension is a frequently encountered problem in small animal patients. Several potential etiologies exist for this common presentation. A thorough history and clinical examination are the first steps toward making a diagnosis and instituting treatment.

CLINICAL APPROACH TO ABDOMINAL DISTENSION

History, Signalment

The importance of a good history cannot be overemphasized in investigating abdominal distension. The presentation of an animal with an acute history versus chronic history together with physical examination findings can assist in determining if abdominal distension is something that can be determined easily and methodically or something that that may present as a catastrophe requiring immediate treatment (Figure 2.1.1). Diet, previous illness, reproductive status, age and breed, and duration of clinical signs are important to ascertain prior to examination.

The "6 Fs" and Clinical Examination

This "6 Fs" acronym has been used for many years to guide the clinician with a simple but effective way to examine the patient, formulate a differential diagnosis, and interpret clinical findings.

The "6 Fs" are categories of diseases that cause abdominal distension.

1. Flatus

Flatus is gaseous distension of the abdomen secondary to gastric dilation, bowel obstruction, ileus, or pneumoperitoneum (Figure 2.1.2).



FIGURE 2.1.1 Abdominal enlargement in a dog with ascites. A fluid wave was present on abdominal ballottement. Note there is some loss of muscle along the spine and the normal taper of the abdomen caudally is lost. This dog was diagnosed with a pericardial effusion as the cause of ascites.

A generalized taught feeling or drum-like ping on auscultation occurs on palpation and percussion. Abdominal distension may be more on one side than the other.

2. Fluid

Intraperitoneal fluid collection is associated with symmetrical abdominal enlargement (Figure 2.1.3). A fluid wave may be palpable on ballottement with an accompanying dullness to percussion.

3. Feces

Accumulation of feces in the colon can produce abdominal and gaseous distension of more proximal bowel. Feces is generally recognized as firm to hard lumps usually in the caudal-dorsal abdomen. The segments of

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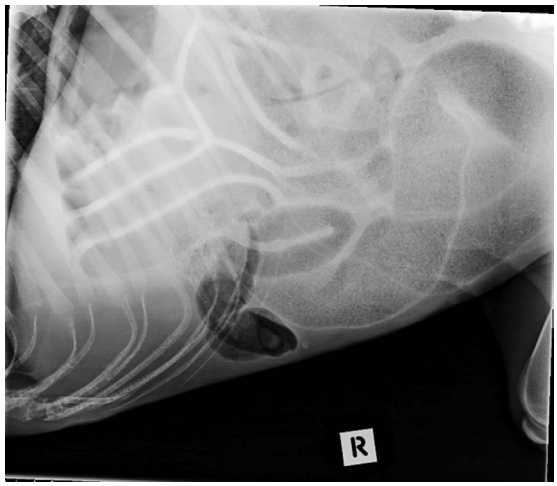


FIGURE 2.1.2 Radiography of a dog presented for vomiting with abdominal enlargement. The dog has severe tympany on abdominal percussion. There is marked generalized intestinal gas distension evident on radiograph. Ultrasound examination of the abdomen showed a mass located at ileocecal valve as the cause of the obstruction and accompanying distension. Cytology of the mass confirmed lymphoma.

colon overlying the brim of the pelvis may be felt on caudal abdominal palpation.

4. Fetus

Pregnancy and the associated enlarged uterus produce a form of organomegaly. The swelling is confined to the lower abdomen. Feti are usually identifiable on abdominal palpation in the second half of gestation.

5. Fat

Within the abdomen, fat commonly produces abdominal distension (Figure 2.1.4). It does not have characteristic features on clinical examination. Obesity related to endocrine disorders, such as hyperadrenocorticism and hypothyroidism, may be associated with characteristic skin changes and other clinical examination findings. Hepatomegaly is a prominent feature of hyperadrenocorticism.



FIGURE 2.1.3 Ascites fluid removed from a dog's abdomen. Note the fluid is serosanguineous. Analysis of the fluid was consistent with a modified transudate. The dog was investigated for right-side heart failure and diagnosed with cor pulmonale secondary to chronic heartworm disease.



FIGURE 2.1.4 This dog presented for abdominal enlargement. The physical examination revealed hepatomegaly, thin skin, and alopecia. Additionally, loss of muscle mass and increased abdominal fat are evident. Examination using abdominal ultrasonography showed the abdominal enlargement was due to hepatomegaly which added to the effect of abdominal myasthenia. Investigation revealed pituitary hyperadrenocorticism as the cause of hepatomegaly.

6. "Fantastically" Big Organs

Organomegaly is a frequent cause of abdominal enlargement (Figure 2.1.5).

Careful palpation may elucidate the origin of the organomegaly. Hepatomegaly is associated with palpation of the liver beyond the ventral rib margin. Splenomegaly may palpate as an elongated firm mass within the mid to midventral abdomen.

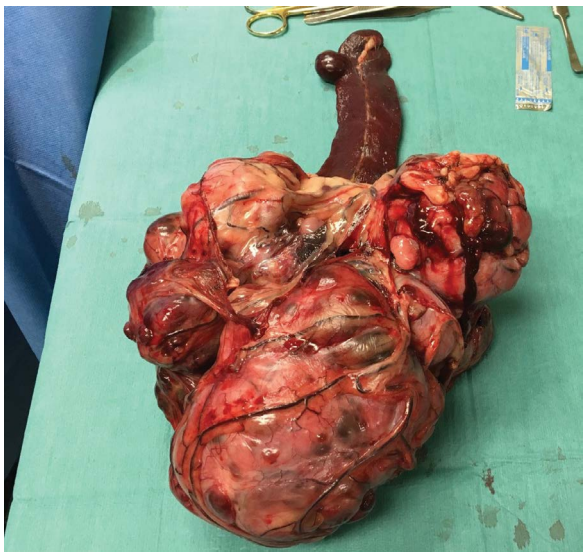


FIGURE 2.1.5 Image of a massively enlarged spleen following splenectomy. This dog was presented for abdominal enlargement. The abdomen was noted to be extremely enlarged and firm to palpate over all areas. Investigation using radiography and ultrasonography identified a large splenic mass that occupied 80% of the abdominal cavity. Surgical removal was required for definitive diagnosis. Histopathology diagnosed it as benign splenic hematoma.

Additionally, very large splenic masses may present as firm hard masses too large to palpate completely. Similarly, distension of the urinary bladder may reach extremes in animals with bladder emptying disorders and may be difficult to differentiate from ascites fluid. Prostatic masses are typically located in the caudal-dorsal abdomen and are firm to palpation. Large paraprostatic cysts may be located more cranially within the caudal to midabdomen. The sublumbar lymph nodes when enlarged may also present as firm masses in the caudal dorsal abdomen. Rectal palpation in such cases may assist with interpretation. Renomegaly may be unilateral or bilateral. This is more easily detected in the cat where the kidneys are more mobile and are located midabdomen. In the dog, renomegaly is palpated within the craniodorsal quadrant.

Initial Categorization Following Clinical Examination

Following physical examination, abdominal imaging may be helpful in establishing a diagnosis. Radiographic examination is most often used to confirm which category of "F" is the cause of abdominal enlargement. Alternatively, ultrasound examination of the abdomen may be used. It is best suited for detection of fluid or organomegaly. However, it is less useful for identifying the cause of gaseous distension. Following this initial characterization, careful investigation of differential diagnoses is instigated.

DIFFERENTIAL DIAGNOSIS

1. Flatus

Gastric Dilatation-Volvulus

Gastric aerophagia (seen with upper respiratory tract diseases, cats with cryptococcosis, asthma).

Ileus (paralytic, dysautonomia, or due to intestinal wall infiltrative disease (leiomyositis/pseudo-obstruction)).

Pneumoperitoneum

This most commonly occurs with perforating injuries to the abdomen wall or internal organs such as the stomach, intestine, or urinary bladder. It may be seen, for example, with rupture of a gastric dilatation-volvulus. It is identified on radiographs as free air in the abdomen associated with increased serosal detail.

2. Fluid (Ascites)

Radiographically, fluid is identified by a loss of abdominal detail. Ultrasound can reliably detect small volumes of fluid and is a useful first-line imaging modality for clinical triage. It is useful for guidance of abdominocentesis for fluid analysis (see algorithm). Fluid may accumulate due to different pathomechanisms (Figure 2.1.6). These include transudation due to alteration in osmotic effects and Starling forces, exudation (the movement of cells and fluid, septic or nonseptic), and modified

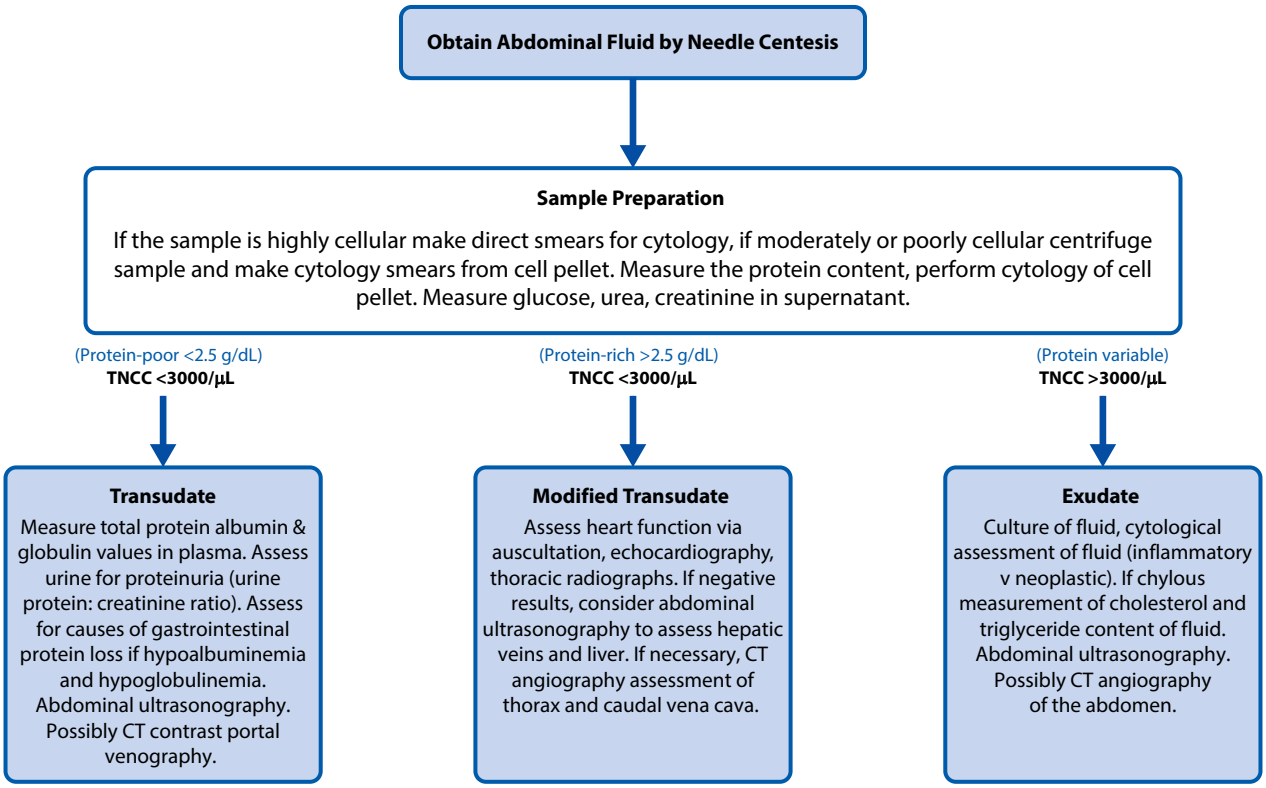


FIGURE 2.1.6 Characterization of abdominal fluid types.

transudates (cells and fluids).[1–3] When detected, recovered fluid should undergo analysis, which should include measurement of specific gravity, protein content, and microscopic examination. Bacterial culture, glucose, and lactate concentrations of effusions are performed in suspected septic exudates. Fluid analysis should be interpreted in light of clinical examination, complete blood count, biochemical testing, and urinalysis. Additional testing may be required in some cases such as pancreatitis (canine pancreatic lipase immunoreactivity or cPLi) or FIP (immunohistochemistry). The classification of fluid type and associated etiologies is seen in Table 2.1.1.[2–3]

3. Feces

The accumulation of feces may be due to dietary factors such as ingestion of bone material or water imbalance/dehydration such that stools are too hard or painful to pass. Distal intestinal obstruction etiologies include neoplasia, anal/rectal stricture, pelvic fracture, and intrapelvic masses. Failure to defecate may also occur with damage to the pelvic nerve or intramural nerve/muscular elements.

4. Fetus

Abdominal enlargement associated with pregnancy may be unexpected when animal's reproductive history is unknown. This is particularly common in cats. Radiography and ultrasonography can assist with differentiating pregnancy from pyometra or other uterine abnormalities.

5. Fat

Obesity may be multifactorial in origin. Investigation requires consideration of dietary factors (caloric intake) and exercise levels/inactivity assessment. A genetic propensity has been identified in Labradors and likely exists in other breeds of dogs. Obesity may also occur secondary to underlying endocrine disorders such as hypothyroidism or hyperadrenocorticism. Specific laboratory testing should be considered where history and physical examination is supportive.

6. "Fantastically" Big Abdominal Organ

It is important to recognize that any abdominal organ may become enlarged. Etiologies vary, with neoplasia, abscesses, and cystic structures predominating, although multiple other causes are identified (Table 2.1.2). The clinician must be aware that the prognosis is not linked to the size of the organ and that accurate diagnosis is essential. Accurate diagnosis is usually accomplished by diagnostic imaging and/or tissue biopsy methods

TABLE 2.1.1 Etiopathology, characteristics, and analysis of ascites fluid

Effusion type	Etiopathology
Transudate (protein-poor <2.5 g/dL) TNCC <3000/μL	Hypoalbuminemia (GI loss, renal loss, starvation)
	Liver failure with presinusoidal portal hypertension (may have hypoalbuminemia also), e.g., cirrhosis
	Prehepatic portal hypertension, portal vein hypoplasia, post-portosystemic shunt ligation
	Splenic vein thrombosis
Modified transudate (protein-rich >2.5 g/dL)	Right-sided congestive heart failure with its associated postsinusoidal hypertension
TNCC <3000/μL	Pericardial disease
	Post-sinusoidal hepatic portal hypertension
	Caudal vena cava thrombosis (Budd-Chiari syndrome)
	Liver disease with sinusoidal hypertension such as chronic hepatitis
Exudate (cell-rich and protein-rich >2.5 g/dL)	
TNCC >3000/μL	
Septic (bacteria identified, culture positive)	GIT leakage
	Penetrating wounds
	Migrating foreign bodies
	Urogenital tract rupture
	Hematogenous spread or primary bacterial peritonitis
Nonseptic (bacteria not identified culture negative)	Inflammatory (pancreatitis)
	Hemorrhagic
	Chylous
	Bile
	Neoplasia associated exfoliation (lymphoma, mesothelioma, other)
	Inflammatory (FIP in cats)
	Sclerosing encapsulating peritonitis

FIP, feline infectious peritonitis; GIT, gastrointestinal tract; TNCC, total number of cells counted.

TABLE 2.1.2 Differential diagnosis for organomegaly

Organomegaly	Common differential diagnosis
Liver	– Neoplasia (primary carcinoma, adenoma) metastatic neoplasia, abscess, hepatitis – Metabolic diseases, including hyperadrenocorticism (amyloidosis cats), lipidosis, glycogen storage diseases
Spleen	– Neoplasia (hemangiosarcoma, lymphoma, mast cell tumor, plasma cell/myeloma, histiocytic sarcoma, metastatic neoplasia, other) – Large splenic hematoma – Torsion, portal hypertension, lymphoid hyperplasia – Splenitis (infection or inflammation-associated) – Sedation, splenic vein thrombosis
Kidneys	– Hydronephrosis and pyonephrosis, abscess, cysts (single or polycystic) – Neoplasia (carcinoma, lymphoma)
Adrenal glands	– Neoplasia (adenoma, adenocarcinoma, pheochromocytoma, lymphoma) – Note: Severe retroperitoneal hemorrhage may be associated with adrenal masses causing abdominal enlargement and pain
Uterus	– Neoplasia, pregnancy, and pyometra
Prostate	– Adenocarcinoma, paraprostatic cyst(s), prostatic abscess, hyperplasia
Ovary/Retained testis	– Neoplasia (ovarian carcinoma, testicular Sertoli cell, Leydig cell tumor and seminoma) – Ovarian cysts
Urinary bladder	– Urethral obstruction (tissue, calculi), neurogenic paralysis of bladder
Stomach	– Neoplasia (carcinoma, leiomyoma/sarcoma), gastric outflow obstruction (pyloric antral hypertrophy) – Gastric pythiosis
Pancreas	– Rarely large enough to cause abdominal distension, except for cystic adenocarcinoma in cats
Intestine	– Rarely large enough to cause abdominal distension – However, distal obstructions (neoplastic or anatomical) may cause feces to accumulate to extraordinary amounts – Megacolon, for example

Not all differentials may cause organomegaly; however, "fantastically big" organomegaly may cause clinically apparent abdominal distension.

(cytology of fine-needle aspirates and/or tissue biopsy and histopathology). Abdominal radiography (3 orthogonal views) has the advantage of giving a "global" view of the abdomen. Ultrasound examination may provide information on structure, blood supply, and fluid content and is useful for assisting rapid diagnosis in the emergency patient.[5] Ultrasound guidance is also used for obtaining samples for cytology, culture, and histopathology. Where surgical removal of a large mass is contemplated, contrast CT scanning may be useful for delineating margins and identifying vasculature.

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CHAPTER 2

Common Clinical Problems

CHAPTER 2.2 Cough

Elizabeth Rozanski

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Cough is a common presenting complaint for dogs and, to a lesser extent, cats. Cough is a sign of an underlying disorder and not a primary diagnosis. Therefore, the cause of the cough should be identified and treated, if possible. In some cases, the cause of cough may be simple to identify and easy to correct, such as kennel cough. In other cases, the cough may be multifactorial or relatively resistant to therapy.

Cough is defined as a sudden expiratory effort producing a noisy expulsion of air from the lungs. A cough usually signals an effort to clear the lungs of real or imagined foreign material. Cough can be productive or dry, although this may be at times hard for the owners to determine if the cough is productive, as animals rarely expectorate and tend to swallow any mucus that is produced. Cough can be classified as acute or chronic. A cough is considered chronic if it lasts for 2 months or longer.

Most coughing in animals is presumed to be an involuntary response. The cough reflex is the primary defense mechanism to prevent aspiration of large particles or debris.

Stimuli to cough include pressure on the outside of the airway, presence of foreign material or perception of foreign matter, excessive secretions, or recurrent aspiration. Cough plays an important function both by aiding in the clearance of foreign debris and by enhancing the actions of the mucociliary elevator.

HISTORY

Historical information and a description of the cough may help to pinpoint the etiology. Cough may also be classified as to a specific time of day (e.g., night, morning) or coupled with an event such as drinking, eating, running, or pulling on a leash. Coughing at nighttime may result in more complaints due to interference with the owner's own sleep, especially for owners that are away during the daytime. In cats, cough may be confused with retching or attempts to vomit hairballs. Kennel cough or canine infectious respiratory disease complex (CIRD) is common in dogs, and even brief exposure to other apparently healthy dogs can result in infection. As always, questions about prior therapy and any apparent benefit or lack of benefit may help improve the diagnostic and therapeutic option.

PHYSICAL EXAMINATION

Pets that are presented for evaluation of cough should be immediately assessed as "stable" or "unstable." Congestive heart failure most commonly presents as tachypnea and/or respiratory distress, but occasionally, signs are misinterpreted to be only cough, particularly when large volumes of pulmonary edema are present. Tracheal collapse may result in severe respiratory distress due to airflow obstruction, although affected dogs may have cough occasionally as well. Other unstable causes of cough include pneumonias and pleural space disease, such as spontaneous pneumothorax or chronic pleural effusion. Unstable pets should be rapidly administered supplemental oxygen, and diagnostic testing should be pursued promptly.

In stable patients, a complete physical examination of the cardiopulmonary system is warranted, including examination of the oral cavity, palpation of the neck for masses or lymphadenopathy, auscultation of the upper and lower airways and heart, and abdominal palpation. Dogs with a visible expiratory "push" commonly have obstructive lower airway disease, while a dog with a palpably dorsoventrally flattened trachea is more commonly affected with obstructive tracheal disease in the cervical or thoracic inlet regions. Pets should be evaluated for weight loss or loss of muscle mass, which may accompany primary or metastatic neoplasia,

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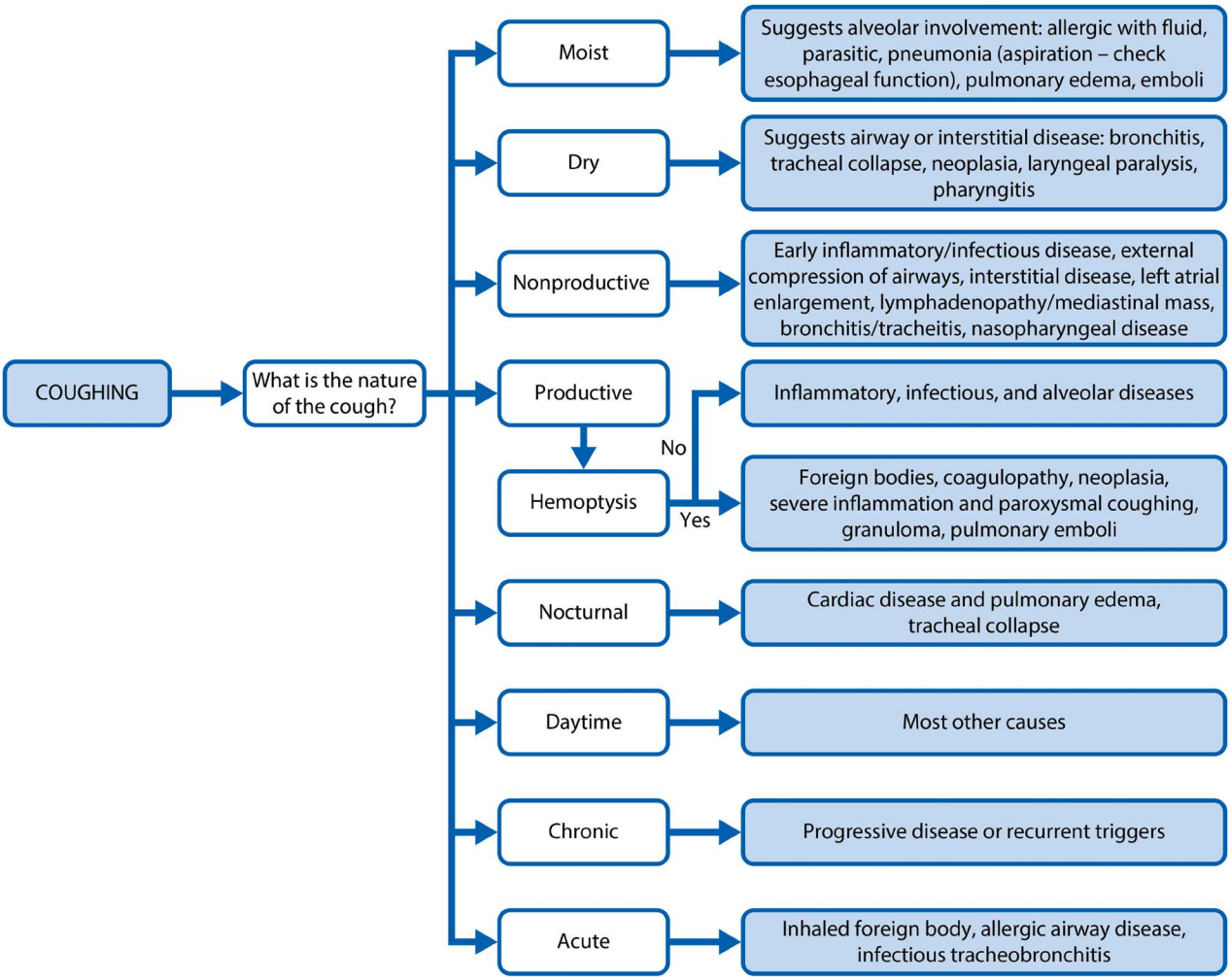


FIGURE 2.2.1 An algorithm showing the various characteristics and causes of different types of coughs.

heart disease, or severe obstructive pulmonary disease. Esophageal (megaesophagus) and laryngeal dysfunction may lead to recurrent pneumonias due to aspiration. Recent work has supported an increasing role of aerodigestive disorders in causing cough (see algorithm, Figure 2.2.1).

DIAGNOSTIC IMAGING

Thoracic imaging is recommended for evaluation of the patient with cough. Thoracic radiographs enable evaluation of lung parenchyma, large airways, as well cardiac size and pleural space. Computed tomography (CT) may be used as well for pulmonary diagnostics and may provide additional information about airway and lung parenchyma.

At a minimum, dogs and cats with a cough should have thoracic radiographs performed to not only try and identify an underlying cause but also to direct appropriate therapeutics. Point-of-care ultrasound has been gaining in popularity for evaluating evidence of pulmonary infiltrates, as assessed by the presence of B-lines or other pulmonary pathology. In dogs undergoing bronchoscopy to assess airway structure, an initial laryngeal examination should be performed, especially in animals with concurrent stridor. Bronchoscopy is considered the "gold standard" for evaluating airway structure and should be combined with focused bronchoalveolar lavage (BAL) sampling.

SAMPLING

Sampling of the airways for cytology, aerobic culture and sensitivity testing, and/or polymerase chain reaction (PCR) testing should be considered in dogs and cats without a clear diagnosis from history, physical examination, and thoracic radiographs. Any anticoagulant medication precludes a transthorasic fine needle aspiration. Airway cytology is useful to document infection, inflammation, or eosinophilic infiltrates. Cultures should be interpreted in light of the cytological findings as normal airways may not be sterile. Parasites are occasionally identified in airway washes.

MANAGEMENT

Treatment of cough is varied depending on the identified underlying cause. Specific therapy is more likely to be useful than simple supportive care. If no specifically treatable cause is found, supportive care should be used.

The most common cause of chronic cough in dogs and cats is chronic bronchitis and feline lower airway disease/asthma, respectively. Lifestyle changes are important and may help significantly to reduce both the frequency and severity of the cough. Changes include:

1. Switching from a collar to a harness
2. Avoiding excessive excitement (and accompanying barking)
3. Avoiding indoor air pollutants (e.g., cigarette smoke and perfumes)
4. Weight loss to reduce the cough and exercise intolerance

Additionally, avoiding contact with dogs that may have infectious respiratory disease, such as kennel cough complex, is beneficial. Vaccination against the kennel cough complex may be helpful. Using mobile groomers may also help to limit exposure.

Controlling inflammation is helpful in dogs with chronic bronchitis and cats with lower airway disease and is most often achieved through oral or aerosolized glucocorticoids. Glucocorticoids decrease airway inflammation, which subsequently decreases cough. Glucocorticoids are usually extremely effective against cough but may have side effects, such as weight gain, panting, polyphagia, and polydipsia, which preclude long-term high-dose use. Oral glucocorticoids may be tapered to the lowest dose that controls signs. Inhaled glucocorticoids (e.g., fluticasone) are gaining in popularity for treatment of airway disease and may be very useful for long-term control. Most patients can be trained to accept the inhaler.

While chronic bronchitis is not primarily an infectious disease, treatment with antibiotics may be warranted during exacerbation of coughing episodes. In people with chronic obstructive pulmonary disease (COPD), treatment with macrolides, such as azithromycin, reduce hospitalizations. Fluoroquinolones and doxycycline are also useful as long-term antimicrobials. Owners should be advised that in patients with chronic bronchitis, an acute exacerbation of a cough may represent an antibiotic "deficiency" as secondary infections may develop, magnifying the cough. Deworming (e.g., fenbendazole) is appropriate, although the likelihood of parasites in adult dogs and cats is relatively low.

Cough suppressants are also used for the treatment of chronic bronchitis. In general, the cough reflex is essential to help clear secretions or trapped foreign particles. Chronic cough may be very tiring for both the dog and the family. Antitussives may be divided into central and local-acting substances. Centrally acting drugs act by depressing the cough center within the brain to the various stimuli. Opioids are effective central-acting antitussives. Opioids may have additional properties, such as sedation, impaired micturition, or constipation. In some animals, one opioid may be clearly more effective than another. Thus, if significant coughing is still occurring, it may be useful to try another medication or to increase the dose, as tolerance may develop after prolonged usage. It is particularly helpful to give sedative cough suppressants to the dog before bedtime to help both the pet owner and the pet sleep through the night.

Central-acting cough suppressants used in veterinary medicine include codeine, butorphanol, and hydrocodone. Dextromethorphan is available over the counter in many human cough medications and is occasionally effective in dogs. It is available in combination with guaifenesin as "cough tabs."

In some cases, concurrent pulmonary hypertension may develop, associated with chronic pulmonary disease. If this can be documented, treatment with sildenafil may be beneficial.

Maropitant, gabapentin, and tricyclic antidepressants have been proposed for chronic cough. In humans, gabapentin has been effective in chronic cough but has not been formally studied in dogs. One small clinical trial of maropitant in dogs with chronic bronchitis showed a moderate benefit.

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CHAPTER 2

Common Clinical Problems

CHAPTER 2.3 Diarrhea

Frédéric Gaschen

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INTRODUCTION

Diarrhea is characterized by decreased fecal consistency, increased fecal volume, and/or increased defecation frequency.

All cats and dogs with diarrhea have intestinal dysfunction due to primary intestinal disease or secondary intestinal involvement associated with disorders originating outside the intestine. The clinical signs vary depending on whether the disease primarily originates in the small intestine or in the colon (Table 2.3.1 and Figures 2.3.1–2.3.6). However, not all animals with intestinal disease experience diarrhea. For instance, cats with inflammatory bowel disease (IBD) or small-cell intestinal lymphoma may present with weight loss, hyporexia, lethargy, and/or vomiting without diarrhea in spite of significant involvement of their intestinal mucosa. Also, dogs with protein-losing enteropathy (PLE) may show significant protein loss in the absence of diarrhea.

TABLE 2.3.1 Clinical signs associated with small and large bowel diarrhea

Clinical sign	Small intestinal disease	Large intestinal disease
Frequency of defecation	Normal or only slightly increased	Moderately to severely increased
Fecal volume per defecation	Normal to large	Small
Presence of mucus	No	Common
Presence of blood	Melena (digested blood) and possibly hematemesis if lesion in the duodenum or above Hematochezia if lesion in the jejunum or ileum	Hematochezia (fresh blood)
Steatorrhea	Possible	No
Tenesmus	No	Common
Urgency	No	Common
Dyschezia	No	Common
Flatulence, borborygmi	Possible	Uncommon
General condition	May be decreased (lethargy)	Usually unchanged
Appetite	Hyporexia common	Usually unchanged
Abdominal discomfort	Possible	Possible
Vomiting	Relatively common (especially in cats)	Possible but occasional
Weight loss	Common (if chronic)	Uncommon

Commonly, the disease process may involve both the small and large intestine, and affected animals present with a mixture of clinical signs indicating small and large bowel diarrhea.

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FIGURE 2.3.1 A 4-year-old male neutered Weimaraner with dietary indiscretion and bloody diarrhea.

Secondary signs that may occur in diarrheic animals include dehydration, lethargy, dysorexia, abdominal pain, borborygmi, flatulence, hematochezia, melena, and anal/perianal irritation. Animals with chronic small intestinal diarrhea may present with weight loss (including loss of muscle mass) and possibly ascites in case of significant intestinal protein loss.



FIGURE 2.3.2 Liquid diarrhea of small bowel origin in a cat with inflammatory bowel disease.



FIGURE 2.3.3 Hematochezia with soft stool in a dog with diet-responsive chronic enteropathy.



FIGURE 2.3.4 Melena and diarrhea in a Boxer with GI bleeding secondary to duodenal adenocarcinoma. (*Courtesy of M. Schaer.*)

PATHOPHYSIOLOGY

The following mechanisms are commonly involved in the pathogenesis of diarrhea. In many instances, several mechanisms contribute concurrently to the onset of diarrhea in intestinal diseases.



FIGURE 2.3.5 Cow-pat-like feces from a 9-month-old Mastiff with exocrine pancreatic insufficiency.



FIGURE 2.3.6 Mucoid feces from a dog with chronic idiopathic colitis.

Osmotic Diarrhea

Osmotic diarrhea occurs in the presence of large, poorly absorbable, osmotically active molecules such as undigested carbohydrates, solutes that may additionally undergo fermentation by intestinal microbiota. These molecules ultimately result in a lack of water absorption and loss of water and nutrients in the feces. Osmotic diarrhea may occur following dietary indiscretion and with maldigestion secondary to exocrine pancreatic insufficiency or severe intestinal mucosal inflammation. Unlike most other forms of diarrhea, it typically resolves after the affected animal is fasted.

Secretory Diarrhea

Secretory diarrhea is the result of activation of cellular pathways leading to the secretion of electrolytes and water by the enterocytes. Inflammatory cytokines, fatty acids, bile acids, and bacterial endotoxins may trigger this pathway. IBD and enteropathogenic *E. coli* may elicit diarrhea through this pathway.

Increased Mucosal Permeability

This results from a loss of integrity of the intestinal mucosal barrier, which may occur through loss of enterocytes or compromise of paracellular structures such as the tight junctions connecting the enterocytes. Examples of diseases include parvovirus infection, IBD, intestinal lymphoma, and PLE.

Abnormal Intestinal Motility

This develops in the presence of mucosal inflammation. Giant aboral contractions (small intestine) and giant migrating contractions (colon) are common and may severely shorten intestinal transit times.

DIFFERENTIAL DIAGNOSES

There is a myriad of possible causes for diarrhea in dogs and cats. Therefore, it is meaningful to differentiate acute from chronic diarrhea and young from adult animals when preparing a list of differential diagnoses. In addition, the environment plays an important role: Dogs and cats in group housing are more susceptible to developing infectious diseases (animal shelters, boarding facilities, and breeding facilities). Common differential diagnoses for dogs and cats with acute and chronic diarrhea are summarized in Tables 2.3.2 and 2.3.3.

Acute Diarrhea

In young dogs and cats, acute diarrhea is often caused by enteric infections, and parvovirus infection is an obligate initial rule out in puppies/kittens presenting with acute-onset vomiting and bloody diarrhea. Additionally, parasitic infestations with nematodes (e.g., roundworms, hookworms, whipworms) or protozoa (e.g., various coccidia, *Giardia*) are very frequent causes of acute diarrhea. Alternatively, diarrhea may also be dietary in origin (dietary overload, dietary indiscretion, abrupt change in diet).

In adult dogs and cats, parasitic and dietary causes of diarrhea are also very common and need to be ruled out early in the diagnostic process. Acute flare-ups of chronic recurring diarrhea should be differentiated from truly acute disease. Acute hemorrhagic diarrhea syndrome (AHDS) is a disease of unknown etiology that typically but not exclusively affects middle-aged dogs of small and toy breeds (Figure 2.3.7). Severe cases may have a fatal outcome without aggressive treatment.

With the exception of shelters, boarding and breeding facilities, or dogs with acute hemorrhagic diarrhea

TABLE 2.3.2 Common causes of acute diarrhea in dogs and cats

	Dog	Cat
	Infectious	
Viral	Parvovirus*, coronavirus*	Parvovirus*, FeLV, FIV
Bacterial	*Campylobacter* spp., *Clostridium perfringens, Clostridium difficile, E. coli, Salmonella* spp., *Neorickettsia helminthoeca*†	*Campylobacter* spp., *E. coli, Salmonella* spp., *Clostridium perfringens, Clostridium difficile*
Parasitic	Nematodes (roundworms, hookworms, and whipworms)	Nematodes (roundworms and hookworms)
	Protozoa: Coccidia (*Isospora* spp.*, *Cryptosporidium* spp.), *Giardia* spp.	Protozoa: Coccidia, (*Isospora* spp.*, *Cryptosporidium* spp.), *Giardia* spp., *Tritrichomonas fetus*‡
Diet	Dietary indiscretion, abrupt diet change	Abrupt diet change, dietary indiscretion
Toxins, drugs	Numerous plants, drugs (e.g., antibiotics, chemotherapy drugs), chemicals	Same as dog
Idiopathic	Acute hemorrhagic diarrhea syndrome	
Diseases originating outside the intestine	Pancreatitis, liver disease, kidney disease, toxemia, sepsis	Same as dog

* Puppies and kittens;
† in endemic areas;
‡ young cats, multi-cat housing.

TABLE 2.3.3 Common causes of chronic diarrhea in dogs and cats

	Dog	Cat
Bacterial	*Campylobacter* spp., *Clostridium perfringens, Clostridium difficile, E. coli, Salmonella* spp., *Neorickettsia helminthoeca*‡	*Campylobacter* spp., *E. coli, Salmonella* spp., *Clostridium perfringens, Clostridium difficile*
Fungal, oomycetes, algal	*Histoplasma capsulatum*‡, *Pythium insidiosum*‡, *Prototheca* spp.‡	*Histoplasma capsulatum*‡
Parasitic	Nematodes (round, hook, and whipworms), *Heterobilharzia americana*‡	Nematodes (round and hookworms)
	Protozoa: Coccidia (*Isospora* spp.*, *Cryptosporidium* spp.), *Giardia* spp.	Protozoa: Coccidia, (*Isospora* spp.*, *Cryptosporidium* spp.), *Giardia* spp., *Tritrichomonas fetus*†
Diet	Diet-responsive diarrhea	Diet-responsive diarrhea
Dysbiosis	Present in most chronic inflammatory and neoplastic intestinal diseases	Present in most chronic inflammatory and neoplastic intestinal diseases
Chronic inflammation	Inflammatory bowel disease, granulomatous colitis!	Inflammatory bowel disease
Neoplasia	T-cell intestinal lymphoma	Small-cell intestinal lymphoma (T-cells)
Idiopathic diseases	Idiopathic intestinal lymphangiectasia	
Diseases originating outside the intestine	Atypical hypoadrenocorticism, exocrine pancreatic insufficiency, chronic pancreatitis, liver disease, kidney disease	Hyperthyroidism, exocrine pancreatic insufficiency, chronic pancreatitis, liver disease, kidney disease

* Puppies and kittens;
† young cats, multi-cat housing;
‡ in endemic areas;
! Boxers and Bulldogs.

syndrome, the role of bacterial enteropathogens is probably peripheral, since these bacteria and their toxins have been detected with similar frequency in the feces of healthy and diarrheic animals.

Chronic Diarrhea

As is the case with acute diarrhea, parasites (nematodes and protozoa) are also very frequently involved.

Chronic enteropathies (CE) are associated with intestinal mucosal inflammation. A complex relationship exists between the intestinal microbiota and the gut immune system, which is disrupted in chronic intestinal diseases. Additional factors such as dietary antigens may also contribute to the inflammation. Considerable and long-lasting changes in the composition of the microbiota have been documented in dogs and cats with CE. The differential diagnoses of canine CE include diet-responsive diarrhea, idiopathic intestinal dysbiosis (most common in young, large breed dogs such as German Shepherd Dogs), IBD, and T-cell intestinal lymphoma. Diet-responsive disease and IBD are also very common causes of feline CE and must be differentiated from small-cell intestinal lymphoma (T-cells), which may show similar clinical signs.



FIGURE 2.3.7 Liquid bloody diarrhea from a mixed-breed dog with acute hemorrhagic diarrhea syndrome.

CLINICAL APPROACH

A thorough history should be obtained that includes a description of the onset and duration of diarrhea, appearance of the feces, description of defecation, including frequency, and clinical course of the disease. Acute and new problems should be differentiated from recurrent or chronic issues. Additionally, the presence of factors that may trigger the development of diarrhea, such as dietary changes or administration of drugs such as antibiotics or nonsteroidal anti-inflammatory drugs (NSAIDs), should be discussed. Anthelmintic treatment and vaccination history should be obtained. The owner should also be asked if other animals in the household have the same signs and if the diarrheic dog/cat also shows additional signs such as hyporexia, vomiting, weight loss, polydipsia, and polyuria.

Acute Diarrhea

At the time of initial presentation, puppies and kittens that could have highly contagious parvovirus infection should be identified on the basis of clinical signs and absent/incomplete vaccination status. They should be immediately triaged and screened for the presence of viral antigen in the feces. Cage-side fecal tests have excellent specificity, and positive animals should be isolated from the rest of the hospital population while they receive treatment. However, fecal antigen test sensitivity is good but not perfect, and a negative result does not rule out the presence of virus. Consequently, in unvaccinated or incompletely vaccinated animals, suggestive clinical signs are sufficient to justify isolation.

In adult animals, acute diarrhea is often self-limiting, particularly if the underlying problem (parasites, diet) can be eliminated. Feces should be collected for parasitological testing (e.g., direct smear, zinc sulfate flotation, fecal *Giardia* antigen test). Alternatively, a broad-spectrum anthelmintic drug such as fenbendazole can be administered empirically (50 mg/kg orally [PO] q.24h. for 3 days). Further diagnostic tests such as screening for additional infectious diseases may be indicated in kennel, cattery, or shelter situations.

Treatment is supportive and focused on fluid therapy to address dehydration, the most common complication of acute diarrhea. Dogs and cats with limited systemic repercussions of diarrhea and mild dehydration may benefit from oral and subcutaneous (SC) fluids; however, lethargic, anorexic, and moderately to severely dehydrated animals require intravenous (IV) fluid therapy designed to rapidly and efficiently correct existing fluid and electrolyte deficits.

All animals with acute diarrhea generally benefit from a 12-hour fasting period followed by frequent small meals consisting of easily digestible food (commercial intestinal diet or home-prepared boiled skinless chicken breast and rice) for 3–5 days before being progressively reintroduced to their regular diet. Importantly, young puppies and kittens should not be systematically fasted as they may become hypoglycemic if not fed regularly. Antidiarrheal drugs are rarely necessary in small animals with acute diarrhea. Antimicrobials are generally not recommended in the treatment of acute diarrhea, except in the presence of severely compromised mucosal barrier and evidence of severe systemic repercussions such as severe depression, marked leukocytosis, or leukopenia, or in shelter animals. In a few clinical studies, probiotics have been documented to shorten the time to passage of normal feces and the time to discharge. A 2- to 4-week treatment extending well beyond expected clinical recovery is generally recommended.

Chronic Diarrhea

Dogs and cats with small or large bowel diarrhea and absent or minimal systemic repercussions (e.g., lethargy, dysorexia, weight loss) benefit from a sequential approach using various empirical treatment trials (**Box 2.3.1**). First and foremost, intestinal parasites must be eliminated using a broad-spectrum anthelmintic drug such as fenbendazole. Then, a dietary trial using either a novel protein or a hydrolyzed peptide commercial diet should be implemented. Clinical studies have shown that 50%–65% of dogs and cats with chronic diarrhea respond to such a dietary trial within 1–2 weeks. The proportion of responders is even higher among young, large breed dogs with mostly large bowel diarrhea. Dogs that do not respond to the elimination trial could benefit from a second elimination trial with a different

diet. Alternately, addition of a highly concentrated multistrain probiotic or use of antibiotics could be beneficial to address changes in the intestinal microbiota (dysbiosis), as outlined in Box 2.3.1. Finally, if empirical treatment is not successful, a full workup is indicated.

In sick dogs and cats with chronic diarrhea and dysorexia, lethargy, weight loss, or ascites, a more aggressive approach is recommended. This includes a minimal database with CBC, biochemical profile, and urinalysis, as well as abdominal ultrasound, if available. Depending on the severity of disease, these tests may reveal an inflammatory leukogram, panhypoproteinemia (hypoalbuminemia and hypoglobulinemia), and increased liver enzymes. Abdominal ultrasound may document intestinal wall lesions in all or select segments of the intestine. In parallel to the diagnostic plan, correction of fluid and electrolyte deficits may be required. Ultimately, intestinal mucosal biopsies may need to be collected endoscopically or surgically and evaluated histologically. In severely debilitated patients that are poor anesthetic risks or in cases with financial limitations, a carefully designed treatment trial for the most likely cause of the chronic diarrhea can be initiated if indicated (for further details, see Chapter 9, Digestive Diseases).

The recommended approach to chronic large bowel diarrhea is illustrated in the algorithm (Figure 2.3.8).

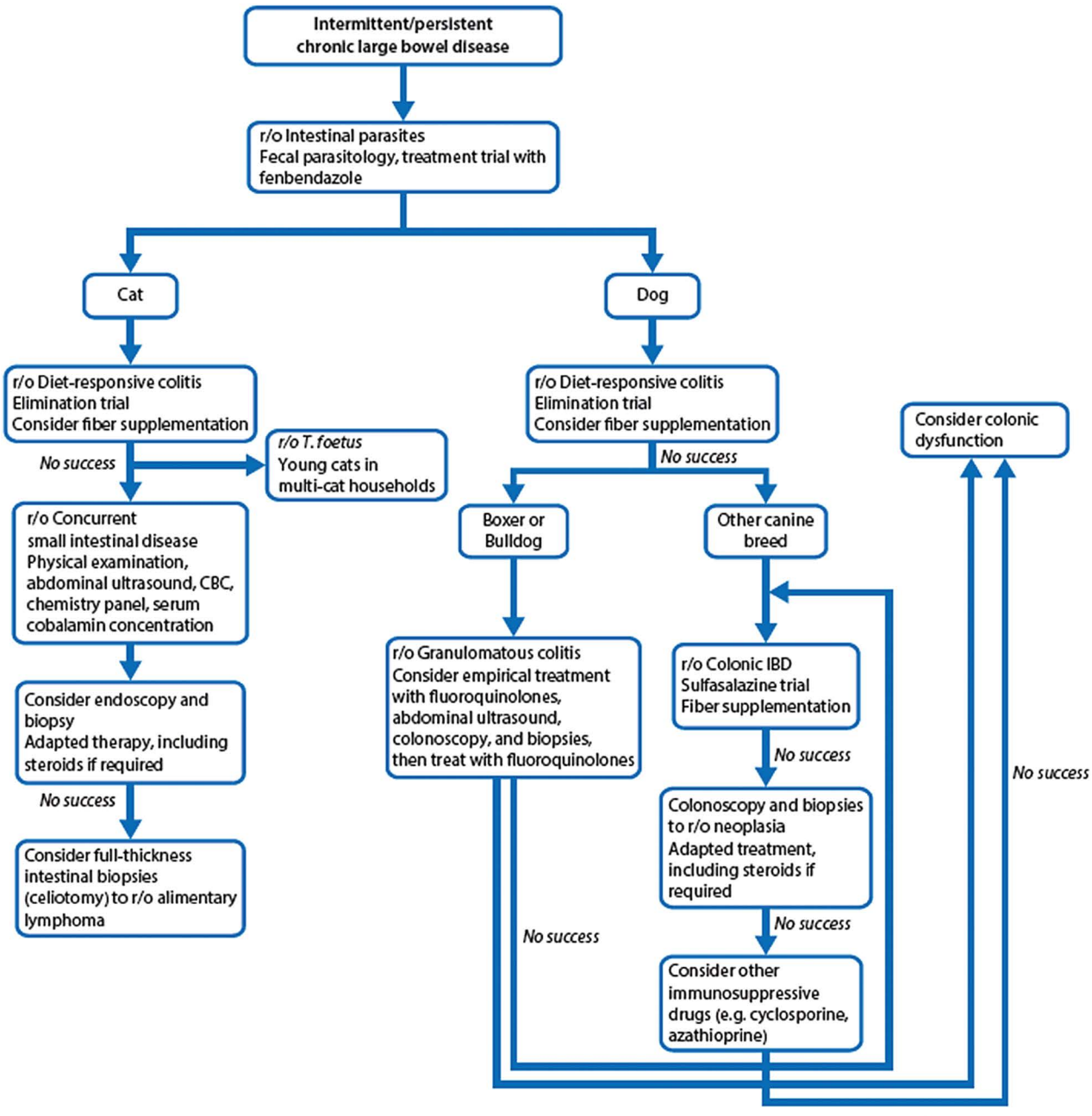


FIGURE 2.3.8 Clinical approach in cats and dogs with intermittent or persistent chronic large bowel diarrhea. r/o, rule out.

BOX 2.3.1 Approach to chronic diarrhea in dogs with minimal or absent systemic signs. While a sequential application of the following steps is theoretically preferable, they can also be combined (e.g., parasiticide and diet initiated at the same time).

- **Rule out intestinal parasites**
  Repeated parasite screenings and/or treatment with broad-spectrum anthelmintic drug (e.g., fenbendazole 50 mg/kg q.24h. for 3 days).

- **Rule out diet-responsive enteropathy**
  Elimination trial with hypoallergenic diet; a response should be seen within 2 weeks. In case of failure, some cases may benefit from a second trial with a different diet:
  - Novel protein diet (based on patient's dietary history)
  or
  - Hydrolyzed peptide diet

- **Rule out persistent intestinal dysbiosis**
  Administer a highly concentrated multistrain probiotic (e.g., 100–400 billion colony-forming units [CFU] per dog per day). Alternately, antibiotics such as tylosin (10–20 mg/kg p.o. q.12h.), or metronidazole (10–15 mg/kg p.o. q.12h.) have been used as well; a response should be seen within 2 weeks. If successful, treatment with probiotics or antibiotics should be pursued for an additional 2 or more weeks following improvement of clinical signs.

- If none of the above approaches works, obtain a minimal database with complete blood count (CBC), biochemistry panel, urinalysis, and abdominal ultrasound. Finally, endoscopy and intestinal biopsy or full-thickness surgically obtained intestinal biopsies might be required for a histopathologic diagnosis.

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CHAPTER 2

Common Clinical Problems
CHAPTER 2.4 Dyspnea

Claire R. Sharp

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Dyspnea represents a true emergency in dogs and cats, and rapid attention is warranted to limit the sensation of difficulty breathing, and institute appropriate diagnostic and therapeutic interventions. Some authors prefer to avoid the term dyspnea, as it defines a sensation of breathlessness in people, which dogs and cats are unable to describe. As such, the terms respiratory distress, shortness of breath, or abnormal breathing pattern may be used interchangeably.

CLINICAL APPROACH TO THE DYSPNEIC PATIENT

Supplemental oxygen should be immediately provided to a dog or cat in respiratory distress, by flow-by or mask if patient handling is required, or in an oxygen cage in a "hands-off" approach. A hands-off approach is particularly appropriate for cats, since additional handling when they are already in distress may precipitate decompensation and respiratory arrest. Table 2.4.1 outlines the various methods for providing supplemental oxygen.

Sedation may also provide therapeutic relief (Table 2.4.2). An (intravenous) IV catheter should be placed when feasible and initial blood samples collected. Point-of-care blood tests indicated on all patients in respiratory distress include packed cell volume, total solids, and venous blood gas. Additionally, the clinician must be prepared to intubate and provide positive pressure ventilation to patients with extreme respiratory distress.

Localization of the problem causing dyspnea is vital to guide diagnostic and therapeutic choices. The four most common anatomical causes of respiratory distress are upper airway obstruction, lower airway obstruction, pulmonary parenchymal disease, and pleural space disease. Respiratory lesions can generally be localized to one of these four sites by a combination of physical examination and thoracic auscultation (Figure 2.4.1). Other less common causes of respiratory distress include chest wall disease, pulmonary thromboembolism, abdominal distention, and look-alike diseases.

Physical examination of the respiratory system should start with an assessment of the breathing pattern and thoracic auscultation. Is their effort increased on inspiration, expiration, or both? Do they have stridor, signs of trauma, or abdominal distention? Are their lung sounds increased or decreased on auscultation?

UPPER AIRWAY OBSTRUCTION

See also Chapter 6, Respiratory Disorders.

Upper airway obstruction is classically associated with inspiratory difficulty and an externally audible noise termed stridor. Stridor is a continuous sound heard during inspiration. Hyperthermia is often present as these patients are unable to dissipate heat. An upper respiratory tract (URT) obstruction occurs due to mechanical or functional obstruction of the large airways and may occur at the level of the pharynx, larynx, or extrathoracic trachea (Table 2.4.3). The most common causes of URT obstruction are laryngeal paralysis (particularly in large breed, older dogs), tracheal collapse (particularly in small breed dogs), and brachycephalic obstructive airway syndrome (BOAS). Aspiration pneumonia may complicate cases of URT obstruction.

Initial treatment of URT obstruction includes sedation, cooling if hyperthermic, and oxygen supplementation. Various sedative drugs can be considered (Table 2.4.2). Depending on the nature and severity of the obstruction, the airway may need to be cleared and/or secured via orotracheal intubation or, rarely, an emergency tracheostomy. An anti-inflammatory dose of glucocorticoids (e.g., 0.1–0.15 mg/kg dexamethasone SC, IM, or IV) may also be considered to reduce URT

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TABLE 2.4.1 Comparison of the fraction of inspired oxygen achieved by different methods of oxygen supplementation, their advantages and disadvantages

Method	Fraction of inspired oxygen (FiO_2) achieved	Advantages	Disadvantages
Flow-by	Generally low 25%–40% with a flow rate of 2–3 L/min versus 30%–90% if 5 L/min and held within a few centimeters of nostrils	– Noninvasive – Well tolerated – Easy access to patient – Useful during triage	– Wasteful of oxygen – Short term only – Labor intensive – requires someone to hold in front of patient
Face mask	5–12 L/min FiO_2 up to 50%–60% versus 80%–90% if tight-fitting	– Noninvasive – Relatively high FiO_2 – Easily administered – Easy access to patient	– Rebreathing of CO_2 and hyperthermia can occur if tight-fitting mask – May not be tolerated in awake and coherent patients – Labor intensive
Oxygen hood (e.g., Elizabethan collar with plastic wrap over the top)	0.5–1.0 L/min flow rate can achieve FiO_2 of 30%–40% High flows may achieve close to 100% FiO_2 Must have an outflow	– Noninvasive – Generally well tolerated – Economical – Minimal equipment	– CO_2 accumulation and hyperthermia if not adequately vented – Condensation interferes with visualization
Oxygen cage	Up to 60+%	– Noninvasive – Minimal patient stress – Tight control of FiO_2 – Temperature and humidity controlled if using a commercially available cage	– CO_2 accumulation if no soda lime – Expensive – Use large volumes of oxygen – Opening cage results in loss of high FiO_2 – No direct patient access
Traditional nasal prongs / catheters	Flow rates of 50–150 mL/kg per minute achieve 30%–60% FiO_2	– Minimally invasive – Generally well tolerated – Allow patient access	– Can be irritating → sneezing, epistaxis – Not tolerated by all animals – May require sedation to place – May require local anesthetic to reduce local irritation
High-flow nasal cannulae	Up to 100% depending on the flow rate	– Minimally invasive – Can provide continuous positive airway pressure (CPAP)	– Require specialized equipment – Pneumothorax, pneumomediastinum, and SC emphysema have been reported in humans
Transtracheal oxygen (rarely indicated)	~70% depending on flow rate	– Higher FiO_2 – A degree of CPAP – Bypass URT obstruction – Useful during tracheobronchoscopy – Easy to maintain once in, if immobile patient – Allows patient access	– Invasive unless via existing tracheostomy – More labor intensive – Often require sedation for percutaneous placement or anesthesia for surgical approach – Easy to dislodge or kink – Potential for SC emphysema – Contraindicated in coagulopathy
Intubation (and ventilation)	Up to 100%	– Indicated if hypoxemia (PaO_2 < 60 mmHg, SpO_2 < 90% despite oxygen supplementation), hypercapnia (PCO_2 > 60 mmHg), or respiratory fatigue – Fine control of FiO_2, PEEP, and all aspects of ventilation	– Invasive – Requires anesthesia – Mechanical ventilation – Expensive

CPAP, continuous positive airway pressure; CO_2, carbon dioxide; FiO_2, fraction of inspired oxygen; PCO_2, partial pressure of carbon dioxide; SC, subcutaneous; URT, upper respiratory tract.

TABLE 2.4.2 Drugs commonly used for the emergency treatment of dyspneic dogs and/or cats depending on lesion localization

Drug name and rationale	Drug class	Dosing guide	Considerations
Sedatives/anxiolytics			
Butorphanol	Opioid analgesic	0.1–0.3 mg/kg IM or IV	First-line sedative for respiratory distress Minimal cardiovascular depression
Acepromazine	Phenothiazine sedative, premedicant	0.005–0.03 mg/kg IM or IV	Dose-dependent hypotension Long duration of action
Medetomidine	α2-adrenergic agonists with sedative, premedicant, and analgesic properties	2–5 mcg/kg IV 5–10 mcg/kg IM	Induce vasoconstriction and bradycardia Reversible with atipamezole
Dexmedetomidine		1–5 mcg/kg IV 3–10 mcg/kg IM	
Trazodone	Serotonin (5-HT) antagonist/reuptake inhibitor antidepressant	Starting dose 1–6 mg/kg p.o. q.8–12h.	Avoid in patients receiving other serotonergic drugs (due to risk of serotonin syndrome)
Bronchodilators			
Terbutaline	Short-acting β2-adrenergic agonist bronchodilator	0.01 mg/kg IM or SQ once	Indicated for rescue treatment of asthma in cats and chronic bronchitis in dogs
Albuterol / Salbutamol		1 puff (90 mcg) via metered-dose inhaler, spacer, and mask; may repeat q.30 minutes	
Epinephrine / Adrenaline	Potent, nonselective adrenergic agonist	0.01 mg/kg IM	Indicated for anaphylaxis only
Diuretics			
Furosemide	Loop diuretic	2–4 mg/kg IV or IM initially, repeating q.2-8h. depending on severity	CRI may be more effective for refractory pulmonary edema
Vasodilators / Afterload reducers			
Pimobendan	Inodilator; positive inotrope and vasodilator via selective inhibition of phosphodiesterase 3 and calcium sensitization	0.15 mg/kg IV or 0.25 mg/kg p.o. q.8–12h.	Indicated for dogs in congestive heart failure (CHF)
Nitroprusside	Parenteral arterial and venous vasodilator (via nitric oxide release)	1 mcg/kg/min CRI starting dose, titrate up or down as needed	Dose dependent hypotension Indicated for dogs with severe CHF
2% nitroglycerin paste	Transdermally administered arterial and venous vasodilator	Paste applied inside pinna or to skin in axilla, groin, or flank q.6–12h. – 1/8–1/4 inch cats – 1/4–1/2 inch small dogs – 1/2–1 inch medium dogs – 1–2 inches large dogs	Wear gloves to avoid transdermal absorption

swelling. Cooling can involve administration of room temperature IV fluids, wetting the fur coat with water, and application of a fan.

The diagnostic approach to an URT obstruction starts with a sedated upper airway examination by laryngoscopy and/or tracheoscopy. Cervical radiographs, thoracic radiographs, and/or fluoroscopy may also be indicated. Ongoing treatment will then be determined by the definitive diagnosis and may be medical or surgical.

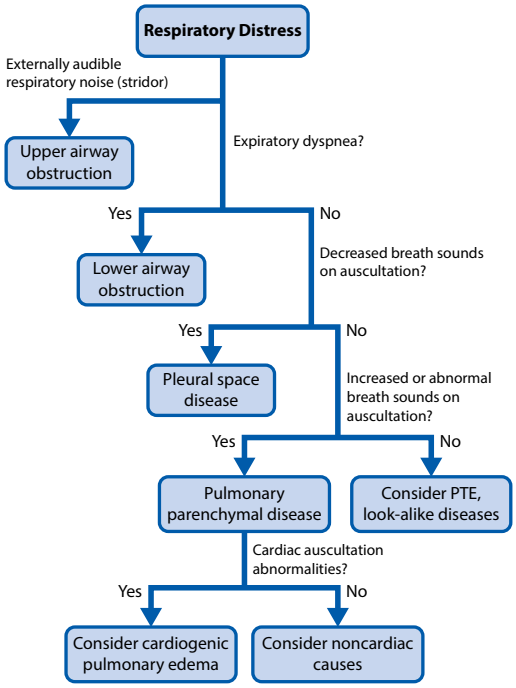


FIGURE 2.4.1 Localizing the cause of respiratory distress based on the abnormal breathing pattern and findings on thoracic auscultation.

LOWER AIRWAY(S) OBSTRUCTION

See also Chapter 6, Respiratory Disorders.

A lower airway obstruction is classically associated with expiratory difficulty and wheeze. Wheezes refer to continuous musical sounds heard on expiration during thoracic auscultation with a stethoscope. Severe cases may even have an expiratory grunt. Lower respiratory tract (LRT) obstruction occurs due to narrowing of the intrathoracic trachea or bronchi, which can occur secondary to bronchospasm, diffuse bronchomalacia, intrathoracic tracheal collapse, accumulation of mucus, and/or bronchial wall edema (Table 2.4.3).

History and signalment can be useful in cases of LRT obstruction. For example, cough is often present in cats for many months or years before they present with respiratory distress due to asthma. Asthma also tends to affect young to middle-aged cats. Similarly, a history of a harsh or honking cough in an older small breed dog increases the index of suspicion for chronic bronchitis, intrathoracic tracheal collapse, and/or bronchomalacia.

In addition to oxygen supplementation, a bronchodilator trial is indicated as part of treatment, particularly for cats with LRT obstruction (Table 2.4.2). Once the patient has stabilized, diagnostics should include thoracic

TABLE 2.4.3 Differential diagnoses for respiratory distress in dogs and cats based on anatomic localization

Localization of respiratory disease	Differential diagnoses
Upper respiratory tract obstruction	– *Pharynx:* Polyp, mass, foreign body, elongated soft palate, hematoma (especially with coagulopathy or trauma) – *Larynx:* Laryngeal paralysis, collapse, neoplasia – *Extrathoracic trachea:* Collapse, foreign body, stenosis, stricture, mass (intra- or extraluminal) – *Brachycephalic obstructive airway syndrome:* Combination of primary and secondary abnormalities, including stenotic nares, macroglossia, elongated soft palate, everted laryngeal saccules, enlarged tonsils, hypoplastic trachea
Lower respiratory tract obstruction	– *Intrathoracic trachea:* Collapse, foreign body, stenosis, stricture, mass (intra- or extraluminal) – *Bronchospasm:* Feline asthma, lungworm, heartworm-associated respiratory disease – *Diffuse bronchomalacia:* Severe (end-stage) chronic bronchitis – *Accumulation of mucus or other exudate:* Particularly in asthma and chronic bronchitis – *Bronchial wall edema:* Anaphylaxis
Pulmonary parenchymal disease	– *Pneumonia:* Primary infectious etiology versus aspiration – *Pulmonary edema:* Cardiogenic versus noncardiogenic – *Interstitial lung disease:* Interstitial fibrosis, eosinophilic bronchopneumopathy – *Pulmonary neoplasia:* Primary versus metastatic pulmonary contusions, hemorrhage – Lung lobe torsion
Pleural space disease, and/or chest wall disease	– *Pleural effusion:* Transudate or modified transudate, pyothorax, chylothorax, hemothorax – *Pneumothorax:* Traumatic (blunt or penetrating trauma) or spontaneous (latter due to ruptured blebs or bullae) – *Space occupying lesion:* Large chest wall mass – Diaphragmatic hernia – Flail chest (traumatic) causes visually obvious focal flail segment – Respiratory compromise is usually due to concurrent pulmonary contusions and/or pneumothorax, pain
Pulmonary thromboembolism	– Predisposing conditions include anything that predisposes to thrombosis (e.g., immune-mediated hemolytic anemia, protein-losing nephropathy, protein-losing enteropathy, neoplasia, acute necrotizing pancreatitis, etc.)
Abdominal distention	– Impedes thoracic expansion during inspiration, but respiratory condition is not usually dire (e.g., gastric dilatation and volvulus, marked hepatomegaly, abdominal masses, late-stage pregnancy)
Look-alike syndromes	– Apparent difficulty breathing (increased respiratory rate and/or effort) caused by nonrespiratory conditions – Considerations include pain, severe metabolic acidosis (e.g., diabetic ketoacidosis), severe anemia, hyperthermia

radiographs and potentially tracheobronchoscopy and/or bronchoalveolar lavage cytology. Heartworm and lungworm testing may also be indicated. Following a definitive diagnosis, chronic treatment may involve corticosteroids, bronchodilators, and/or antiparasitic drugs.

PULMONARY PARENCHYMAL DISEASE

Pulmonary parenchymal disease may result in both inspiratory and expiratory difficulty or rapid shallow breathing. Breath sounds will usually be increased on auscultation, and crackles may be present. Crackles are discontinuous popping sounds heard on thoracic auscultation.

Pulmonary parenchymal disease includes diseases of the terminal and respiratory bronchioles, interstitium, and alveoli. Differential diagnoses include pneumonia, pulmonary edema (cardiogenic versus noncardiogenic), interstitial lung disease, pulmonary neoplasia, and pulmonary contusions (Table 2.4.3). Auscultable cardiac abnormalities and tachycardia increase the index of suspicion for cardiogenic pulmonary edema, as does jugular venous distention. In these cases, empirical furosemide can be considered. In contrast, a low heart rate and/or respiratory sinus arrhythmia is suggestive of primary respiratory disease. The distribution of abnormal lung sounds may also be helpful in ranking differential diagnoses and mirrors that of diagnostic imaging abnormalities (Table 2.4.4). Patients with cardiogenic pulmonary edema may be hypothermic, while those with pneumonia or infectious respiratory disease may have a fever.

TABLE 2.4.4 Diagnostic investigations indicated for patients with respiratory distress depending on lesion localization

Diagnostic test	Abnormalities identified in different diseases
Pulse oximetry	SpO_2 < 95% = hypoxemia and indicates the need for supplemental oxygen SpO_2 < 90 mmHg = severe hypoxemia
Arterial blood gases	PaO_2 < 80 mmHg = hypoxemia and indicates the need for supplemental oxygen PaO_2 < 60 mmHg = severe hypoxemia
NT-proBNP	Increased in dogs and cats with left atrial enlargement; high NT-proBNP in patient with respiratory distress suggestive of heart failure
Point-of-care thoracic ultrasound	Pleural effusion Absence of a glide sign = pneumothorax Increased B-lines / lung rockets = pulmonary parenchymal disease Increased left atrial:Aortic ratio (LA:Ao) suggestive of congestive heart failure
Upper airway examination and laryngoscopy (under sedation and/or anesthesia)	Will usually identify the cause of upper respiratory tract obstruction
Tracheobronchoscopy	Facilitates visualization of tracheal and bronchial collapse, as well as obstruction due to an intraluminal foreign body or mass lesion
Fluoroscopy	Useful to identify dynamic airway collapse (e.g., tracheal and/or main stem bronchial collapse)
Thoracic radiographs *Further information can be found in Chapter 3*	Feline lower airway disease (asthma) characterized by a generalized bronchointerstitial pattern, bronchial thickening ("doughnuts" and "tramlines"), and diaphragmatic flattening associated with hyperinflation Cardiogenic pulmonary edema in dogs associated with cardiomegaly, left atrial enlargement, pulmonary venous engorgement, and an increased opacity (interstitial to alveolar) in the perihilar region Noncardiogenic pulmonary edema classically associated with interstitial to alveolar pattern in caudodorsal lung fields with normal cardiac silhouette Aspiration pneumonia characterized by alveolar pattern in right middle lung lobe and/or ventral lung fields Nodular pattern commonly associated with pulmonary neoplasia or infectious causes (especially systemic mycoses) Pleural effusion associated with scalloped lung lobes (retracted from chest wall) and border effacement of the cardiac silhouette and diaphragm
Thoracic CT scan	With angiography is the diagnostic modality of choice for PTE given inconsistent abnormalities on radiographs Also imaging modality of choice for interstitial lung disease and identifying pulmonary metastases
Airway sampling (transtracheal wash, endotracheal wash or bronchoalveolar lavage)	Fluid analysis, cytology, culture and susceptibility will aid in determining cause of inflammatory or infectious pulmonary parenchymal diseases
Lung biopsy	Often required for a definitive diagnosis of interstitial lung disease and pulmonary neoplasia

LA:Ao, left atrial: aortic ratio; NT-proBNP, N-terminal pro brain natriuretic peptide; PaO_2, partial pressure of oxygen; PTE, pulmonary thromboembolism; SpO_2, oxygen saturation.

Diagnostics including point-of-care ultrasound (POCUS), thoracic radiographs, lower airway cytology, echocardiography, thoracic CT, and even lung biopsy may be indicated. Ongoing therapy depends entirely on the diagnosis.

PLEURAL SPACE DISEASE

See also Chapter 7, Diseases of the Pleural Space.

Pleural space disease can result in inspiratory difficulty (without stridor), paradoxical breathing, or rapid shallow breathing. Normally, the chest and abdomen move together, out on inspiration and in on expiration. In a paradoxical breathing pattern, the abdomen moves inward during inspiration and outward during expiration (i.e., inverse to thoracic motions). Pleural space disease will also result in decreased lung sounds on thoracic auscultation.

Pleural space disease occurs due to abnormal accumulations within the pleural space. This may be fluid (i.e., pleural effusion), air (i.e., pneumothorax), a space occupying/mass lesion, or abdominal organs, as in the case of diaphragmatic hernia (**Table 2.4.3**).

While supplemental oxygen may provide slight relief to a patient with pleural space disease, urgent thoracocentesis is indicated in cases with pleural effusion or pneumothorax. Pleural effusion will be identified by the presence of fluid deep to the chest wall on POCUS, while pneumothorax is identified by the absence of a glide sign.

Thoracocentesis can be both diagnostic and therapeutic in cases with pleural effusion or pneumothorax. If coagulopathy is a differential diagnosis for pleural effusion, clotting times should be checked, and the coagulopathy corrected prior to thoracocentesis. Fluid analysis should be performed to differentiate the major types of pleural effusion and narrow the differential diagnoses.

The prognosis for dogs and cats with dyspnea depends on the ability of the clinician to stabilize the patient and the underlying cause.

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CHAPTER 2

Common Clinical Problems

CHAPTER 2.5 Dysuria

Isabelle Cattin

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INTRODUCTION

Dysuria is defined as difficulty urinating. It can be combined with pain during urination, pollakiuria (frequent urination), stranguria (extreme difficulty in passing urine (Figure 2.5.1), and hematuria (blood in the urine). A timely evaluation of the patient is essential, as inability to urinate can lead to potentially life-threatening complications.

EVALUATION OF THE PATIENT WITH DYSURIA

The initial evaluation of a patient presenting with dysuria should include signalment, history, and a physical examination (Figure 2.5.2). A detailed signalment can be helpful as some conditions associated with dysuria might be seen more readily at a certain age or in specific breeds. Typically, cystitis occurs commonly in both adult and young animals, whereas neoplastic processes can be seen in geriatric patients. A complete history, including duration of clinical signs, general health, and description of the urination pattern along with the appearance of the urine is necessary. Pigmenturia (bilirubinuria or hemoglobinuria) can signal other disorders in the body. Evaluation of the urination pattern includes voiding frequency, urine volume, ability to pass urine, pain, urination in inappropriate places, and passing discolored/bloody urine. The presence of systemic signs may reveal the existence of an underlying disease. Especially with feline patients, one should try to differentiate straining to defecate from straining to urinate to avoid missing a urinary obstruction. Palpation of the urinary bladder informs about size, shape, and tonicity of the bladder wall. A large, tonic, painful bladder in a cat suggests acute urethral blockage, whereas a large, flaccid (easy to express) bladder might point toward a neurologic problem. Passing a urinary catheter in male dogs can help confirm the presence of a urethral obstruction.



FIGURE 2.5.1 Cat with stranguria and hematuria associated with urethral obstruction and cystitis. (*Courtesy of M. Schaer.*)

ETIOLOGY

Causes of dysuria can be variable: Inflammatory/infectious, obstructive, neurogenic, and traumatic. The first two are the most prevalent in dogs and cats.

Inflammatory/Infectious Causes

Bacterial or less commonly fungal urinary tract infections are seen in both cats and dogs and can result in dysuria. Urinalysis and a urine culture are necessary to confirm the presence of infection. In intact male dogs, prostatic infections (prostatitis, prostatic abscess) should be ruled out. Less commonly, congenital malformations (e.g., remnant urachus) can cause urinary infections. Noninfectious, inflammatory conditions can occur in various locations of the urinary tract. "Idiopathic" (noninfectious) cystitis is very common in

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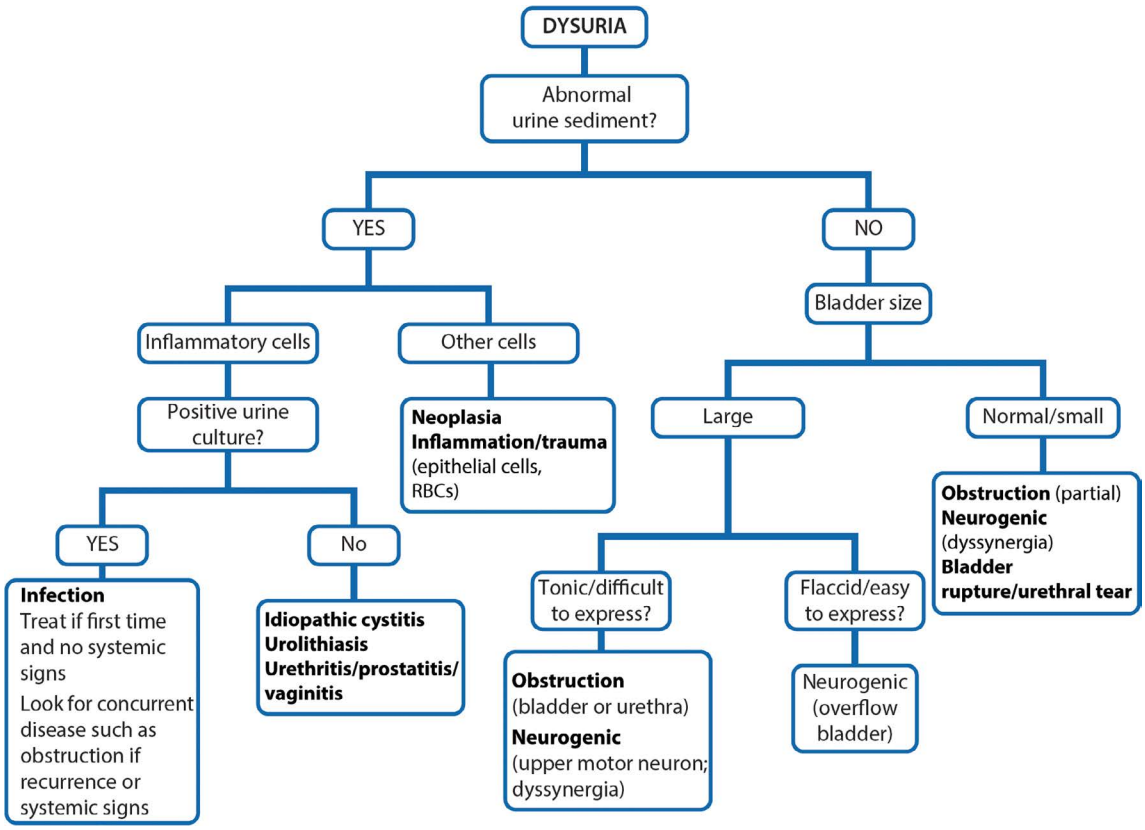


FIGURE 2.5.2 Algorithm for the clinical approach to dysuric dogs and cats.

cats and has a multifactorial origin. Behavioral issues play an important role here, thus showing the importance of taking a thorough history to differentiate between anatomical urinary tract pathology and behavioral issues. Granulomatous urethritis is a proliferative condition seen mostly in female dogs.

Obstructive Causes

Obstruction of the lower urinary tract can result in urination problems. Intraluminal obstructions can be caused by urolithiasis, urethral blood/mucus plugs, urethral strictures, or neoplastic processes. Discomfort associated with bladder wall inflammation can cause dysuria, but urethral obstruction should always be ruled out because it requires immediate care. In cats, blood clots or mucus plugs are a frequent cause of urethral obstruction. Urethral strictures can occur with severe urethritis or secondary to local trauma (stones, traumatic catheterization, surgery). Neoplastic processes in the urinary bladder or the urethra can cause inflammation or partial/complete obstruction. Extraluminal urethral obstructions can be seen with prostatomegaly due to prostatitis, prostatic abscess (Figure 2.5.3a, b), cyst or neoplasia.

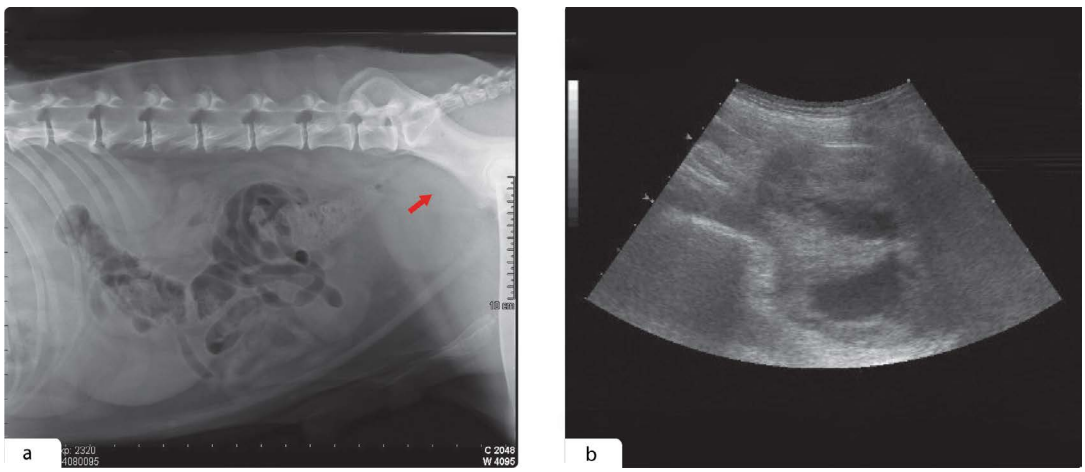


FIGURE 2.5.3 A lateral radiograph **(a)** and an ultrasound image **(b)** of a dog with a prostatic abscess. (*Courtesy of M. Schaer.*)



FIGURE 2.5.4 This plain radiograph shows emphysematous cystitis in a dog with an atonic urinary bladder from a lumbosacral intervertebral stenosis. Note the similarity to a pneumocystogram, but no such procedure was done in this patient. (*Courtesy of M. Schaer.*)

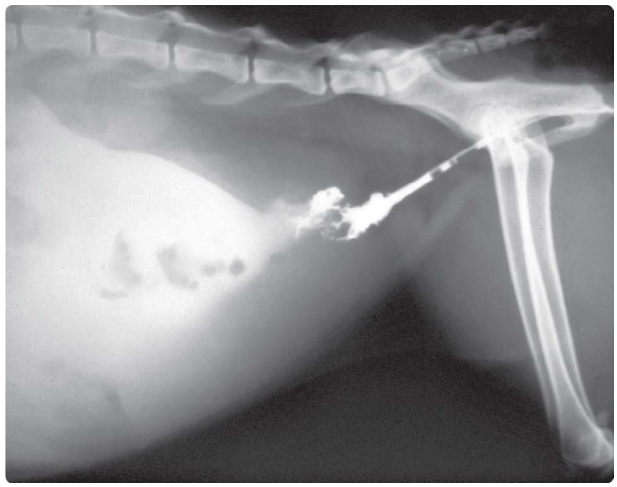


FIGURE 2.5.5 Cystogram showing a ruptured urinary bladder caused by excessive palpation. (*Courtesy of M. Schaer.*)

Neurogenic Causes

Upper or lower motor neuron diseases can cause either decreased ability to contract the bladder or increased spasticity of the external urethral sphincter, causing difficulty in urinating. A full neurologic examination and palpation of the urinary bladder are important steps in these cases. Increased urethral sphincter tone can cause a dynamic obstruction, while a decreased bladder tone can result in pollakiuria or incontinence ("overflow bladder"). In animals experiencing prolonged difficulty in emptying the bladder (as in urethral obstruction), the chronically distended urinary bladder can cause neurogenic dysuria (Figure 2.5.4). The problem should be promptly recognized and resolved, as the damage to the muscles and nerves of the urinary bladder can be irreversible. Reflex dyssynergia is seen in large breed dogs: Inadequate coordination between the bladder detrusor muscle and the urethral sphincter musculature leads to difficulty urinating, as the urethral muscle fails to relax when the bladder contracts.

Traumatic Causes

Trauma can lead to lesions of the urinary bladder or urethra. Causes include road traffic accidents, gunshots, blunt abdominal trauma, iatrogenic rupture (palpation or instrumentation) (Figure 2.5.5), or urinary calculi.

FURTHER INVESTIGATIONS

These include routine tests and sometimes more specialized methods (endoscopy or cystometry/urethral pressure profile) that require referral to a specialist.

Laboratory Testing

Urinalysis should include urine specific gravity (SG) and a sediment analysis. Cystocentesis is the preferred method to sample urine. Catheter samples are adequate, while voided samples may be contaminated by cells and bacteria from the lower genital tract. Sediment analysis may reveal the presence of red and/or white blood cells, crystals, organisms, parasite ova (*Capillaria* [*Pearsonema*] spp., *Schistosoma* spp.), and neoplastic cells. The absence of crystals does not rule out the presence of uroliths.

Urine culture will document an infection and assist in the choice of appropriate antibiotic treatment. In immunosuppressed animals, urine sediment may not show any signs of inflammation despite an ongoing infection. Blood chemistry and complete blood count (CBC) can help detect underlying conditions or, for example, life-threatening electrolyte imbalances. In dogs, cytologic analysis of an ultrasound-guided fine-needle aspiration of the prostate can help document any prostatic changes.

Imaging

Radiography and ultrasonography are useful to diagnose causes of dysuria.

Radiography can show the size and position of the urinary bladder and document the presence of uroliths, although not all types of uroliths are radiopaque. Extraurinary structures can be assessed (prostate, sublumbar lymph nodes, bony structures). Evidence of vertebral abnormalities might represent a neurologic cause of the dysuria (discospondylitis, lumbosacral stenosis (Figure 2.5.4), intervertebral discs, or spinal neoplasia). Radiographic contrast studies (double contrast cystogram, retrograde urethrogram) can help identify causes of urinary obstruction that cannot be seen on plain radiographs, such as radiolucent stones, narrowing of the urethral lumen (urethral strictures or spasms), or mucosal inflammation in the urinary bladder or urethra (Figure 2.5.6). Urinary leakage can also be diagnosed with this method.

Ultrasonography is helpful to evaluate the urinary bladder (mucosa, stones, or masses), the prostate, and the surrounding organs (kidneys, lymph nodes).



FIGURE 2.5.6 A double contrast cystogram in a cat with a transitional cell carcinoma in the urinary bladder that caused a radiographic filling defect. (*Courtesy of M. Schaer.*)

Evaluation of the complete urethra is more difficult due to the intrapelvic location and limited visibility (Figure 2.5.7).

Other Diagnostic Methods

Endoscopy is a useful diagnostic tool for confirming urethral strictures and mucosal abnormalities. Mucosal biopsies can be collected to differentiate inflammatory from neoplastic processes. Furthermore, endoscopic removal of bladder stones using lithotripsy has been reported.

Cystometry and urethral pressure profilometry are specialized techniques used to assess the function of the urinary bladder and urethral muscles in cases of suspected neurogenic dysuria (like reflex dyssynergia). A review of the indications for the different diagnostic tests used in dysuria is shown in Table 2.5.1.



FIGURE 2.5.7 Ultrasound image of a dog with prostatic carcinoma showing urethral pathology caused by tumor invasion. (*Courtesy of M. Schaer.*)

SUMMARY

A systematic stepwise approach to dysuria cases is necessary to localize the problem and to assess if urgent care is needed. Dysuria potentially leads to serious complications; thus, those patients need prompt evaluation.

TABLE 2.5.1 Clinical usefulness of various tests in dysuric cats and dogs

Test	Indication/suspected process	Advantages	Disadvantages
Urinalysis	Any case of dysuria	Fast and cheap Can be helpful to document infection, crystalluria, possibly neoplasia	Nonspecific Some causes can be missed (neoplasia, urolithiasis)
Urine culture (usually aerobic)	Abnormal urinalysis Recurrent signs Underlying disease with risk of silent infection Evaluation of treatment success	Readily available Reasonable cost Allows targeted treatment	Delayed results (48–72 hours) Does not always preclude further testing (an infection can be secondary to other causes)
Radiography (plain)	Urolithiasis Extraurinary diseases Posterior abdominal extraluminal masses	Readily available Easily performed Evaluation of extraurinary/bony structures	Radiolucent uroliths not seen Mucosal abnormalities rarely visible
Radiography (with contrast)	Mucosal abnormalities Urolithiasis Urethral disease	Minimally invasive Allows evaluation of urethral content/mucosa	Requires technical skills Sedation or anesthesia usually necessary
Ultrasound	Urolithiasis Bladder wall abnormalities Extraurinary diseases Diseases of the proximal urethra	Frequently available Excellent image of bladder mucosa Allows sampling Can show all types of uroliths	Requires technical skills Urethra cannot be fully viewed
Endoscopy	Urethral disease Urolithiasis Bladder wall abnormalities	Allows direct visualization of mucosa Allows sampling Therapeutic in some cases (urolithiasis, polyps)	Only available in limited facilities Needs experienced operator Anesthesia necessary Increased cost

History taking and complete physical examination are essential, and knowledge of the different diseases and their clinical expression helps in choosing further diagnostic steps. Treatment recommendations for the different conditions mentioned in this chapter are discussed in Chapter 13, Nephrology/Urology.

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CHAPTER 2

Common Clinical Problems

CHAPTER 2.6 Epistaxis

Samantha Wigglesworth and Amber Vitalo

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PATHOPHYSIOLOGY

Epistaxis is defined as hemorrhage coming from the nasal cavity. The nasal cavity begins at the nostrils and extends caudally to end at the choanae as the cavity opens up into the pharynx. It is composed of the nasal planum, paired nasal cavities, and three paranasal sinuses. Within the nasal cavities are turbinates that are lined by thin epithelium. This epithelium contains a large blood supply which originates from the maxillary branch of the external carotid artery. Due to the presence of this complex network of blood vessels, even a small amount of damage can lead to significant bleeding.

Epistaxis is a common disorder that can have local (intranasal) or systemic (extranasal) origin. Local causes include nasal neoplasia, trauma, idiopathic rhinitis, foreign bodies, and infectious disease (i.e., aspergillosis). Systemic causes, such as coagulation disorders or hypertension, are less common but still need to be considered in patients presenting for nasal hemorrhage. The intranasal and extranasal causes of epistaxis are provided in Table 2.6.1.

CLINICAL SIGNS/PHYSICAL EXAM

Epistaxis is typically the primary complaint for patients presenting with nasal hemorrhage. Signalment may help in distinguishing certain disease processes such as a young Dobermann with von Willebrand's disease or young cats with nasopharyngeal polyps. The owner should be questioned regarding chronicity, duration (constant versus intermittent), and description of the nasal discharge (color, odor, single nostril versus both) may also aid in prioritizing differentials. Additionally, obtaining a detailed history from the owner about vaccination status, environment, travel history, medications,

TABLE 2.6.1 Common local and peripheral signs of epistaxis associated with intra- and extranasal etiologies

Intranasal	Extranasal
Trauma Neoplasia – Adenocarcinoma, carcinoma, osteosarcoma, melanoma, lymphoma, etc. Infection – Fungal – aspergillosis, pythiosis, cryptococcus – Viral – calicivirus, feline viral rhinotracheitis – Bacterial – often secondary – Parasitic – nasal mites Inflammatory – Lymphoplasmacytic rhinitis, allergic rhinitis Dental – Tooth root abscess, oronasal fistula Foreign body Vascular malformation	Thrombocytopenia – Infectious, drugs, neoplasia, bone marrow aplasia, immune-mediated, microangiopathy, sequestration Thrombocytopathia – von Willebrand disease (VWD), drugs, uremia, polycythemia vera Coagulation factor deficiency – Hemophilia A (FVIII) and B (FIX), anticoagulant rodenticide, liver failure, disseminated intravascular coagulation (DIC) Hypertension – Primary or secondary (renal failure, Cushing's disease, hyperthyroidism, cardiomyopathy, pheochromocytoma) Hyperviscosity – Hyperviscosity syndrome (Waldenström macroglobulinemia), leukemias Systemic infection – Tick-borne disease, FeLV/FIV, Rocky Mountain spotted fever, hepatozoonosis, septicemia, endotoxemia

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TABLE 2.6.2 Clinical signs associated with intranasal and extranasal causes of epistaxis

Intranasal signs	Extranasal signs
– Unilateral nasal discharge – Ocular discharge (same side as nasal discharge) – Decreased retropulsion of the globe (same side as nasal discharge) – Facial discomfort (pawing, rubbing, painful on palpation) – Other nasal discharge (purulent, serous) – Sneezing – Depigmentation of the nasal planum – Deformities of the oral cavity/palate	– Bilateral nasal discharge – Signs of platelet dysfunction (ecchymosis, petechiation, melena, hematuria) – Coagulopathy (joint swelling, cavitary bleeding, anemia) – Signs of hypertension (retinal hemorrhage and/or detachment, organ dysfunction – brain, kidneys) – Systemic signs (inappetence, lethargy, elevated rectal temperature)

and any additional clinical signs (i.e., sneezing or coughing) at home is very important and may help to repositioning of certain differentials. Knowing if the epistaxis is unilateral or bilateral can also be helpful in distinguishing intra-versus extranasal disease processes.

While it is often a readily visible exam finding, a thorough physical examination is essential in prioritizing possible underlying causes (Table 2.6.2). This should begin with assessing the patient for any facial deformities or discomfort by palpating the face and the muzzle and performing gentle retropulsion of the eyes. Determining the presence of nasal airflow in both nostrils with a glass slide or tuft of cotton can also aid in disease localization. The nasal planum should be examined for ulceration, depigmentation, or obvious masses obstructing airflow. The oral cavity and surrounding lymph nodes should be inspected for any palate deformity, masses, oronasal fistulas, severe periodontal disease, and regional peripheral lymphadenopathy. A complete evaluation of the skin and mucous membranes should be performed to look for evidence of petechiae or ecchymoses that are indicative of hemostatic disorders. Lastly, a rectal exam is recommended to assess for melena, possibly indicative of swallowed blood or hemostatic disorders such as thrombocytopenia or coagulation disorders.

DIAGNOSIS

Epistaxis is a clinical sign, not a diagnosis in itself; therefore, a diagnostic workup is often necessary to determine the underlying cause (Figure 2.6.1). The differential diagnoses for epistaxis can be divided into local (intranasal) and systemic (extranasal) causes for organizational purposes. Typically, systemic disease and coagulopathies are investigated first due to the ease of this preliminary testing. First, a blood pressure should be obtained on presentation to rule out hypertension as the underlying cause of the epistaxis. Initial diagnostic testing should include a minimum database to screen for anemia, thrombocytopenia, and/or liver disease that can lead to hemostatic disorders. Investigating coagulopathies by evaluating platelet counts, a buccal mucosal bleeding time for von Willebrand factor, and clotting factor status with prothrombin time (PT) and partial thromboplastin time (PTT) or viscoelastic testing, such as thromboelastography (TEG), viscoelastic coagulation monitor (VCM), or thromboelastometry (TEM) is recommended to rule out hemostatic disorders as the primary cause. In cats, testing for feline leukemia virus/feline immunodeficiency virus (FeLV/FIV) is recommended, if the status is unknown. Serology for tick-borne disease, heartworm, and cryptococcus can also be performed if exam findings are concerning for these disease processes. Thoracic radiographs are often obtained to screen for metastatic disease indicative of local or systemic neoplasia.

Local disorders are the most common causes of epistaxis and include trauma, neoplasia, infection, inflammation, periodontal disease, and foreign body. Systemic causes include hemostatic disorders, hypertension, and systemic infection.

If initial testing is not indicative of a cause for the epistaxis, then more invasive additional testing is recommended. This includes CT scan of the head to screen for large masses or foreign material followed by rhinoscopy with biopsy of any abnormal tissue. Biopsy samples are submitted for histopathology and may also be submitted for bacterial and fungal cultures. In most cases of epistaxis, a cause can be identified when a thorough history, physical exam, and diagnostic workup are done.

TREATMENT

The goal for treatment is to control the epistaxis until a definitive diagnosis can be obtained. Often epistaxis does not require treatment itself; however, patients with significant and uncontrollable hemorrhage may require local control. Initially, intranasal application of vasoconstrictive drugs such as phenylephrine or epinephrine should be trialed. The use of sedatives can be helpful to relieve anxiety and blood pressure and reduce the amount of hemorrhage present. Patients with severe bleeding may require blood products to replace red blood cells and clotting factors. If these treatment options are ineffective, the patient will need to be sedated and intubated to either apply direct pressure in the nasal cavity or tie off the maxillary artery/vein to control the source of the bleeding.

Once a definitive diagnosis is obtained, therapy should be aimed at the treating the underlying cause. Patients identified to have hypertension should be started on antihypertensive therapy with close monitoring of blood pressure. Most trauma patients will only need monitoring with supportive care. Foreign bodies can often be removed at the time of imaging or rhinoscopy. Nasal tumors may require surgery for debulking followed by radiation and/or chemotherapy. Fungal infections can be treated locally with antifungal infusions as well as systemic antifungal medications. Immune-mediated disease (i.e., immune thrombocytopenia)

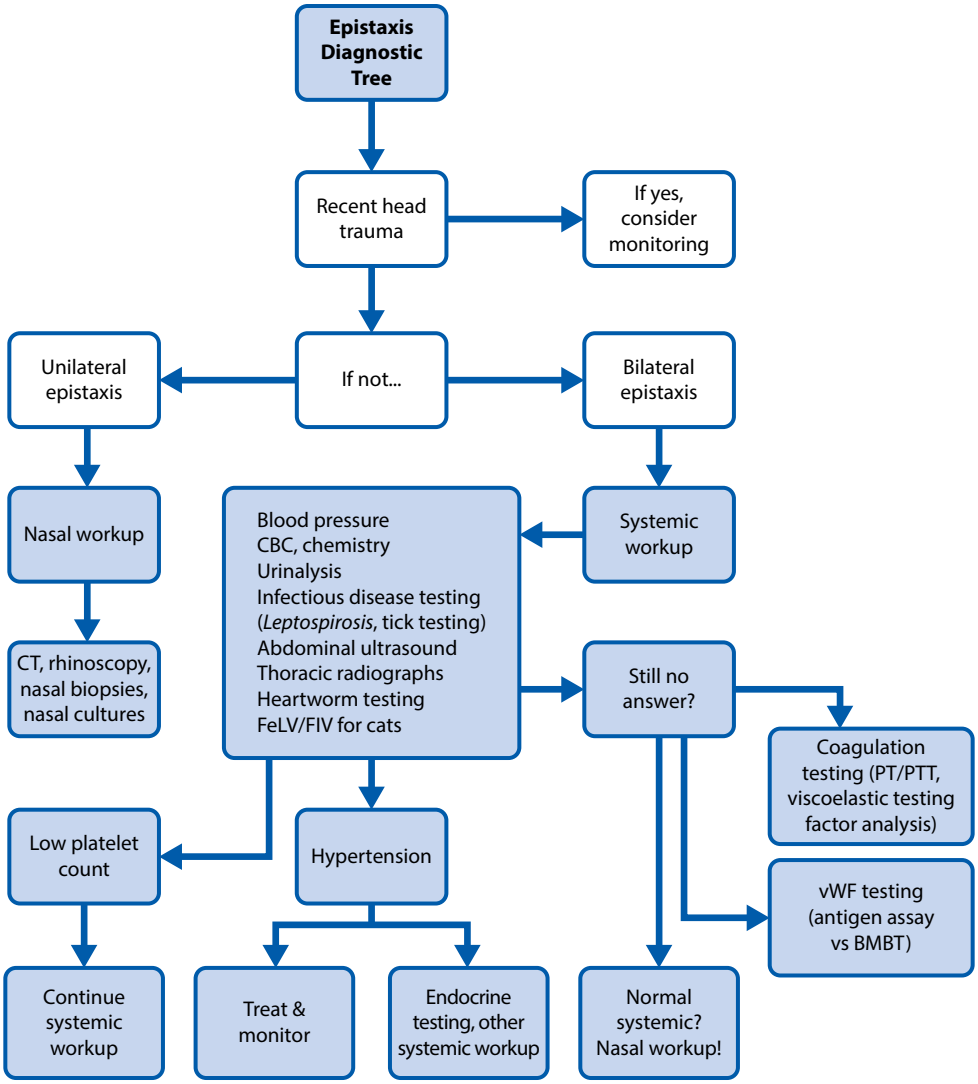


FIGURE 2.6.1 Algorithm for diagnostic workup of epistaxis. BMBT, buccal mucosal bleeding time; CBC, complete blood count; CT, computed tomography; FeLV, feline leukemia virus; FIV, feline immunodeficiency virus; PT, prothrombin time; PTT, partial thromboplastin time; VWF, von Willebrand factor.

should be treated with immunosuppressive doses of glucocorticoids and/or other immunosuppressive medications, which will hopefully allow the platelet count to rebound. In cats, nasopharyngeal polyps should be removed. Supportive therapies for any additional clinical signs present secondary to the underlying disease process should also be initiated.

PROGNOSIS

The long-term prognosis for patients with epistaxis is dependent on the underlying cause. For patients with neoplasia, long-term survival will be much less than those diagnosed with systemic hypertension. As with any disease process, response to therapy is crucial in determining prognosis.

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CHAPTER 2

Common Clinical Problems
CHAPTER 2.7 Fever of Unknown Origin

Robert Armentano

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INTRODUCTION

The classic definition of "fever of unknown origin" (FUO) provided for humans involves an illness of at least 3 weeks' duration, fever (continuous or fluctuating temperature of >104°F [40°C]), and no established diagnosis after at least 1 week of hospital investigation. There is no accepted definition of this term in veterinary medicine, except that the term FUO is used to define any febrile animal patient for which there is no obvious cause after "routine" diagnostic tests have been done. What constitutes routine will vary among different authors. The main diagnostic categories for FUO include infections (local and systemic), neoplasms, and immune-mediated diseases. Other less common causes include granulomatous diseases; noninfectious, inflammatory diseases such as pancreatitis, steatitis, and tissue necrosis and drugs. It is only after a search for the above causes that the clinician is left with the diagnosis of FUO.

PATHOPHYSIOLOGY

Normal body temperature is regulated within a fairly narrow range and is a balance between heat-producing and heat-dissipating mechanisms of the body. Fever is an increase of body temperature as a result of a change in the hypothalamic thermoregulatory center. Substances that cause fever are called endogenous or exogenous pyrogens. The majority of exogenous pyrogens are microorganisms, their products, or toxins. Exogenous pyrogens can act directly on the brain to cause fever but also act by inducing the formation of endogenous products, which stimulate the host's monocytes and macrophages. These endogenous pyrogen-producing substances mainly include antigen–antibody complexes with complement and cytokines.

The major pyrogenic cytokines include IL-1ß, IL-1α, tumor necrosis factor (TNF)-α, TNF-ß, interferon α, and IL-6. These cytokines circulate to the anterior hypothalamus where prostaglandin E2 and other arachidonic acid metabolites are produced. These in turn induce the formation of secondary messengers such as cyclic adenosine monophosphate that cause the rise in the thermoregulating set point leading to fever.

ETIOLOGY

The true incidence of FUO is unknown. A study by Feldman (1980)[4] noted the incidence of FUO in dogs as 40% infectious, 20% neoplastic, 20% immune-mediated disease, 10% miscellaneous disease, and 10% of a true FUO. A true FUO is diagnosed as a fever in which the underlying etiology is never discovered and that either spontaneously resolves or responds to a combination of antibiotics and/or steroids.

There are few retrospective papers documenting FUO in dogs (**Table 2.7.1**). There are no large, published studies in cats, but anecdotally, infectious etiologies are much more common than neoplastic and immune-mediated diseases. The conclusions from three recent retrospective reviews in dogs were that immune-mediated was the most commonly diagnosed category of disease, with immune-mediated polyarthritis as well as steroid-responsive meningitis-arteritis being the most common diagnoses (**Table 2.7.1** and **Figure 2.7.1**). These studies also concluded that imaging (radiographs and ultrasound) and cytology had the highest diagnostic yield (**Figure 2.7.2**).

Infections should always be considered first in the search for the etiology of FUO. See algorithms and **Table 2.7.2** for a complete list of localized and systemic

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TABLE 2.7.1 Study review of diagnoses in dogs with FUO (prevalence)

	Retrospective study		
Disease category	**Dunn KJ[1]**	**Battersby IA[2]**	**Chervier C[3]**
Immune-mediated	22%	34.8%	48%
Bone marrow	22%	NA	NA
Infectious	16%	5.8%	18%
Neoplasia	9.5%	7.6%	6%
Miscellaneous	11.5%	9.1%	0%
True FUO	19%	22.7%	28%

[1] Dunn KJ, Dunn JK (1998). Diagnostic investigation in 101 dogs with pyrexia of unknown origin. *J Small Anim Pract* 39(12):574–580.

[2] Battersby IA, et al. (2006). Retrospective study of fever in dogs: Laboratory testing, diagnoses and influence of prior treatment. *J Small Anim Pract* 47(7):370–376.

[3] Chervier C, et al. (2010). Causes, diagnostic signs, and the utility of investigations of fever in dogs: 50 cases. *Can Vet J* 53(5):525–530.



FIGURE 2.7.1 Shifting leg lameness in a dog consistent with a polyarthropathy.

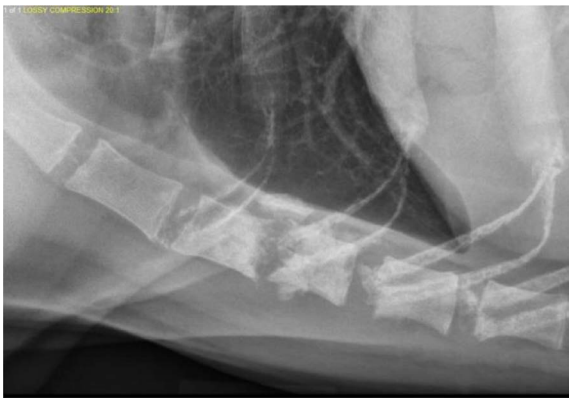


FIGURE 2.7.2 Lytic sternal lesion, consistent with discospondylitis.

infections that should be included as a differential for an FUO.

Neoplasia is a fairly common cause of fever. Feline leukemia virus (FeLV)-related cancers (e.g., lymphoma or myeloproliferative disease) in cats are the most common cause of fever in this class. The fever can be a paraneoplastic syndrome associated with the tumor itself, or it can be due to secondary infections. Solid tumors can also cause fever as the result of the host's immune response to the tumor or tumor necrosis.

Noninfectious inflammatory disease, including immune-mediated diseases, are not so rare. Some immunologic diseases, such as immune-mediated hemolytic anemia (IMHA), pemphigus, and systemic lupus erythematosus, can be readily identified. Others such as the polyarthropathies, sterile meningitis, and polymyositis are other examples of immune-mediated inflammatory disease.

There are many other causes of noninfectious inflammatory fevers. Examples of these include noninfectious inflammatory diseases such as amyloidosis (Figure 2.7.3); drug-associated fever as commonly reported with tetracycline and not so commonly with others, including sulfonamides, penicillins, nitrofurantoin, amphotericin B, barbiturates, atropine, cimetidine, salicylates, antihistamines, buprenorphine, and procainamide; and metabolic and endocrine diseases. This information is summarized in Table 2.7.2.

DIAGNOSIS

The key to obtaining a diagnosis includes a systematic approach for the medical evaluation for FUO. The most important steps prior to implementing a diagnostic plan include obtaining a thorough history and doing a complete physical examination that should include orthopedic, neurologic, funduscopic, and

TABLE 2.7.2 Common differential diagnoses (not all inclusive) and common tests available

Category		Disease	Dog	Cat	Tests available
Infectious disease					
Bacterial	Systemic	Infectious endocarditis	X		Echocardiogram, blood cultures (Figure 2.7.5)
		Meningitis	x	x	Cerebrospinal fluid tap for cytology, cultures
		Bacteremia	X	X	CBC, blood culture
Bacterial	Localized	Pyelonephritis	X	X	Urine culture, AUS, pyelocentesis
		Cholangitis/cholecystitis	x	x	Serum liver enzymes, ultrasound, bile fine-needle aspirate, liver biopsy
		Pyothorax	X	X	TXR, thoracentesis, culture
		Peritonitis	X	X	AUS, abdominocentesis, culture, glucose/lactate blood-fluid comparison
		Discospondylitis	X	X	Radiographs, CT/MRI, FNA
		Infectious arthritis	x	x	Arthrocentesis for cytology and culture
Bacterial	Specific	Leptospirosis	X		MAT serology, urine PCR
		Borreliosis	X		4DX, C6 antibody
		Brucellosis	X		Serology
		Mycobacteriosis	X	X	Culture, PCR
		Bartonellosis	X	X	Serology, PCR, BAPGM culture/PCR
		Plague		X	Serology, cytology, FA
		Mycoplasmosis	X	X	Culture, PCR
Viral		Feline leukemia		X	Serology (antigen), IFA
		Feline infectious peritonitis		X	Histopathology, IFA of macrophages, cytology, Rivalta test
		FIV		X	Serology (antibody)
		Calicivirus		X	PCR
		Distemper	X		FA, serology
Vector-borne		Ehrlichiosis	X	X	Serology, PCR, blood smear
		Anaplasmosis	X		Serology, PCR
		Rocky mountain spotted fever	X		Serology, PCR
		Hemotropic mycoplasmosis	X	X	PCR, blood smear
Fungal		Blastomycosis	X	X	Urine antigen, cytology/histopathology
		Cryptococcosis	X	X	Serology (latex agglutination)
		Coccidiomycosis	X	X	Serology
		Histoplasmosis	X	X	Urine antigen, cytology/histopathology
		Aspergillosis (other)	X		Cytology/histopathology, fungal culture, PCR, galactomannan serology
Protozoal		Toxoplasmosis	X	X	Serology (IgG/IgM), histopathology
		Neosporosis	X		Serology, histopathology, PCR
		Hepatozoonosis	X	X	PCR, histopathology
		Babesiosis	X	X	PCR
		Leishmaniasis	X	X	Serology, cytology, PCR

(Continued)

TABLE 2.7.2 Common differential diagnoses (not all inclusive) and common tests available (*Continued*)

Category	Disease	Dog	Cat	Tests available
Immune/ Inflammatory				
Immune-mediated	Systemic lupus erythematosus	X		Cytology/histopathology, ANA
	Immune-mediated polyarthritis	X	X	Cytology, rheumatoid factor
	Steroid responsive meningitis	X		CSF cytology
	Vasculitis	X	X	Histopathology
	Immune-mediated neutropenia	X		CBC, bone marrow cytology/histopathology
Inflammatory	Nodular panniculitis	X	X	Histopathology
	Lymphadenitis	X	X	Histopathology
	Steatitis	X		Histopathology
	Pancreatitis	X	X	AUS, CT, c/f PLI, histopathology
	Granulomatous	X	X	Cytology, histopathology
	Hypereosinophilic	X	X	Histopathology, CBC
Neoplasia				
Solid tumors	Any, hepatic, GI, pulmonary	X	X	TXR, AXR, AUS, cytology, histopathology
Hematopoietic	Lymphoma	X	X	TXR, AXR, AUS, cytology, histopathology, PARR, flow cytometry
	Leukemia	X	X	CBC, bone marrow cytology, flow cytometry
	Myeloma	X	X	Globulin, radiographs, Bence-Jones proteinuria, bone marrow cytology
	Malignant histiocytosis	X	X	Histopathology
Miscellaneous				
	Portosystemic shunt	X	X	Chemistry, bile acids, AUS, abdominal CT, nuclear scintigraphy
	Drug reaction	X	X	Eliminate medications
	Amyloidosis	X	X	Histopathology

AUS, abdominal ultrasound; AXR, abdominal radiographs; BAPGM, Bartonella alpha-Proteobacteria growth medium; CT, computed tomography; FIV, feline leukemia virus; IFA, immunofluorescent antibody; PARR, PCR for antigenic rearrangement; PCR, polymerase chain reaction; TXR, thoracic radiographs.



FIGURE 2.7.3 Shar Pei with swollen, edematous hocks consistent with Shar Pei fever (amyloidosis).

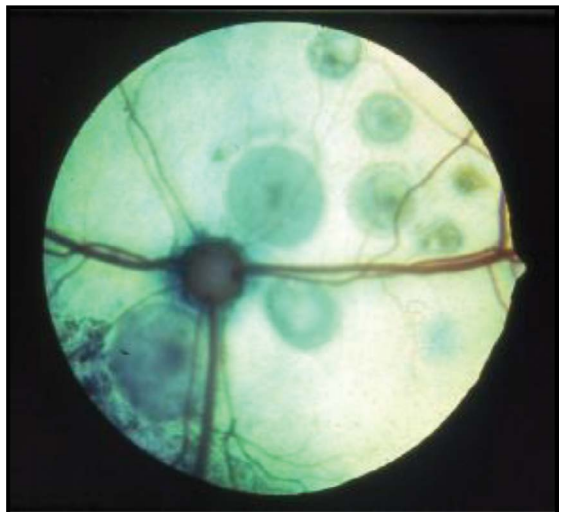


FIGURE 2.7.4 Funduscopic exam of a cat with *Cryptococcus* spp. infection.



FIGURE 2.7.5 Blood culture vials. To maximize culture utility large sample volume is recommended (16–20 mL in large dogs, 5 mL in small dogs and cats), as well as using vials with antibiotic binding beads, and aerobic and anaerobic culture media. Sterile collection is required, ideally at two venous (+/– one arterial) sites.

rectal examinations (Figures 2.7.4 and 2.7.6). A staged diagnostic approach should be implemented in patients with vague clinical signs and no definitive lesion identified (Table 2.7.2 and Figure 2.7.7).

Stage one testing includes the history and physical examination as well as screening laboratory testing. The routine tests should include a serum chemistry panel, CBC with pathologist review, and a complete urinalysis. Screening infectious disease testing such as a 4DX/Accuplex in dogs (heartworm, Lyme, Anaplasma, and Ehrlichia enzyme-linked immunosorbent assay [ELISA] test) and FeLV/FIV testing in cats should also be done. If the physical examination findings indicate a body cavity lesion, such as lung crackles, or long bone pain, radiographs should be included in stage one testing. Occasionally, there is enough diagnostic information from stage one to start treatment as indicated below.

Stage two testing would consist of additional imaging tests and further diagnostic sampling (Table 2.7.2 and Figure 2.7.7). Cytology samples will often have the highest diagnostic yield if a lesion is identified.

Infectious disease testing is a key component to the diagnostic workup. Specific tests should be selected based on the clinician's differential diagnoses, patient signalment, duration of clinical signs, and geographic locale. Bacterial culture and sensitivity testing should be done on urine, specific abnormal tissues, and blood if sepsis is suspected. Blood cultures, if indicated, should be performed early in the diagnostic phase, since it often takes days for results to become available, which can lead to potentially detrimental delays in prescribing the correct antimicrobial treatment (Figure 2.7.5).

Stage three diagnostic testing includes advanced imaging or more invasive tissue sampling techniques. (Table 2.7.2 and Figures 2.7.6 and 2.7.7) These tests include arthrocentesis and echocardiography, even if a lesion is not identified (no apparent murmur, no joint effusion), as disorders in these locations can remain sequestered and asymptomatic early in the disease process.

TREATMENT

Medications used for empiric treatment of the febrile patient often include antibiotics and/or antipyretics. Broad-spectrum antimicrobials are targeted against a multitude of different bacterial agents or more specifically toward vector-borne disease. Doxycycline or azithromycin are often used in cases of the latter etiology. Antipyretics should not be used in the acute phase of disease unless temperatures exceed 106°F (41.1°C). Anti-inflammatory medications will often mask the underlying disease and can compromise the patient. Nonsteroidal anti-inflammatory drugs (NSAIDs) side effects such as GI ulceration, as well as hepatic and renal damage, must be considered when prescribing these medications in debilitated and dehydrated patients. If the patient's body temperature exceeds 106°F (41.1°C), intravenous (IV) fluid therapy should be administered to replace any increased water losses caused by peripheral vasodilatation. NSAID therapy may be considered if the risks of adverse reactions appear to be minimal. External cooling using fans is not recommended, as this will only combat the thermoregulatory mechanisms, causing compensatory shivering to maintain the hypothalamic set point. Depending on the status of the patient, it is often appropriate to forego an empiric medication trial and pursue staged diagnostic testing as noted in order to identify the underlying etiology. Steroids and other immunosuppressive medications are used if an autoimmune disease is diagnosed and/or infectious disease has been deemed highly unlikely. The prognosis for FUO is dependent on the underlying etiology and the ability to implement an early and appropriate treatment plan.

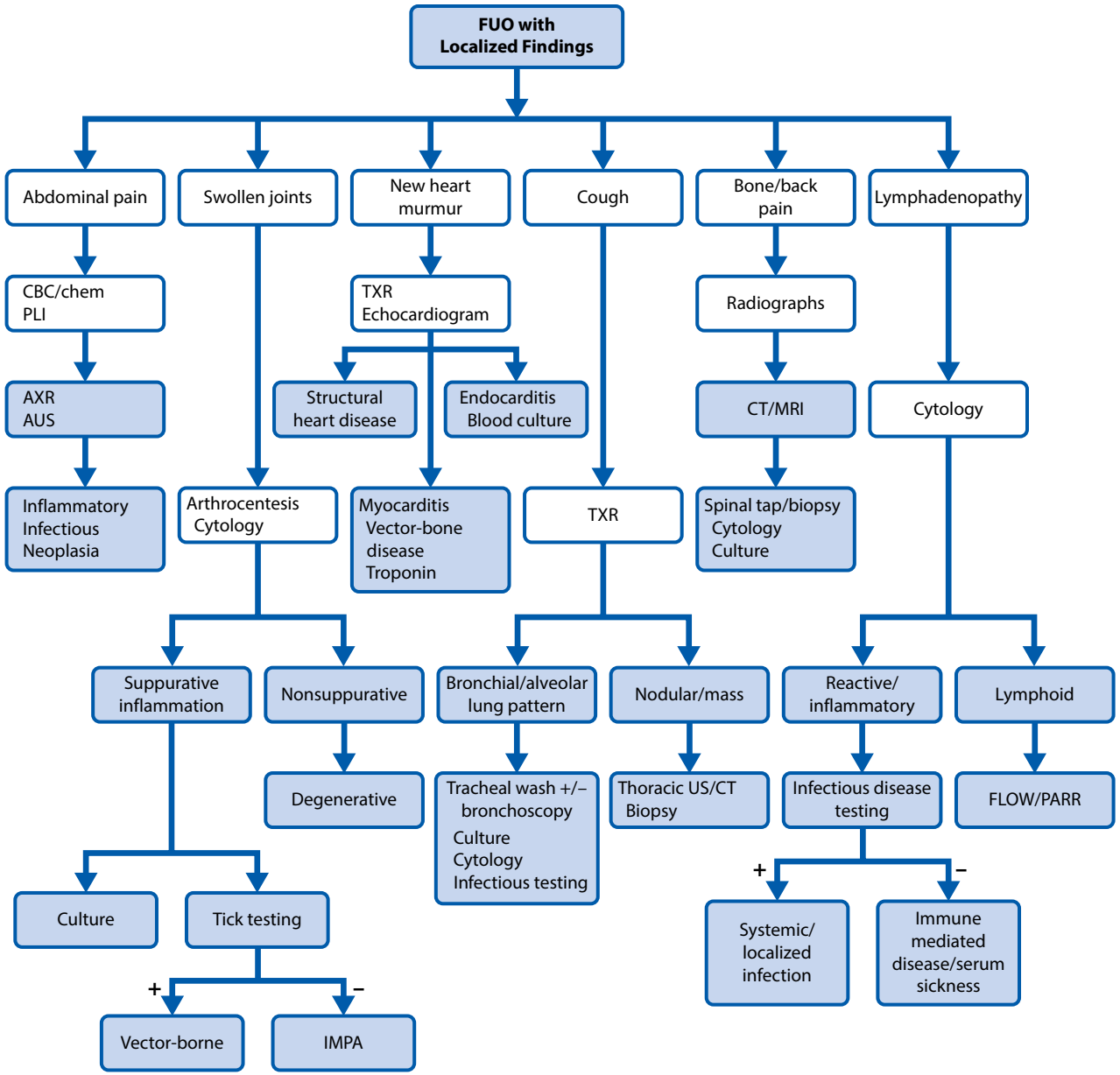


FIGURE 2.7.6 Strategic diagnostic workup for FUO with common localized exam findings. TXR, thoracic radiographs; AUS, abdominal ultrasound; IMPA, immune mediated polyarthritis; PARR, PCR for antigenic receptor rearrangement.

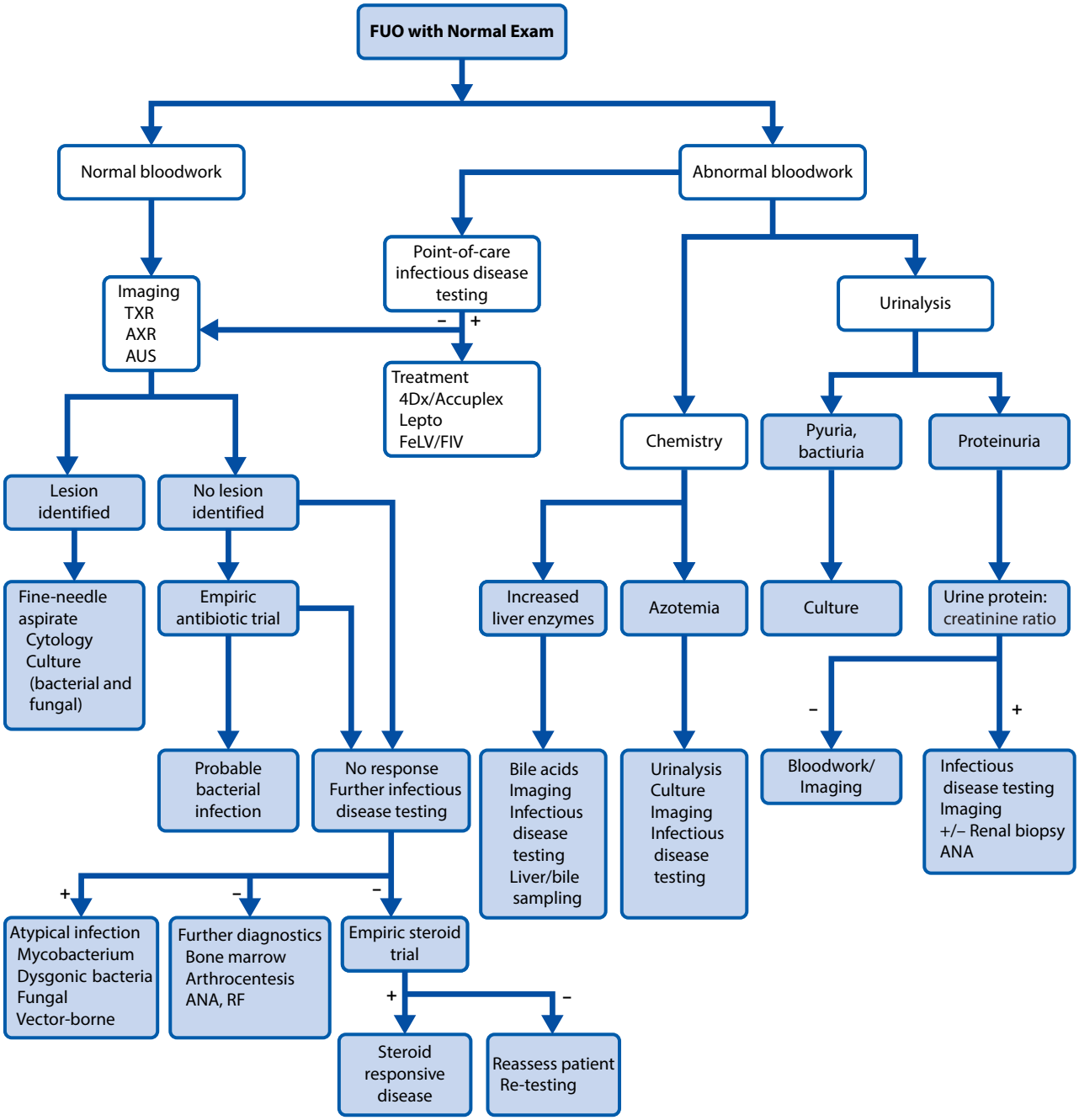


FIGURE 2.7.7 Strategic diagnostic workup for FUO with normal exam findings. TXR, thoracic radiographs; AXR, abdominal radiographs; AUS, abdominal ultrasound; ANA, antinuclear antibody; RF, rheumatoid factor.

RECOMMENDED FURTHER READINGS

1. Battersby IA, et al. (2006). Retrospective study of fever in dogs: Laboratory testing, diagnoses and influence of prior treatment. *J Small Anim Pract* 47(7):370–376.
2. Chervier C, et al. (2012). Causes, diagnostic signs, and the utility of investigations of fever in dogs: 50 cases. *Can Vet J* 53(5):525–530.
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CHAPTER 2

Common Clinical Problems
CHAPTER 2.8 Icterus

Julien R.S. Dandrieux

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INTRODUCTION

Icterus (or jaundice) is a clinical finding that is characterized by the yellow discoloration of tissues (sclerae, mucous membranes, and skin) and body fluids (plasma and urine) secondary to hyperbilirubinemia and bile pigment deposition. This chapter outlines the diagnostic approach to the icteric animal. The reader is referred to the chapters discussing anemia and liver and biliary diseases for an in-depth discussion of the different diseases or their treatment.

In the normal physiologic state, bilirubin is constantly produced from the degradation of heme (contained principally in hemoglobin but also in other hemoproteins) by phagocytes in the liver, spleen, and bone marrow. Hydrophobic unconjugated bilirubin (UB) is produced and transported in the plasma noncovalently bound to albumin. Bilirubin is processed by the hepatocytes to conjugated bilirubin (CB), a hydrophilic form, which is then excreted through the biliary system into the intestinal lumen (rate-limiting step). CB is further metabolized by intestinal bacteria and is the origin of the normal color of feces (stercobilin). Acholic (pale to white) feces are sometimes seen in animals with lack of CB secretion in the intestine due to complete extrahepatic bile duct obstruction (EBDO).

If CB cannot be excreted into the biliary system, it will backflow in the blood and be excreted in the urine. Renal tubular resorption of bilirubin in dogs is very limited, which explains why bilirubinuria can precede hyperbilirubinemia. Furthermore, dogs (male more than female) have the capacity to process heme in the renal tubules to UB and then CB. For this reason, mild bilirubinuria is often detected in healthy dogs with a urine specific gravity (SG) of 1.025–1.040 (1+) or moderate levels with an SG higher than 1.040 (up to 2+). Cats have a higher capacity for tubular resorption and are not able to process bilirubin in their kidneys. For these reasons, bilirubinuria is always considered pathologic in this species.

Bilirubin can also be covalently bound to albumin (albB, also called delta-bilirubin or biliprotein). This form occurs spontaneously in disease but not in healthy animals. The half-life of albB is the same as albumin (about 8 days in dogs) and can explain persistence of jaundice in some animals after resolution of the cause. It needs to be considered in an animal that is clinically improving despite persistent icterus.

Urobilinogen is a colorless compound formed from the degradation of bilirubin in the intestine and passively absorbed by the small bowel mucosa. The fraction that is not removed from the portal blood by hepatocytes enters the blood and is excreted in the urine. Urobilinogen is detected in the urine with a dip stick reagent but is not commonly tested because of its nonspecific interpretation.

In summary, bilirubin in a healthy animal predominantly consists of UB with negligible concentrations of CB and albB.

ETIOLOGY

Hyperbilirubinemia can occur either when the rate of UB production exceeds the rate of UB uptake in the hepatocytes (hemolysis), when UB is not converted to CB or transported into the biliary tract (hepatic insufficiency), or when CB cannot be excreted through the biliary tract (biliary tract disease). Hence, the main causes for icterus are as follows:

- *Prehepatic icterus:* Increase in red blood cell destruction
- *Hepatic icterus:* Liver insufficiency
- *Posthepatic icterus:* Obstruction at the level of the biliary system (intra- or extrahepatic) or rupture of the biliary tree
- *Others:* Sepsis (cholestasis induced by tumor necrosis factor alpha and endotoxin), resorption of large hematomas (rare)

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FIGURE 2.8.1 Icteric sclera in a dog with immune-mediated hemolytic anemia secondary to lymphoma. Note the bright yellow color of the sclera.

TABLE 2.8.1 Interpretation of bilirubinuria and plasma thresholds for detection of icterus

Where	Concentration/Degree of bilirubinuria or bilirubinemia*
Urine	Cat: Any degree is abnormal Dog: Up to 2+ bilirubin with SG >1.040 can be normal; bilirubinuria can precede hyperbilirubinemia
Serum or plasma	>0.9 mg/dL (15 µmol/L)
Sclera	>1.5 mg/dL (25 µmol/L)
Mucous membrane (nonpigmented)	>2.6 mg/dL (45 µmol/L)

* These are not absolute values, and the threshold for visual detection of icterus varies between individuals.

CLINICAL APPROACH

The icteric animal can be identified on physical examination (Figure 2.8.1) or by the color of its plasma or serum. Concentrations at which jaundice becomes visible in different locations are summarized in Table 2.8.1.

The first step after detection of icterus is to inquire about possible toxic or infectious causes with a thorough history, including vaccination status and travel history (common causes are listed in Table 2.8.2).

The second step is to determine whether other abnormalities are present on physical examination. A good body condition score is suggestive of an acute disease (e.g., acute cholangiohepatitis, hemolytic anemia, hepatotoxic insult) whereas a poor body condition score suggests chronic disease (e.g., chronic cholangiohepatitis, neoplastic process, end-stage liver disease). Generalized peripheral lymphadenomegaly is suggestive of infectious disease or lymphoma, and cytologic evaluation can help in reaching a diagnosis. If ascites is present, fluid sampling for analysis should be done. Findings such as septic peritonitis or bile peritonitis (biliary tree rupture) are strong indications for exploratory laparotomy.

TABLE 2.8.2 Common causes of icterus in dogs (D) and cats (C)

Type	Toxin	Infection	Others
Prehepatic → hemolysis	Copper; drugs (acetaminophen/ paracetamol [C, HB]; fenbendazole); onions (HB); zinc (HB)	*Dirofilaria* (caval syndrome [D]); *Cytauxzoon felis* (C)	DIC; erythrocyte congenital defect (e.g., PFK); hypophosphatemia (C>D); neoplasia (e.g., hemangiosarcoma)
Prehepatic → immune-mediated hemolysis	Drugs (cephalosporin, penicillin, potentiated sulfonamides)	*Babesia* (D); *Ehrlichia* (D); FeLV (C); hemotropic *Mycoplasma* spp. (C)	Blood transfusion; idiopathic IMHA (D>C); neoplasia (e.g., lymphoma); inflammation (e.g., pancreatitis, prostatitis)
Hepatic	Aflatoxins; mushrooms (*Amanita* spp.); blue–green algae; copper accumulation; drugs (acetaminophen/ paracetamol [C>D], diazepam [C], ketoconazole, itraconazole, lomustine, methimazole [C], NSAIDs [D], phenobarbital, trimethoprim/sulfonamide); sago palm; xylitol (D)	Virulent calicivirus (C); coronavirus (C); canine adenovirus (D); *Histoplasma capsulatum; Leishmania* (D); *Leptospira* (D); *Toxoplasma* (C>D); Hepatozoon (D); Cytauxzoon (F)	End-stage chronic liver disease; heat stroke; hepatic lipidosis (C); hepatitis/ cholangiohepatitis; neoplasia (carcinoma, lymphoma)
Posthepatic		Liver flukes (C) *Platynosomum* liver fluke (C)	Cholecystitis; cholelithiasis; gallbladder rupture; gallbladder mucocele (D); neoplasia (biliary adenocarcinoma); pancreatitis

DIC, disseminated intravascular coagulation; FeLV, feline leukemia virus; HB, formation of Heinz bodies; IMHA, immune-mediated hemolytic anemia; PFK, phosphofructokinase deficiency.

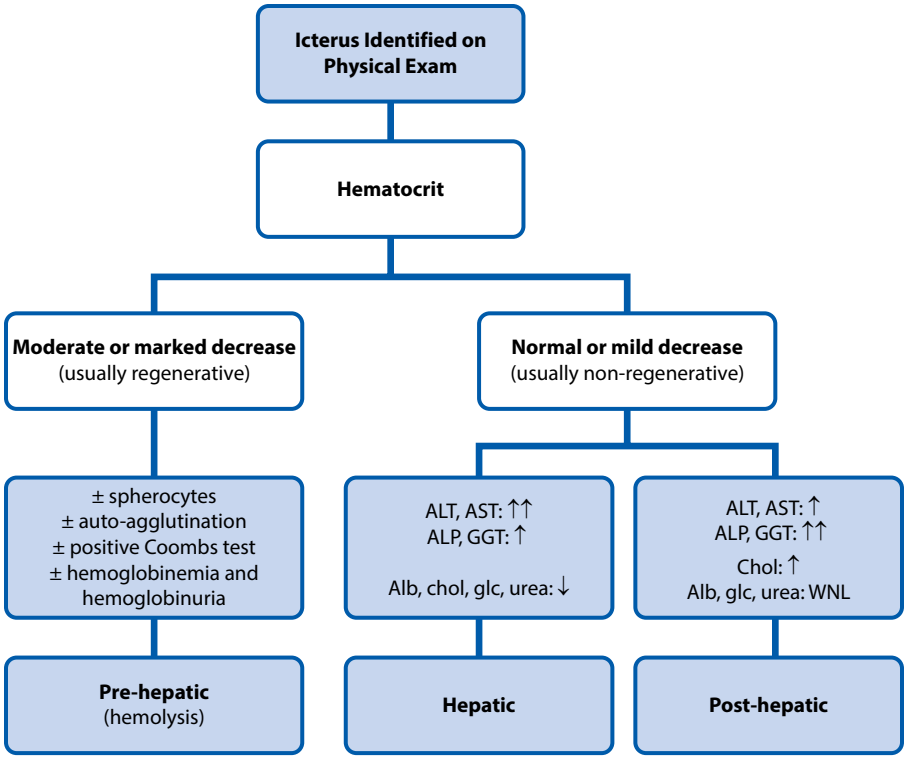


FIGURE 2.8.2 Flow chart showing the findings on laboratory blood work that can help determine the origin of icterus. Alb, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; Chol, cholesterol; GGT, gamma-glutamyl transferase; Glc, glucose; WNL, within normal limits; ↑, relative increase; ↓, relative decrease. See text for limitations in the interpretation. Further workup is then needed to determine the disease process.

Splenomegaly and hepatomegaly are common findings with prehepatic icterus secondary to extramedullary hematopoiesis, which can accompany immune-mediated diseases, but it can also be seen with neoplastic or infectious diseases.

Laboratory testing, including hematology, biochemistry, and urinalysis, is the next step to determine the cause of the icterus, and typical findings are outlined in Figure 2.8.2. A packed cell volume is very useful as a first step, as moderate-to-marked anemia is expected with prehepatic icterus and should become regenerative within 3–5 days, whereas anemia is usually mild and non-regenerative with other causes. In an animal with icterus of hepatic origin, hepatocellular enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are expected to be increased to a higher magnitude than biliary epithelium enzymes such as alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT), whereas the opposite is expected with a posthepatic icterus. Liver functional parameters (albumin, urea, cholesterol, and glucose) might also be decreased with significant loss of liver function. These parameters are expected to be normal with posthepatic obstruction, except for the increased cholesterol (cholestatic disease). Although these changes can help determine the origin of the icterus, they have many limitations. For example, prehepatic icterus often causes hepatic hypoxia with increases in ALT and AST. The serum activity of these two enzymes might normalize in end-stage liver disease because of the decrease in functional tissue. Additionally, hepatocytes will often be affected by processes causing posthepatic icterus over time, resulting in increases in ALT and AST. Therefore, all abnormal test results must be interpreted within the context of the animal and its stage of disease. If liver disease or complete EBDO is suspected, a coagulation profile, including fibrinogen concentration, is recommended prior to taking biopsies, as coagulopathies may develop secondary to these conditions.

If prehepatic icterus is suspected, the next diagnostic step is to determine its origin. Immune-mediated hemolytic anemia (IMHA) is a common cause of hemolysis. Dogs are more prone to primary (idiopathic) IMHA and cats to secondary IMHA from a variety of primary diseases. Imaging and testing for different infectious diseases, depending on the travel history and geographic location of the animal, is indicated.

Imaging modalities, particularly abdominal ultrasound, are very useful for differentiating hepatic from posthepatic icterus (Figures 2.8.3 and 2.8.4). Abdominal ultrasound can help confirm the location of the problem and suggest possible causes such as microhepatica in end-stage liver disease, changes in liver echogenicity or outline with infiltrative disease (Figure 2.8.5), or dilation of the common bile duct with long-standing post-hepatic obstruction (Figure 2.8.4). Abdominal ultrasound is also useful for collecting samples for cytology, histology, and culture, as indicated, to obtain a final diagnosis (Figure 2.8.6), although in some cases, surgical biopsies are

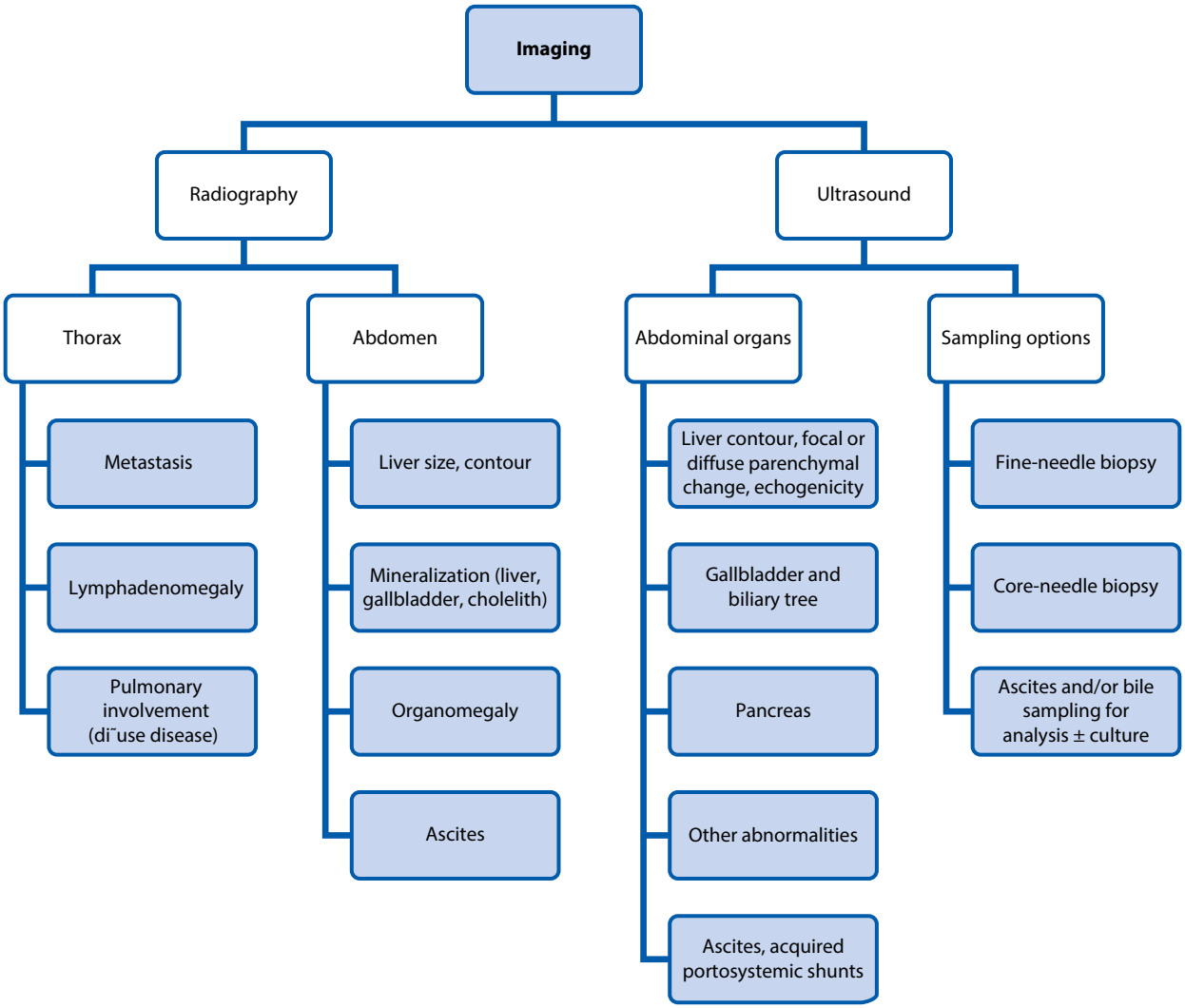


FIGURE 2.8.3 Flowchart showing the imaging modalities for the workup of the icteric patient. Radiographs are an adequate first step to get an overview of the abdominal organs and the chest if a systemic disease is suspected. Ultrasound can be very helpful, but yields are dependent on machine quality and operator. It allows targeted sampling.

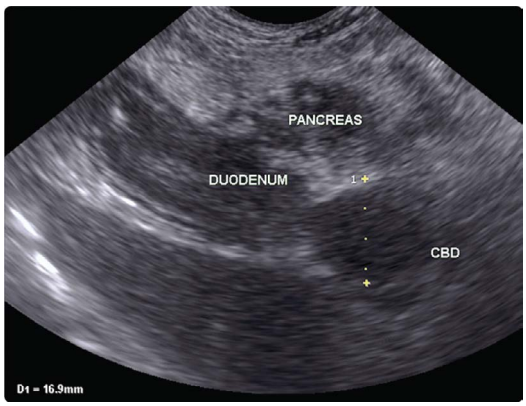


FIGURE 2.8.4 Ultrasound image of the common bile duct in an icteric cat. Anatomically, the duodenum, pancreas, and common bile duct (CBD) are in close contact with each other, as can be appreciated on this ultrasound picture. This explains how a severe pancreatitis can lead to development of icterus. Note in this patient that the CBD is markedly enlarged (16.9 mm; normal is less than 3 mm). (*Courtesy of C. Beck*.)



FIGURE 2.8.5 Ultra sonographic appearance of the liver in a dog presented with icterus. The parenchyma is heterogeneous with hyper- and hypoechoic nodules. Fine-needle aspirates were taken, and the cytology is depicted in **Figure 2.8.6**. (*Courtesy of D. Tyrell*.)

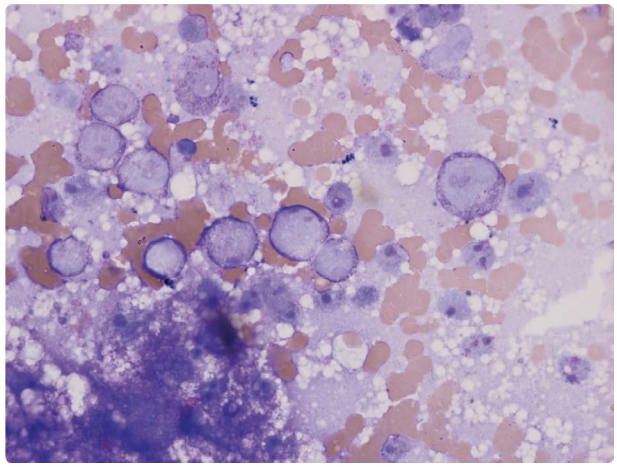


FIGURE 2.8.6 Cytologic slide from a fine-needle liver aspirate in an icteric dog (from the dog in **Figure 2.8.5**). Hepatocytes can be seen in the bottom left corner displaying marked vacuolation. A population of large atypical round cells with round nuclei containing fine chromatin and a thin rim of cytoplasm is also present. These cells are consistent with lymphoma. (*Courtesy of C. Connolly*.)

preferred. If available, other modalities such as CT and MRI may be helpful in complex cases.

If neoplasia is high on the list of differentials, chest radiographs or CT should be considered to screen for metastasis.

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CHAPTER 2

Common Clinical Problems

CHAPTER 2.9 Pallor

Elisa M. Mazzaferro

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INTRODUCTION

Pallor is defined as an extreme or unnatural paleness of the skin. Pallor can be caused by anemia, peripheral vasoconstriction, hemorrhage, stress, or death. In humans, pallor is most readily observed in the skin and mucous membranes. In animals with fur and pigmented mucous membranes, pallor may be less easily identified. In general, pallor is a subjective visual index of tissue perfusion and oxygen delivery to the skin and mucous membranes, including the conjunctiva.

ETIOLOGY/PATHOPHYSIOLOGY

A clinician's index of suspicion as to the cause of a clinical problem, including pallor, starts with a thorough patient signalment and history. Some of these key questions are found in Table 2.9.1.

Oxygen delivery is a function of cardiac output, peripheral vascular resistance, and arterial oxygen content (Figure 2.9.1). Cardiac output is a function of the heart rate and the stroke volume. The latter involves the cardiac preload (the amount of blood that is delivered to the heart), cardiac afterload (the force against which the heart must contract), and myocardial contractility. Hemorrhage and hypovolemia, including that caused by severe dehydration, in addition to obstructive causes such as pericardial effusion/tamponade and/or gastric dilatation-volvulus (GDV) or large masses within the abdominal cavity, can result in impaired cardiac preload. Hypothermia as well as the release of catecholamines to promote vasoconstriction as an adaptive mechanism to maintain perfusion during states of hypovolemia can increase cardiac afterload. Finally, primary cardiac disease such as dilated cardiomyopathy, end-stage mitral insufficiency, as well as impaired contractility due to circulating inflammatory cytokines with sepsis can all result in impaired myocardial function and decreased cardiac output.

TABLE 2.9.1 Key historical questions for diagnosing pallor

– Could an animal have ingested any toxins, including a vitamin K antagonist rodenticide or zinc-containing objects, including U.S. pennies minted after 1982?
– Is there a potential history of trauma?
– Is there a travel history outside of the patient's normal location?
– Have there been recent vaccinations or medications, including over-the-counter or homeopathic remedies?
– Has there been a change in appetite, vomiting, diarrhea, weight loss, or apparent weight gain? Has there been a change in the color of the feces or the urine?
– Has there been any coughing, hemoptysis, or gingival or other bleeding?
– Do the clients use flea and tick preventatives?

Note: A clinician's index of suspicion as to the cause of a clinical problem, including pallor, starts with a thorough patient signalment and history.

A second important contributor to pallor or lack thereof is red blood cell mass and saturation of hemoglobin. Conditions associated with blood loss, such as hemorrhage, body cavity effusions/bleeding, GI ulceration, and immune-mediated destruction of red blood cells, can result in regenerative anemia. Inadequate erythropoiesis, as observed with end-stage renal disease, or inadequate production at the level of the bone marrow, as observed with myelophthisis or bone marrow aplasia, can also result in inadequate production of red blood cells. Iron deficiency can result in inadequate production of hemoglobin and a microcytic, hypochromic

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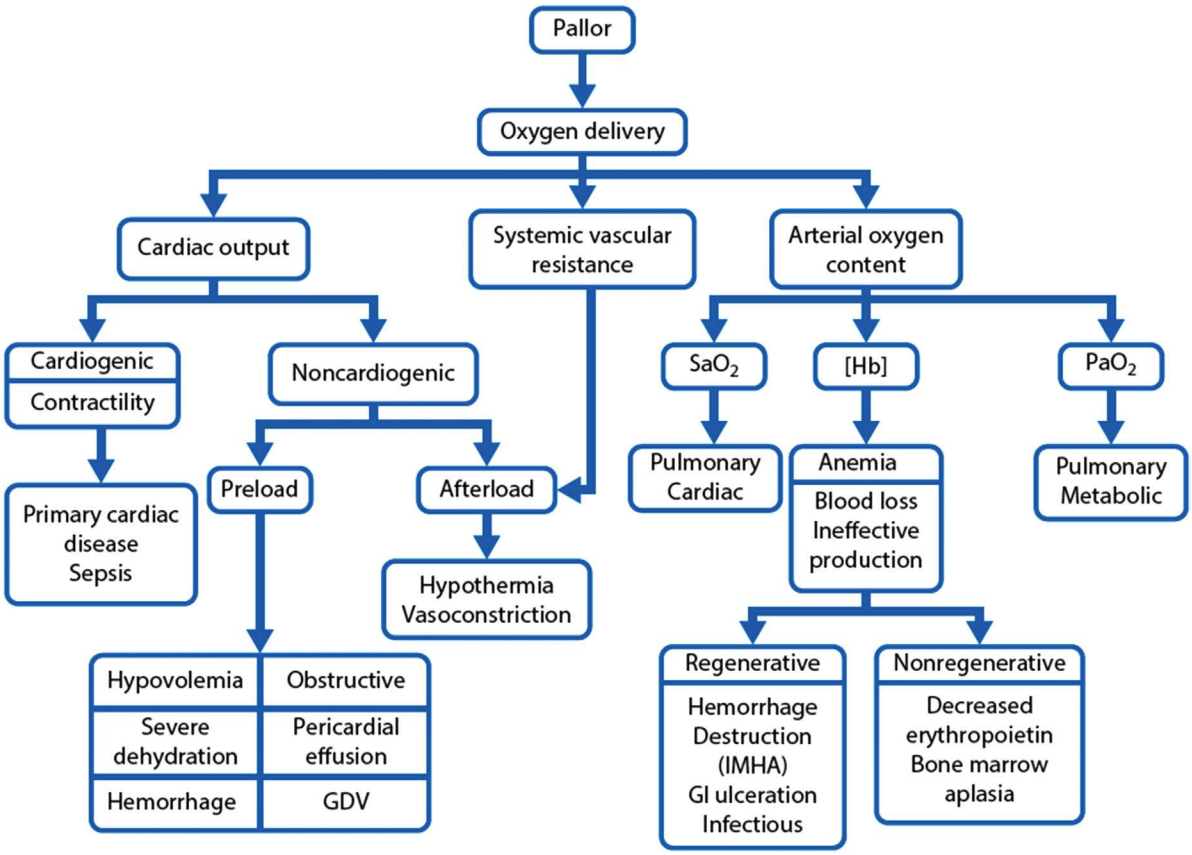


FIGURE 2.9.1 Algorithm for the pathophysiology of pallor.

anemia. Finally, lack of adequate saturation of hemoglobin with oxygen due to primary or secondary pulmonary disease can also result in clinical signs of pallor.

CLINICAL APPEARANCE

Once a thorough history is obtained, the physical examination should be performed, with careful attention paid to perfusion parameters: Heart rate, capillary refill time (CRT), pulse rate, synchrony and quality, body temperature, and peripheral extremity warmth. The CRT normally should be 1–1.5 seconds in a small animal patient. A brisk CRT (<1 second) may be observed with compensatory shock or sepsis, whereas a prolonged CRT (>2 seconds) is observed in decompensatory shock or hypothermia. Extreme tachycardia (>160 beats per minute [bpm] in dogs, >220 bpm in cats) or cardiac dysrhythmias may be observed with compensatory hypovolemic shock, anemia or due to primary cardiac disease or other conditions such as GDV. In addition, extremely low bradyarrhythmias such as that observed with sick sinus syndrome, third-degree AV block, or end-stage decompensatory shock can also result in the clinical signs of pallor. Although perfusion parameters are very different than hydration parameters, marked eye retraction within the globe, dry mucous membranes, and extreme skin turgor are also physical examination signs of severe dehydration, which can result in hypovolemia. Careful attention should be paid to auscultation of the heart and the lungs. Muffled heart sounds may be present with pericardial tamponade, severe hypovolemia, or pleural effusion. The presence of both muffled heart and muffled lung sounds should lead the clinician to consider pleural space disease such as pleural effusion or pneumothorax. Harsh lung sounds may be present with pulmonary contusions, pneumonia, or hemorrhage, for example.

DIAGNOSIS

At the time a physical examination is being performed, the patient's blood pressure should be measured and ECG performed to rule out systemic hypo- or hypertension and cardiac dysrhythmias (Table 2.9.2). Pulse oximetry should be considered to determine whether the patient is hypoxemic. Initial diagnostic blood work should include a packed cell volume (PCV) and total solids (TS), as well as a complete blood count (CBC). If a patient is anemic (low PCV) with a concomitant low TS, a source of whole blood loss should be considered. If, however, the PCV is low with a normal TS, destruction of red blood cells or lack of production should be considered. That is where the CBC with a reticulocyte count is important to determine if the anemia is regenerative or non-regenerative. If an automated CBC is not possible, performing a saline agglutination test and a

TABLE 2.9.2 Differential diagnosis for pallor

Anemia
Regenerative
- Blood loss
  - Hemorrhage
    - Trauma
    - Neoplasia
    - Toxin (vitamin K antagonist rodenticide)
  - GI ulceration
  - Body cavity effusion
  - Destruction
    - Immune mediated
    - Infectious
    - Toxin (zinc, *Allium* spp.)

Non-regenerative
- Decreased erythropoietin – renal disease
- Bone marrow aplasia
- Anemia of chronic disease

Decreased oxygen delivery
Decreased cardiac output
- Decreased preload
  - Hemorrhage/hypovolemia
  - Abdominal mass/effusion/GDV
  - Pericardial mass or effusion/tamponade
  - Pleural effusion
  - Pneumothorax/tension pneumothorax
- Increased afterload
  - Peripheral vasoconstriction
    - Compensatory from cardiogenic or hypovolemic shock
    - Increased catecholamines (pheochromocytoma)
    - Hypothermia

Depressed myocardial contractility
- Primary cardiac disease
  - Dilated cardiomyopathy
  - End-stage mitral insufficiency
  - HCM/HCOM/RCM/unclassified
- Secondary to circulating myocardial depressant cytokines
  - Sepsis
  - Systemic inflammatory response

Decreased saturated hemoglobin
Pulmonary disease
- Pulmonary hemorrhage
- Pulmonary contusions/trauma
- Pulmonary edema
- Pneumonia
- Neoplasia
- Pulmonary hypertension

Pleural space disease
- Pleural effusion
- Pneumothorax

Metabolic/toxic
- Methemoglobinemia

GDV, gastric dilatation volvulus; HCM, hypertrophic cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; RCM, restrictive cardiomyopathy.

peripheral blood smear to evaluate for the presence of spherocytes, red blood cell parasites, anisocytosis, red blood cell pallor, and thrombocytopenia can be useful in an emergency situation. Tests of coagulation, particularly the prothrombin time, can be useful as a screening test for vitamin K antagonist rodenticide intoxication. A simple whole blood clotting time can be used when other coagulation tests cannot be run where the failure of blood to clot in a serum tube after 10 minutes is strongly suspicious. Thoracic and abdominal radiographs may be useful to investigate for dilated cardiomyopathy, pericardial effusion, pulmonary parenchymal disease, pneumothorax, pleural effusion, abdominal effusion and masses, metallic foreign material, GDV, or peritoneal effusion. Finally, a focused assessment using sonography of the abdomen and thorax may prove to be useful in scanning for pericardial, pleural, or peritoneal effusions or pneumothorax.

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CHAPTER 2

Common Clinical Problems

CHAPTER 2.10 Peripheral Edema

Stuart Walton

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Peripheral edema is a pathologic expansion of interstitial fluid volume in tissue resulting from either increased net filtration of fluid from the vascular space or impaired return of fluid by lymphatics. Peripheral edema can affect any part of the body and is characterized as either generalized, regional, or local. Moderate-to-severe increases (≈30%) in interstitial fluid volume are evident on visual examination as a result of the physical changes in the tissue.

Under normal circumstances, interstitial fluid volume is kept within tight boundaries so that peripheral edema does not result. Typically, there is a dynamic flow of fluid (water and small solute molecules) from the intravascular space in the capillaries and venules to the interstitial space bathing cell. This is described according to the revised Starling's forces equation.

$$J_v = L_p S\left[\left(P_c - P_i\right) - O'\left(\pi_{esl} - \pi_b\right)\right]$$

J_v is the net fluid movement from the intravascular space to interstitial space
L_P is the hydraulic permeability coefficient
S is the surface area
P_c and P_i are the capillary hydrostatic and interstitial hydrostatic pressures, respectively
O' is the reflection coefficient for protein
π_{esl} and π_b are the oncotic pressure in the endothelial glycocalyx layer and the subglycocalyx, respectively

This net fluid movement is important not only for cellular nutrition but also for the removal of metabolic waste products. Factors that control interstitial fluid flow include hydrostatic pressure, oncotic pressure, endothelial integrity, and the lymphatic system. Under normal circumstances, the net hydrostatic pressure difference is greater than the net colloid osmotic pressure difference, favoring filtration of fluid from the intravascular to interstitial space. Excess plasma filtrate within the interstitium is then removed via the lymphatic system and returned to the systemic venous circulation via the cranial thoracic duct.

Several safety factors help to regulate interstitial fluid volume and resist the tendency of fluid to accumulate in the interstitium. These include:

a. Reduced tissue compliance, which limits the volume of fluid that can accumulate (i.e., increased interstitial fluid pressure from reduced tissue compliance opposes/limits further filtration).
b. Automatic readjustment of a similar magnitude of interstitial oncotic pressure in response to either increases in capillary filtration or interstitial hydrostatic pressure.
c. Increased lymphatic flow due to increased interstitial volume and pressure.

Excessive accumulation of interstitial fluid is detrimental to tissue function due to compromised cellular metabolism, both in the effective delivery and removal of oxygen/nutrients and toxic cellular metabolism by-products, respectively. This simultaneous reduction of plasma volume and increase of extracellular fluid space results from:

1. Increased capillary hydrostatic pressure, from either increased arteriole or venous pressures, or by a decreased arteriolar resistance.
2. Decreased plasma or increased interstitial oncotic pressure.
3. Depressed endothelial lymphatic function.

DIAGNOSTIC APPROACH

The diagnostic approach to peripheral edema is provided in Figure 2.10.1. The common challenge and frustration for clinicians is to determine the underlying cause (Table 2.10.1) and find an effective treatment for peripheral edema when an underlying cause remains

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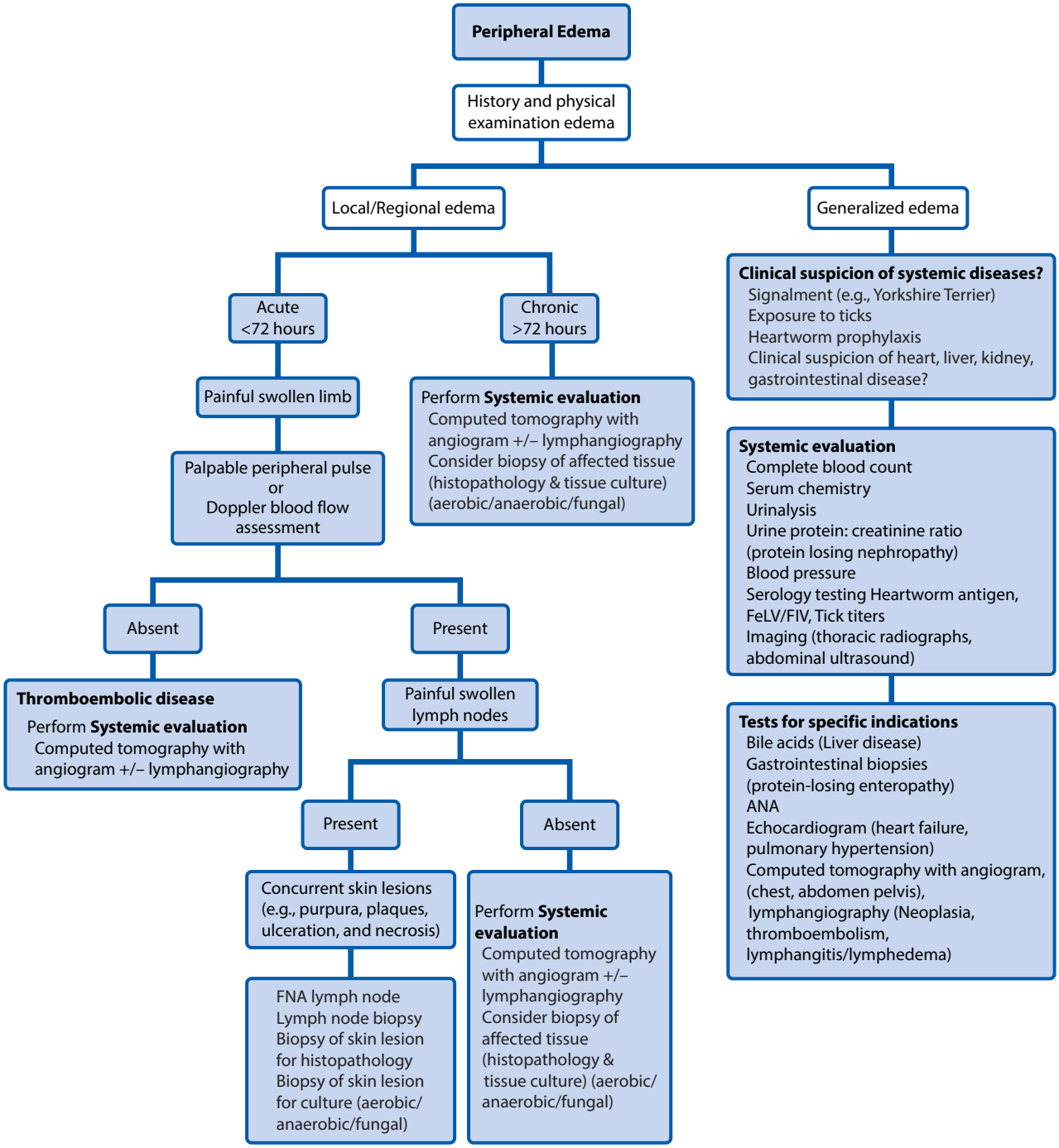


FIGURE 2.10.1 The clinical approach to assessing edema.

elusive despite extensive investigation. A complete history and thorough physical examination may aid in determining the cause of edema. Signalment may help clinicians to prioritize differentials and diagnostic testing (e.g., Yorkshire Terrier and protein-losing enteropathy [PLE], Abyssinian cat with renal amyloidosis).
Owners should be questioned regarding:

1. Chronicity and duration of the clinical signs (i.e., acute versus chronic, localized versus generalized, static versus progressive disease)
2. Does the patient seem painful (i.e., non-weight-bearing lameness, pain when touching the affected limb)?
3. Is there any improvement of the peripheral edema throughout the day?
4. Recent vaccination history
5. Environment (outdoor only, indoor only, indoor/outdoor)
6. Exposure to ticks
7. Heartworm prophylaxis
8. Travel history
9. Current medications (patient and owner)

10. Recent trauma
11. Any currently treated illnesses
12. Additional clinical signs (e.g., vomiting, diarrhea, weight loss, abdominal distension, increased water consumption, or urination)

It is also important to define the type of edema (i.e., local versus generalized). In general, localized edema is confined to a single limb and is due to vascular obstruction (i.e., thrombosis), infection, inflammation, or neoplasia. Generalized peripheral edema may be due to a local cause or systemic disease such as protein-losing enteropathies or nephropathies, among others (Figure 2.10.2).

The affected limb(s) should be palpated for warmth and peripheral pulses. Assessment for pain in the affected limb is important as pain may be consistent with vascular obstruction, inflammation, or infection. Lymphedema is rarely associated with pain. Peripheral regional lymph nodes should be examined for size, consistency, lobulation, adhesions, response to palpation/manipulation, and temperature of overlying skin. Fever, warm swelling, and enlarged, painful lymph nodes may be associated with inflammatory, infectious, or neoplastic etiologies. It is important that the infected limb(s) initially be inspected for concurrent skin lesions (e.g., purpura, plaques, ulceration, and necrosis of affected skin).

Care should be taken by clinicians to not only focus on the affected limb(s), as patients presenting with peripheral edema may have concurrent systemic clinical signs unrelated to peripheral edema. Attention should be paid to auscultation, palpation, and ballottement, looking for new murmurs, pulse character changes, and fluid waves, respectively.

The category of edema (i.e., localized versus generalized) and other pertinent findings discovered on physical examination will determine the next diagnostic steps. Local or regional peripheral edema is most commonly associated with one of the following three mechanisms of formation:

1. Disease of local lymph nodes/lymphatics resulting in poor lymphatic drainage
2. Infection/inflammation of the local tissues
3. Obstruction of local venous drainage

Diagnostics selected should include, but not be limited to, Doppler assessment of the affected limb(s) for blood

TABLE 2.10.1 Causes of peripheral edema

Increased capillary hydrostatic pressure
– Functional or structural obstruction to blood flow
– Congestive heart failure
– Venous obstruction (e.g., thrombosis)
– Compression of a vessel by a mass lesion
– Arteriovenous fistula
Decreased colloid oncotic pressure (hypoalbuminemia)
– Protein-losing enteropathies
– Protein-losing nephropathies
– Decreased hepatic synthesis
– Decreased dietary intake (e.g., malnutrition)
– Chronic hemorrhage
– Exudative lesion with large surface (e.g., burns, peritonitis)
Permeability changes
– Chronic inflammatory disease
– Infectious disease (Figure 2.10.2)
– Rickettsial (e.g., Rocky Mountain spotted fever and ehrlichiosis)
– Bacterial (e.g., bacterial endocarditis, septicemia, mycobacterial disseminated vasotropic)
– Viral (e.g., feline infectious peritonitis, canine coronavirus, and canine circovirus, herpesvirus, feline immunodeficiency virus, feline leukemia virus)
– Fungal (opportunistic)
– Parasitic (e.g., *Dirofilaria immitis*, *Angiostrongylus vasorum*, *Leishmania* spp., *Babesia gibsoni*, trypanosomiasis)
– Protozoan (e.g., Toxoplasma)
– Noninfectious (e.g., drugs, food additives, endogenous antigen, neoplasia, idiopathic)
– Vascular trauma (mechanical versus chemical injury)
– Vasculitis (infectious, iatrogenic, idiopathic)
Decreased lymphatic drainage (lymphedema)
– Primary lymphedema (autosomal dominant) – Bulldogs, poodles, whippets
– Secondary lymphedema
– Infectious (e.g., *Brugia pahangi*, lymphatic filarial infection, Southeast Asia)
– Granulomatous disease
– Neoplastic (e.g., lymphoma, lymphangiosarcoma)
– Traumatic injury (e.g., radiation therapy, thoracic duct ligation)
– Compression of lymphatics
Increased interstitial gel matrix
– Myxedema coma (hypothyroidism) – rare

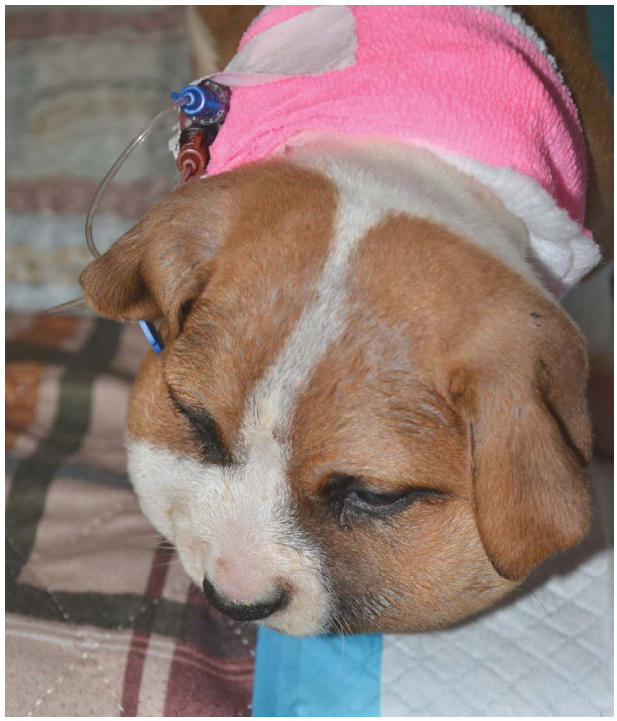


FIGURE 2.10.2 A 4-month-old female Terrier presenting with parvovirus enteritis. During hospitalization, the patient developed significant hypoalbuminemia, hypotension, and both forelimb and facial edema. (*Courtesy of M. Schaer.*)

flow; B-mode ultrasonography to assess venous patency, character, and blood flow; advanced imaging (plain radiographs, computed tomography with angiogram, lymphangiography) as well as biopsy of affected tissue with subsequent histopathology and aerobic/anaerobic bacterial/fungal cultures.

Generalized edema results from the simultaneous reduction of plasma volume with an increase of the extracellular fluid space from either reduced oncotic pressure, increased hydrostatic pressure, or changes in vessel permeability. A reduction in plasma volume results in decreased renal excretion of sodium, presumably by hormonal mechanisms. Sodium retention may further promote extracellular fluid accumulation and can exacerbate edema formation. Reduced oncotic pressure due primarily to hypoproteinemia and hypoalbuminemia usually does not become evident until the serum albumin concentration falls below 1.5 g/dL.

The diagnostic investigation should begin with routine clinical pathology (complete blood count, serum biochemistry, urinalysis, and urine protein-to-creatinine ratio), serology (e.g., heartworm antigen, retroviral testing [FeLV, FIV]), and evaluation of systolic blood pressure. Advanced imaging (thoracic/abdominal radiographs and/or abdominal ultrasound) can be performed to assess thoracic and abdominal organs, including the heart, gastric and intestinal wall, kidneys, and liver, and assess for any masses. Serology should be performed if there are concurrent clinical signs suggestive of viral or rickettsial-induced vasculitis. Specialized laboratory tests (e.g., bile acids, antinuclear antibody [ANA] titer) may be considered based on the information obtained from initial diagnostics in order to identify the primary problem. Contrast radiography with concurrent angiograms or lymphangiograms are indicated to confirm an obstructive lesion or the presence of an arteriovenous fistula.

If sepsis is suspected, then tissue, blood, and urine cultures should be performed. For patients with ulcerative skin lesions, skin biopsies from the active edges of developing lesions should be performed to confirm vasculitis. It is important to recognize that these may not reveal an underlying cause.

TREATMENT

Therapy should be based upon the identification of the underlying cause and mechanism(s) for edema formation. Patients with moderate to severe clinical signs due to reduced plasma oncotic pressure and hypoalbuminemia may require a plasma transfusion and either enteral/parenteral nutrition to prevent further edema formation while treating the primary disease. Additional therapies should be directed toward maximizing patient comfort (e.g., soft/cushioned bedding) while attempting to restore homeostasis.

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CHAPTER 2

Common Clinical Problems

CHAPTER 2.11 Pigmenturia

Leonel Londoño and Michael Schaer

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INTRODUCTION

Pigmenturia is a pathological condition that describes the accumulation of an endogenous or exogenous substance that imparts a different color to the urine. Under normal circumstances, the color of the urine ranges from clear, pale yellow to dark yellow or amber depending on the concentration of two pigments: Urochrome (a sulfur-containing substance) and urobilin (an oxidation product of urobilinogen). Concentrated urine (high specific gravity) may appear darker yellow or amber, and diluted urine (low specific gravity) may appear more clear or pale yellow, but there is no direct relationship between urine specific gravity and color. In small animals, hematuria is a common finding associated with red discoloration of the urine (Figure 2.11.1). Hematuria is not associated with an accumulation of a specific pigment or molecule, but once the concentration of red blood cells in the urine sediment reaches >50 RBCs per high-power field (hpf), then red discoloration of the urine can be observed. The three main endogenous causes of discolored urine secondary to pigment accumulation besides macroscopic hematuria are described in Table 2.11.1.



FIGURE 2.11.1 Severe hematuria in a 4-year-old spayed female dog secondary to immune-mediated thrombocytopenia, leading to urinary tract hemorrhage.

HEMOGLOBINURIA

Intravascular hemolysis is the most common cause of hemoglobinuria in small animals. Accumulation of heme protein can cause oxidative stress and systemic signs of toxicity. Three main mechanisms protect the body from the pathologic or nonpathologic accumulation of heme protein in circulation: Binding by haptoglobins and degradation by the reticuloendothelial system, oxidation of ferrous heme to ferric heme, and oxidation of hemoglobin to soluble methemoglobin by nitrous oxide. Once these mechanisms are saturated with severe hemolysis, hemoglobinuria and its pathological consequences are observed. One of the clinical consequences of hemoglobinuria is pigment-induced acute kidney injury (AKI). Although rarely reported in dogs or cats, it is known to cause significant tubulotoxicity. The exact mechanism of hemoglobin-induced AKI

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TABLE 2.11.1 Classification, clinical description, and most common differentials of endogenous and exogenous causes of pigmenturia

	Hematuria	Hemoglobinuria	Myoglobinuria	Bilirubinuria
Pigment name	N/A	Hemoglobin	Myoglobin	Bilirubin/urobilin
Urine gross color	Red, blood tinged	Pink to dark red	Brown (tea-colored) to port-wine color	Orange
Supernatant urine color	Clear	Pink to dark red	Reddish brown	Orange
Pathophysiology	Upper (kidneys, ureter) or lower urinary tract (bladder, urethra) hemorrhage; vaginal or preputial hemorrhage	Red blood cell lysis, most likely intravascular, allowing for the release of heme protein	Trauma, necrosis, or muscle exertion leads to leakage of striated muscle cell contents, including myoglobin	Any prehepatic, hepatic, or posthepatic causes of hyperbilirubinemia
Differential diagnoses	– Primary or secondary coagulopathies – Neoplasia (TCC, renal carcinoma) – Renal cysts – Urolithiasis – Urinary tract infections – Feline lower urinary tract disease (FLUTD) – Abdominal/pelvic trauma – Preputial/vaginal trauma, foreign bodies or neoplasia – Drugs (cyclophosphamide)	– Immune-mediated hemolytic anemia (IMHA) – Infectious causes in dogs (*Babesia* spp.) and cats (*Mycoplasma haemofelis*, *Cytauxzoon felis*) – Coral snake envenomation – Dirofilariasis – Drug reactions – Blood transfusion reactions – Neonatal isoerythrolysis	– Severe trauma – Seizures, tremors – Strenuous exercise (working dogs) – Heat stroke – Pyomyositis (*Streptococcus* spp., *Staphylococcus* spp., *Clostridium* spp.) – Pitviper envenomation – Sepsis – Hereditary myopathies – Severe hypokalemic rhabdomyolysis	– See Chapter 2.8, Icterus

FLUTD, feline lower urinary tract disease; IMHA, immune-mediated hemolytic anemia; TCC, transitional cell carcinoma.

is unknown, but heme proteins may cause direct cytotoxicity to the tubular epithelium and lead to formation of intratubular casts. Evaluation of urine sediment reveals lack or low numbers of red blood cells, and after centrifugation of a urine sample in a hematocrit tube, the supernatant color is pink to dark red depending on the severity of hemoglobinuria (Figure 2.11.2).

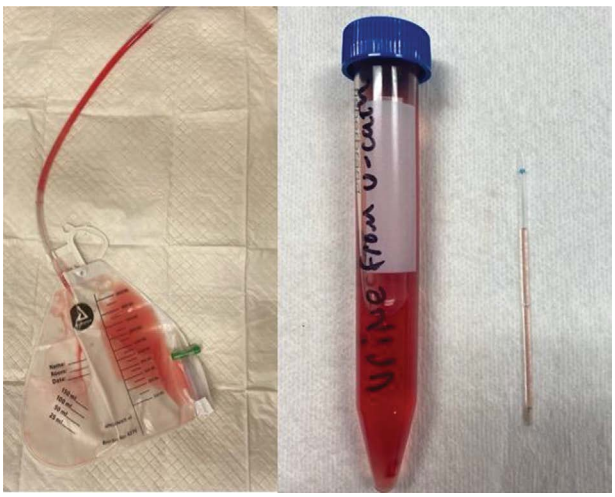


FIGURE 2.11.2 Hemoglobinuria in a 2-year-old male dog with caval syndrome secondary to dirofilariasis and evidence of hemolysis and hemoglobinuria. Note the pink-colored supernatant in the capillary tube representing hemoglobin in the plasma.

MYOGLOBIN

Rhabdomyolysis is a main cause of myoglobinuria and refers to the disintegration of striated muscle, resulting in the accumulation of muscle protein (myoglobin) in circulation. Trauma and crushing injuries are the most common cause of rhabdomyolysis in small animals. Other pathologies that cause depletion of adenosine triphosphate (ATP) and impaired function of ATP-dependent calcium pumps lead to accumulation of sarcoplasmic calcium and activation of proteases and lipases that ultimately disintegrate the myocyte. Pathologic accumulation of myoglobin leads to dark brown to port-wine discoloration of the urine (Figure 2.11.3a, b). Evaluation of urine sediment reveals lack of red blood cells, and after centrifugation of a urine sample in a hematocrit tube, the supernatant color is brown or dark red depending on the severity of myoglobinuria. To differentiate between hemoglobinuria and myoglobinuria, a venous sample is centrifuged in a hematocrit tube, and in cases of hemoglobinuria, plasma color is pink to dark red consistent with intravascular hemolysis, while in cases of myoglobinuria, the plasma color is clear. Similar to hemoglobin-induced AKI, myoglobin can also cause pigment-induced nephropathy secondary to intrarenal vasoconstriction, direct toxicity to proximal epithelial tubular cells, and formation of intratubular casts that obstruct the distal tubular lumen. Once myoglobin is filtered into the renal tubules, it



FIGURE 2.11.3 Myoglobinuria in a 7-year-old spayed female dog with severe bite-wound trauma to all four limbs and extensive crushing injuries. This dog developed AKI with oliguria (urine output 0.6 mL/kg per hour) and serum creatinine of 3.5 mg/dL. Note in the hematocrit tubes filled with **(a)** urine and **(b)** whole blood after centrifugation, the urine remains with dark red supernatant while the plasma color is clear.

precipitates with the Tamm–Horsfall protein, a process that is facilitated by acidic urine.

BILIRUBINURIA

The pathophysiology and causes of icterus are further described in Chapter 2.8. Bilirubin accumulation in the urine is in the form of conjugated bilirubin, while unconjugated bilirubin is bound to plasma proteins in systemic circulation. Canine renal epithelial cells can convert hemoglobin to conjugated bilirubin while the feline renal cells cannot perform this conversion. Dogs have a low renal threshold for clearance of bilirubin. Mild bilirubinuria (1–2+) is not always associated with pathology in this species. Bilirubin causes a neon yellow to orange discoloration of the urine (**Figure 2.11.4**). Bile cast nephropathy has been linked to the pathophysiology of hepatorenal syndrome in people with severe jaundice, but this has not been described in small animals.

EXOGENOUS CAUSES OF PIGMENTURIA

Other causes of pigmenturia in small animals, although rare, may be secondary to administration of medications or accidental ingestion of toxins or certain foods that can lead to discolored urine. Various drugs that can cause pigmenturia in humans are listed in **Table 2.11.2**. An example of drug-associated pigmenturia is shown in **Figure 2.11.5a, b**, which depict methylene blue-induced discoloration of the oral mucosa and blue-green pigmenturia in a cat.

TABLE 2.11.2 Some drugs that can cause pigmenturia in humans, dogs, and cats

Drug	Urine color
Deferoxamine	Red
Rifampin	Red
Hydroxycobalamine	Red
Methylene blue	Blue, green

Adapted from Aycock RD, Kass DA (2012). Abnormal urine color. *South Med J* 105(1):43–47 and Plumb DC (2011). *Plumb's Veterinary Drug Handbook,* 7th ed. PharmaVet, Inc., Wisconsin.



FIGURE 2.11.4 Bilirubinuria in a 10-year-old spayed female Domestic Shorthair cat with severe hepatic lipidosis (total bilirubin 11.5 mg/dL) and marked bilirubinuria.

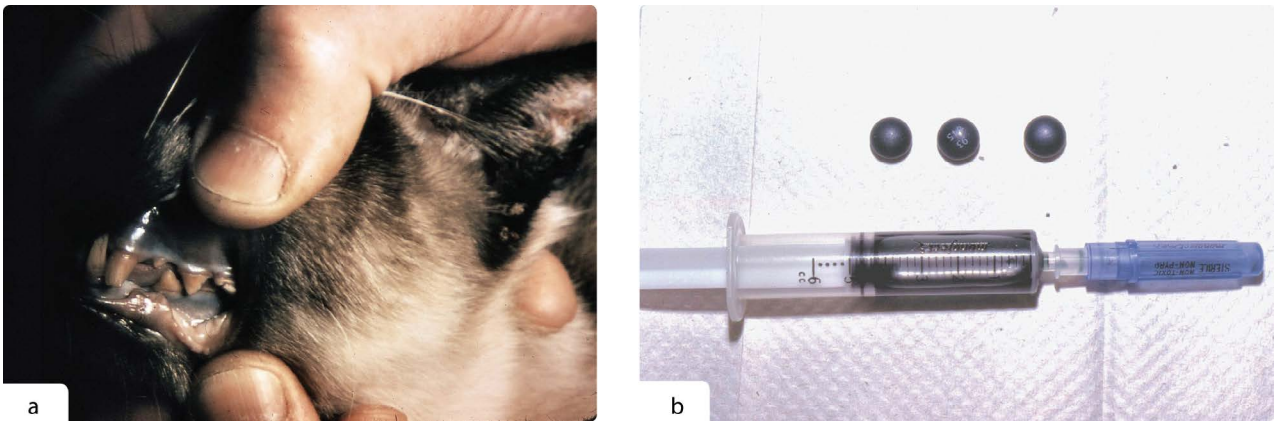


FIGURE 2.11.5 This cat's oral mucous membranes were discolored from the methylene blue contained in its medication for urinary tract disease **(a)**. The cat's urine sample was a blue-green color **(b)**. This product is no longer used in cats because of the associated Heinz body hemolytic anemia that it can cause.

CLINICAL APPROACH TO PIGMENTURIA

Identification of discolored urine should alert the clinician to identify the possible underlying cause of hematuria or pigmenturia. The algorithm in Figure 2.11.6 shows the differential features of pigmenturia. Although AKI in the dog and cat is a rare complication identified with pathological pigment accumulation in the urine, the recognition of AKI is limited to functional markers of renal function (creatinine, symmetric dimethylarginine [SDMA], urine output), which have major limitations in the ability to detect cellular injury and

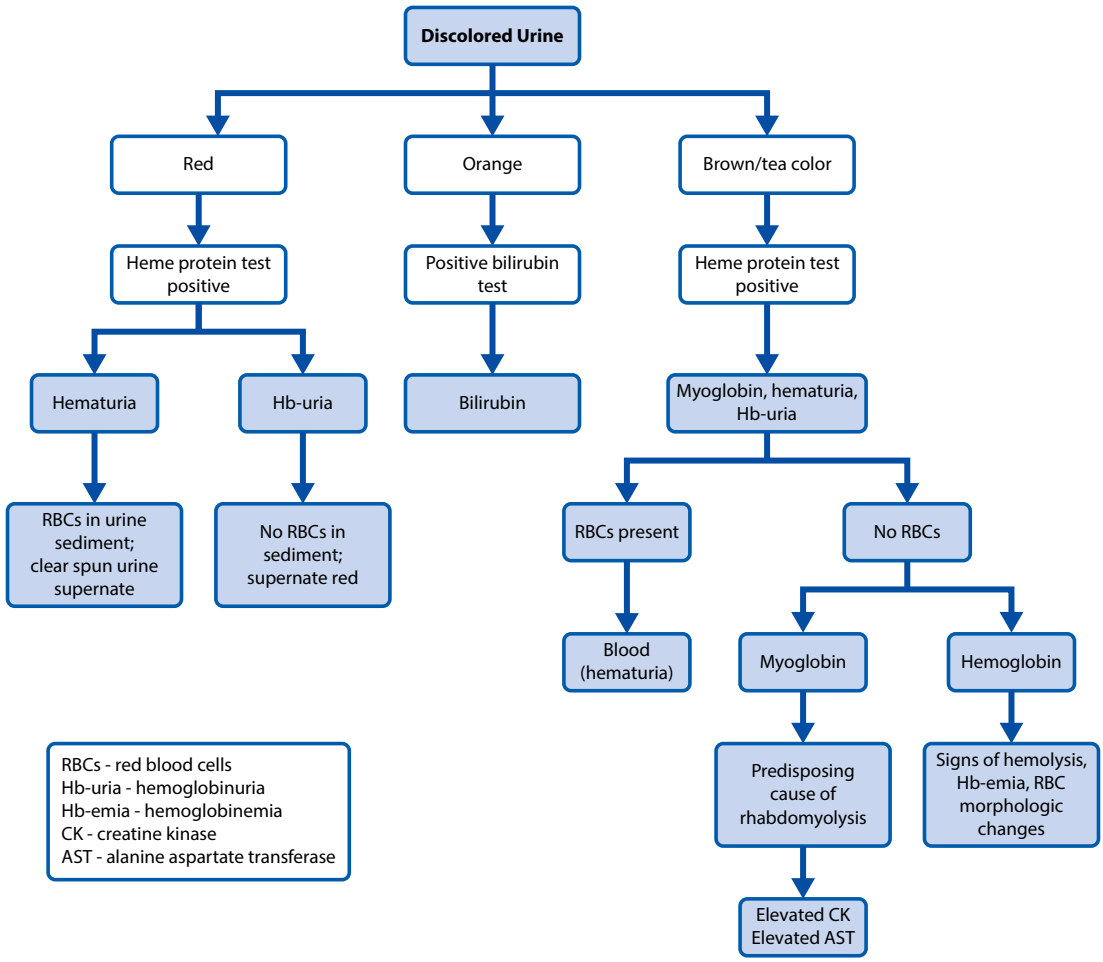


FIGURE 2.11.6 Algorithm showing the differential features of endogenous pigmenturia.

only increase once renal function has declined by more than 40%–75% depending on the functional marker used. Urine microscopy, specifically the detection of tubular casts, may have better sensitivity in recognizing AKI. Tubular casts accumulate in urinary sediment as a result of direct epithelial cellular injury by pigment, although by the time the casts appear, damage has already transpired. The damage associated with myoglobin and hemoglobin-induced AKI is maximized by coexisting metabolic acidosis and acidic urine. Therefore, in order to prevent or minimize the damage to the renal tubular epithelium, rapid restoration of effective circulating volumes and hydration deficits with balanced electrolyte solutions (lactated Ringer's solution [LRS], Normosol-R, or Plasma-Lyte 148) is recommended to not only improve renal perfusion but also to correct blood and urine pH abnormalities. It is recommended that chloride-rich fluids and synthetic colloids be avoided, as these will worsen systemic acidosis and are considered nephrotoxic. In certain cases, the use of sodium bicarbonate is recommended in patients where serum pH cannot be corrected by fluid therapy alone, and urine pH remains acidic.

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CHAPTER 2

Common Clinical Problems

CHAPTER 2.12 Polydipsia and Polyuria

Michael Schaer

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INTRODUCTION

Polydipsia is defined as increased thirst. Normal water consumption in dogs should not exceed 90 mL/kg per day (Figure 2.12.1), while normal water intake in a cat should not exceed 45 mL/kg per day (Figure 2.12.2). Any water intake that exceeds these amounts is described as polydipsia. Normal urine production in the dog and cat ranges from 20–45 mL/kg per day, and an amount that exceeds this range is described as polyuria.

ETIOLOGY

The two main causes of polydipsia and polyuria (PD/PU) syndromes include primary disorders of excess water intake and those that involve excess urine production.



FIGURE 2.12.1 This polydipsic dog was diagnosed with psychogenic polydipsia. He was able to concentrate his urine to 1.025 with the water deprivation test.

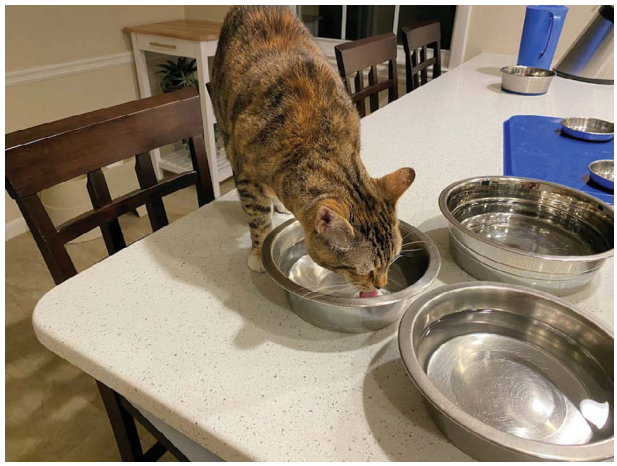


FIGURE 2.12.2 This cat's increased thirst continued for several minutes' duration.

There are approximately 14 endogenous causes of PD/PU and three exogenous causes. These and their main mechanisms are shown in Table 2.12.1. Many of the endogenous causes of PD/PU are accompanied by several other clinical features that characterize the specific disorder (Table 2.12.2). Also, there are certain conditions that can characteristically progress to eventually make the patient overtly ill when dehydration and any associated toxin accumulation occurs (Table 2.12.3).

PATHOPHYSIOLOGY

The pathophysiology underlying each PD/PU disorder varies and depends on the particular syndrome at hand (see Table 2.12.1). Any animal that is able to concentrate its urine >1.025 will usually not qualify as having a PD/PU syndrome unless the increased thirst and urination are periodic, which might characterize

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TABLE 2.12.1 The causes and mechanisms of polydipsia and polyuria

Disease	Mechanism of polydipsia/polyuria
Endogenous causes	
Diabetes mellitus	Osmotic diuresis, hyperosmotic stimulation of the hypothalamic thirst center
Chronic renal disease	Decreased nephron mass, dysfunctional renal medullary countercurrent multiplier
Hypoadrenocorticism	Renal sodium loss and impaired renal countercurrent multiplier
Hyperthyroidism	Hyperdynamic renal blood flow causing increased renal water filtration and impaired medullary concentrating ability Other factors: Aquaporin downregulation and decreased renal filtration fraction
Hyperadrenocorticism	Increase renal plasma blood flow, central thirst stimulation, distal renal tubular resistance to ADH
Hypercalcemia	Nephrocalcinosis, renal distal tubular resistance to ADH
Pyometra	Uterine *E. coli* bacterial endotoxins impairing distal renal tubular response to ADH In some cases, antigen–antibody deposits along with impaired renal perfusion causing acute kidney injury
Diabetes insipidus	Decreased ADH release from posterior pituitary or absent distal renal tubular and collecting duct response to ADH due to various pathologies affecting the distal renal segment
Chronic liver disease	Decreased urea synthesis impairing function of renal medullary countercurrent multiplier, central thirst stimulation
Postobstructive (and postoliguric renal injury) diuresis	Solvent drag associated with the accumulated osmols in the blood subsequently being able to filter through the kidney Polydipsia due to the excessive water loss stimulating the hypothalamic osmoreceptors and the thirst mechanism
Hypokalemia	Primary stimulation of thirst, diminished urine concentrating ability due to diminished renal tubule response to ADH The reason for the latter might be due to decreased expression of aquaporin 2
Psychogenic polydipsia	Psychologically induced disturbance involving the hypothalamic thirst center
Renal glycosuria	Polyuria at high glucose concentrations, asymptomatic at low concentration
Exogenous causes	
Diuretics	Various mechanisms affecting the absorption of electrolytes and water at specific points along the nephron, depending on particular drug
Hyperosmotic solution infusions	Increased renal perfusion and accompanying solvent drag as seen with mannitol Hypertonic saline can increase the plasma osmolality and stimulate the thirst center in the hypothalamus
Excessive parenteral fluid administration	Increased renal blood flow and filtration causing water diuresis Decreased stimulation for ADH secretion
Glucocorticoid drugs	Increased renal plasma flow causing increased glomerular filtration rate, antagonizes ADH at the distal renal tubular segments
Increased sodium chloride ingestion	Increases plasma space tonicity, increased thirst, and increased urination

ADH, antidiuretic hormone.

psychogenic or primary polydipsia (Figures 2.12.3 and 2.12.4). A patient that shows no evidence of any major underlying disease and no response to the water deprivation test should be suspect for having diabetes insipidus (Figure 2.12.5).

CLINICAL SIGNS

Several disorders will not characteristically result in a clinically ill patient so long as water is available and the animal can successfully imbibe and retain the water, as seen in the syndromes of psychogenic polydipsia, diabetes insipidus, and early-stage hyperadrenocorticism. Other conditions that will eventually worsen to cause a clinically ill patient include chronic renal failure, diabetic ketoacidosis, pyometra, hypercalcemia, hypoadrenocorticism, late-stage hyperadrenocorticism, and chronic liver disease. All of these conditions can worsen to involve multiple organ systems, which can cause the patient's eventual demise. One of these is illustrated with diabetic ketoacidosis being accompanied by acute kidney injury (AKI) and sepsis.

Primary polydipsia (psychogenic polydipsia) occurs because of a defect involving the thirst center in the hypothalamus. In humans, there can be underlying diseases such as mental disorders or diseases such as sarcoidosis that can impair hypothalamic function and disrupt the thirst center. Most of these patients, including dogs, are

TABLE 2.12.2 Typical clinical features of the polydipsia/polyuria syndromes

Disease	Classic clinical features (not all signs necessarily present depending on stage of disease)
Diabetes mellitus	PD/PU, eventually dehydration, weight loss, and vomiting, variable hypertension, varying urine SG, hyperglycemia, glycosuria, +/– hyperketonemia/hyperketonuria, other serum chemistry abnormalities (hypokalemia, hyponatremia, hypophosphatemia, lipid abnormalities), metabolic acidosis, azotemia
Chronic renal disease	PD/PU with hypertension, weight loss, and dehydration at moderate and late stages, vomiting, urine SG isosthenuric (1.008–1.012), azotemia, hyperphosphatemia, other electrolyte abnormalities (hyper-, eu-, or hypokalemia, hyper- or hypocalcemia), nonresponsive anemia
Hypoadrenocorticism	Progressive weakness and poor appetite, vomiting, diarrhea, weight loss, dehydration, decreased vitality, hypovolemic shock in late stages, varying urine SG, hyperkalemia and hyponatremia in typical form, hypochloremia, mild anemia, hypoproteinemia, hypocholesterolemia, hypocortisolemia, ACTH stimulation test cortisol <1.0 µg/dL, ECG abnormalities associated with hyperkalemia, small adrenal gland size on ultrasound in some
Hyperthyroidism	Progressive weight loss despite increased appetite, +/– hypertension, heart rate normal or increased, palpable goiters, increased serum thyroxin, decreased TSH, sometimes mild increased liver enzymes, sometimes mild anemia
Hyperadrenocorticism	PD/PU, panting, hypertension, dermatologic changes, abdominal distension, elevated liver enzymes (especially serum alkaline phosphatase in dogs), lipid abnormalities, increased serum cortisol-to-creatinine ratio, increased response to ACTH stimulation, impaired response to dexamethasone suppression, increased plasma ACTH levels with pituitary origin and low ACTH concentration with functional adrenal tumor origin, often adrenomegaly on abdominal ultrasound
Hypercalcemia	PD/PU, lethargy, weakness, dehydration, vomiting, vague abdominal discomfort, urinary calculi, hyper (with nephrocalcinosis) or hypophosphatemia, increased or normal serum PTH, enlarged parathyroid gland on cervical ultrasound examination with primary hyperparathyroidism, low serum PTH with hypercalcemia of malignancy, eventually azotemia and hyposthenuria or isosthenuria regardless of cause
Pyometra	PD/PU, dehydration, decreased appetite, purulent vaginal discharge with open pyometra, uterine enlargement, leukocytosis, sometimes renal dysfunction overt sepsis and septic shock
DI	Marked PD/PU, sometimes decreased appetite, hyposthenuria (urine SG < 1.008), no response to water deprivation, central DI will respond to ADH (**Figure 2.12.4**), nephrogenic form has no response to ADH
Chronic fibrosing liver disease	Decreased appetite and weight loss, encephalopathy (late stage), variable increases in serum liver enzyme tests, hyperammonemia, decreased liver size, increased bile acids, coagulopathy (late stage), anemia, sometimes icterus
Hypokalemia	Low serum potassium (<3.5 mEq/L; 3.5 mmol/L), skeletal and smooth muscle weakness, ECG changes, features of underlying disease (diabetes mellitus, hyperaldosteronism, metabolic alkalosis and its cause [gastric outflow obstruction], chronic renal disease)
Postobstructive and postoliguric renal injury	Features of the underlying urinary tract disease, marked PD/PU
Psychogenic polydipsia	PD/PU, no other signs of organic disease, perhaps a psychological trigger historically, able to concentrate urine with water deprivation test

Note: See specific chapters for details. Note that exact clinical signs are subject to individual patient variation.

ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; DI, diabetes insipidus; PTH, parathyroid hormone.

TABLE 2.12.3 PD/PU disorders that can rapidly progress to cause severe clinical illness*

Chronic renal disease
Diabetes mellitus
Hypoadrenocorticism
Pyometra
Hypercalcemia
Chronic liver disease
Extreme hypokalemia (serum K^+ < 2.5)

* These disorders can progress to cause sick, dehydrated, anorectic animals compared with other PD/PU disorders such as diabetes insipidus, psychogenic polydipsia, and hyperadrenocorticism, which do not typically show such progression. Hypokalemia causes marked skeletal muscle weakness and impaired ventilation (in severe cases).



FIGURE 2.12.3 These two urine samples show urine concentration ability after an 8-hour water deprivation test. The diagnosis was psychogenic polydipsia. It is important to realize that actual measurements of urine specific gravity (SG) or osmolality are the only ways to lend credence to this empirical visual impression.



FIGURE 2.12.4 This series of urine-filled tubes show the results of a positive antidiuretic hormone (ADH) response test in a dog with central diabetes insipidus. The palest colored urine sample was the most dilute, while the progressively darker colored urine was more concentrated when measured with a reflectometer.

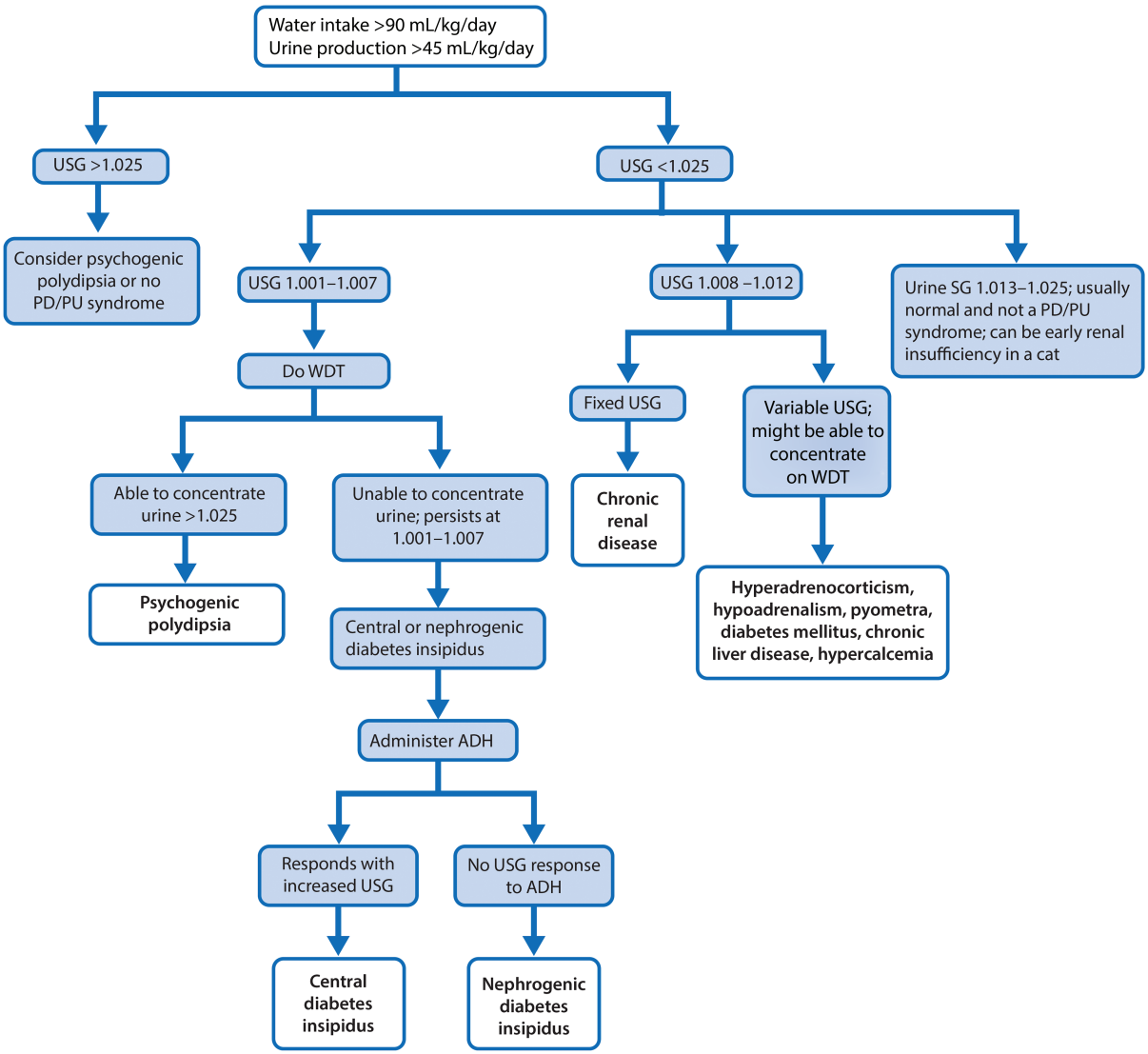


FIGURE 2.12.5 Algorithm demonstrating how to identify the polydipsia/polyuria syndromes using urine SG determination. WDT, water deprivation test; USG, urine specific gravity; ADH, antidiuretic hormone.

able to maintain normal serum sodium concentrations because they are able to excrete the extra water that they have imbibed. In rare situations in humans, the polydipsia can overwhelm the kidney's ability to excrete the excess water, and this can result in water retention and hyponatremia.

The characteristic features of each disorder are provided in Table 2.12.2. Urine specific gravity determination is a useful and practical test to help identify the cause of PD/PU (Figure 2.12.5), although its accurate application must always be used in light of the accompanying clinical findings.

TREATMENT AND PROGNOSIS

A disorder such as psychogenic polydipsia has a very good prognosis because it lacks any life-threatening pathophysiology as compared with other causes of PD/PU, such as chronic renal failure and diabetic ketoacidosis, which can progress to a clinically decompensating disease. A water deprivation test should not be done until the patient is first evaluated for other disorders causing PD/PU because it can cause a negative water balance that can have adverse effects on blood pressure and tissue perfusion. Furthermore, hyperadrenocorticism can cause clinical findings similar to diabetes insipidus.

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CHAPTER 2

Common Clinical Problems
CHAPTER 2.13 Proteinuria

Laura Rayhel and Mark J. Acierno

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INTRODUCTION

Proteinuria refers to increased levels of protein in the urine. Healthy glomeruli prevent filtration of most proteins into the urinary space. The few proteins and peptides that are filtered are degraded and reabsorbed in the proximal tubule. Glomerular disease causes loss of the normal filtration barrier, allowing abnormal amounts of protein to reach the tubules. Alternatively, proximal tubular dysfunction can allow filtered protein to escape reabsorption and make it to the urinary bladder, even if the glomerulus is functioning normally. Excessive amounts of protein are cytotoxic to the renal tubular epithelium over time, causing inflammation, fibrosis, degeneration, atrophy, and altered renal hemodynamics that reduce tubular perfusion. The net result is progressive loss of renal function. Detrimental sequelae like azotemia, thromboembolism, cachexia, hypertension, and nephrotic syndrome (hypoalbuminemia with associated effusion/edema/ascites and hypercholesterolemia) may develop. However, early on, affected animals may be asymptomatic, nonazotemic, and able to concentrate their urine. Early diagnosis and management of proteinuria may prevent uremic complications and death in affected animals.

SOURCES OF PROTEINURIA

Proteinuria resulting from abnormal glomerular filtration or tubular reabsorption of protein is termed renal proteinuria. Renal proteinuria is further subcategorized as glomerular or tubulointerstitial. However, proteinuria does not necessarily imply impaired renal function. Prerenal proteinuria results from systemic states which collaterally increase urine protein. These include fever, strenuous exercise, hyperthermia, seizures, and hypertension, and pathologic states which increase the amount of protein available for filtration such as hemolysis (hemoglobin), rhabdomyolysis (myoglobin), or plasma cell tumor/multiple myeloma (immunoglobulin). Postrenal proteinuria results from infiltration of inflammatory or neoplastic cells into the urine, as in urinary tract infections/prostatitis, urolithiasis, or urothelial cell carcinoma. Importantly, extrarenal neoplastic and inflammatory foci can also cause proteinuria, although the pathology is not fully understood.

TUBULOINTERSTITIAL PROTEINURIA

Proteinuria from proximal tubular dysfunction (tubular proteinuria; **Table 2.13.1**) is generally less severe than that from glomerular disease. The urine protein-to-creatinine ratio (UPC) often (but not always) remains below 2.0. Proximal tubular dysfunction often causes euglycemic glucosuria and/or urine casts alongside proteinuria, implying loss of reabsorptive function and epithelial damage. Inflammation of the renal interstitium (interstitial renal proteinuria) can allow proteins to infiltrate the tubular fluid past proximal tubule, which can also cause mild-to-moderate proteinuria.

GLOMERULAR PROTEINURIA ("PROTEIN-LOSING NEPHROPATHY")

Numerous glomerular diseases can impair the glomerular filtration barrier, causing severe, persistent proteinuria (**Table 2.13.1**); a more thorough discussion of specific glomerulonephropathies is provided in Chapter 13, Nephrology/Urology.

Practically, glomerular diseases in the dog and cat can be categorized as immune-complex glomerulonephritis (ICGN) or non-autoimmune. In ICGN,

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TABLE 2.13.1 Diseases commonly associated with renal proteinuria in cats and dogs

Glomerular	Tubular
*Infectious**	*Infectious*
– Lyme nephritis – Leishmaniasis – Ehrlichiosis – Heartworm disease – Babesiosis – Hepatozoonosis – Coccidioidomycosis (Valley fever) – Feline immunodeficiency virus (FIV) – Feline leukemia virus (FeLV) – Feline infectious peritonitis (FIP)	– Leptospirosis – Pyelonephritis (severe) – Ehrlichiosis – Hepatozoonosis
Autoimmune	*Fibrotic*

– *Systemic*
  – Immune-mediated polyarthritis
  – Immune-mediated hemolytic anemia
  – Systemic lupus erythematosus
  – Autoimmune pododermatitis (cats)
– *Renal (ICGN)*
  – Membranous GN
  – Membranoproliferative GN
  – Proliferative GN
	– CKD (late stages)

Non-autoimmune	*Toxic*
– Amyloidosis – Focal segmental glomerulosclerosis – Podocytopathy (minimal change disease)† – Cutaneous and renal glomerular vasculopathy – Glomerular lipidosis – Glomerulosclerosis in late-stage CKD	– Ethylene glycol – Aminoglycosides – NSAIDs – Lily (*Lilium* and *Hemerocallis* spp.; cats) – Grapes/raisins (dogs) – Heavy metal toxicosis – Jerky treat toxicosis (dogs) – Chlorambucil (cats)
Anomalous (young dogs)	*Anomalous*
– Hereditary nephritis – Collagenofibrotic nephropathy	– Fanconi syndrome
Endocrine	
– Hyperadrenocorticism – Diabetes mellitus	
Iatrogenic	
– Glucocorticoids – Tyrosine kinase inhibitors (Palladia)	

* Infection associated with secondary ICGN; Lyme nephritis requires rapid and simultaneous therapy with antimicrobials (doxycycline) and immunosuppressive agents for survival.

† Despite being classified as non-ICGN, minimal change disease is corticosteroid responsive in humans.

CKD, chronic kidney disease; GN, glomerulonephritis; ICGN, immune-complex glomerulonephritis; NSAID, nonsteroidal anti-inflammatory drug.

glomerular dysfunction results from deposition of immune complexes within the layers of the filtration barrier. These incite an inflammatory response which damages the glomerulus, increasing its permeability. ICGN can occur primarily or may occur secondary to some infections (Table 2.13.1). Non-autoimmune glomerular dysfunction results from scarring, amyloidosis, or other processes; 48% of dogs and 74% of cats with glomerular disease have ICGN and thus may respond to immunosuppression. Non-autoimmune causes of proteinuria may or may not have specific treatments recommended for their management. If no specific treatments exist, proteinuria secondary to non-ICGN glomerulonephropathies must be managed symptomatically (see Figure 2.13.2 on page 73).

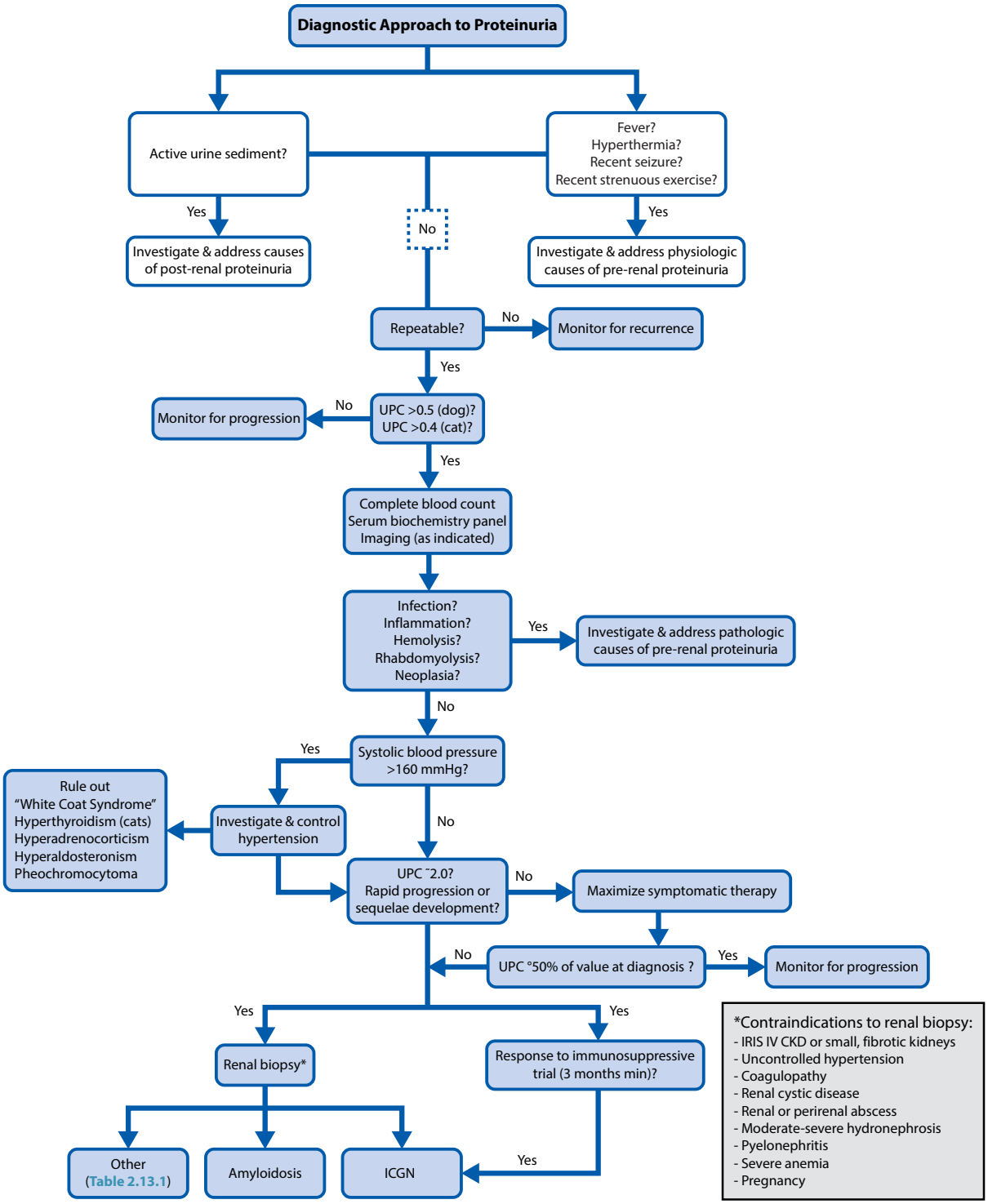


FIGURE 2.13.1 Diagnostic approach to the proteinuric patient.

Symptomatic Therapy for Persistent Renal Proteinuria

Proteinuria Reduction & RAAS Inhibition	Blood Pressure Management	Anticoagulation	Diet
Telmisartan 1 mg/kg PO SID (dogs and cats) Recheck UPC, BP, renal values, serum K q 4 wks Titrate dose upward in 0.5 mg/kg increments Stop titration if: UPC normal or < 50% of baseline SCr increases > 0.3 mg/dL Serum K > 6.0 mg/dL Hypotension Max dose 2 mg/kg PO SID If max dose reached and UPC >50% of baseline, consider adding ACE inhibitor Enalapril or benazepril 0.5–2 mg/kg PO SID-BID If adverse effects, consider switching from telmisartan to ACE inhibitor	Amlodipine starting dose: Cats: 0.625–1.25 mg PO SID Dogs: 0.1–0.2 mg/kg PO SID Combine with RAAS inhibition in dogs Recheck BP q 1 wk Titrate dose upward in 0.625 mg (cat) or 0.1 mg/kg (dog) increments Stop titration if: SBP < 160 mmHg Weakness, collapse, dull mentation Max dose: Cats: 2.5 mg PO SID Dogs: 0.5 mg/kg PO SID-BID If max dose reached & SBP >160 mmHg, consider: RAAS inhibitor (see left) Hydralazine (start low) Prazosin	Clopidogrel preferred: Cats: 18.75 mg PO SID Dogs: 1–3 mg/kg PO SID Or, if cost constraints, aspirin: Cats: 5–81 mg PO q72h Dogs: 1–5 mg/kg PO SID If thromboembolism while receiving, consider: Apixaban Rivaroxaban	Protein restriction: Reduce dietary protein 25–50% (in g/100 kcal) ***Account for treats*** Consider prescription renal diet if azotemic or current diet near AAFCO min protein requirement: Dogs: 4.5 g/100 kcal protein Cats: 6.5 g/100 kcal protein Note: Renal diets often contain less than AAFCO min protein Oral phosphate binder if P > 4.5 mg/dL despite renal diet: Aluminum hydroxide 30–100 mg/kg/day Ensure daily caloric intake above resting energy requirement RER = body weight $(kg)^{0.75} \times 70$ If voluntary caloric intake < RER: Appetite stimulation (mirtazapine, capromorelin) Nausea management (maropitant, ondansetron)

FIGURE 2.13.2 Symptomatic therapies for renal proteinuria. SCr, serum creatinine; K, potassium; RAAS, renin-angiotensin-aldosterone syndrome; UPC, urine protein-to-creatinine ratio; BP, blood pressure; AAFCO, Association of American Feed Control Officials; ACE, angiotensin-converting enzyme.

DIAGNOSTIC APPROACH

A typical diagnostic approach to incidental proteinuria is provided in Figure 2.13.1. In cases of subclinical, mild-to-moderate proteinuria, confirm persistence of proteinuria over three separate assays at least 2 weeks apart. However, a single increased UPC may be sufficient to begin workup or even treatment if markedly increased, or if sequelae associated with renal proteinuria such as azotemia or nephrotic syndrome are progressing rapidly. If disease is stable and UPC is mildly to moderately increased, pre- and postrenal sources should be ruled out. Complete blood count, serum biochemistry, and abdominal ultrasound to evaluate renal function and hunt for contributing extra-renal diseases, urine culture to rule out a postrenal infectious component, and evaluation of systolic blood pressure should be performed. Note that hypertension is both a cause and an effect of proteinuria. Extrarenal causes of hypertension such as hyperthyroidism (cats), hyperadrenocorticism (dogs), hyperaldosteronism, and pheochromocytoma should be ruled out prior to performing invasive diagnostics like renal biopsy or immunosuppressive trials. Thoracic radiographs to screen for metastatic neoplasia or pulmonary infectious/inflammatory disease can be considered based on clinical suspicion.

If investigation does not reveal a cause of pre- or postrenal proteinuria, renal proteinuria should be suspected. Infectious disease testing should be carried out within reason for the region and the patient's travel history (Table 2.13.1). If proteinuria is mild and disease is stable, attempting symptomatic management without further diagnostics is reasonable. No further diagnostics may be necessary if therapeutic goals are reached with symptomatic therapy alone. However, if UPC is markedly elevated, achievement of these goals without addressing the underlying condition is unlikely, and renal failure may develop rapidly. If UPC remains high despite symptomatic therapy, or if azotemia or nephrotic syndrome are developing, a lack of response to symptomatic treatment should prompt reconsideration of renal biopsy or immunosuppressive trials.

Renal biopsy is required for definitive diagnosis of most glomerular diseases and should be discussed if not contraindicated. Complications are uncommon if no contraindications exist, but life-threatening hemorrhage is possible postprocedure. Samples can be obtained surgically or percutaneously with ultrasound guidance and should be sent to an experienced nephron pathologist (United States: The Ohio State University International Veterinary Renal Pathology Service). If biopsy is unsafe or unfeasible, a diagnostic trial with an immunosuppressive medication is reasonable, if tolerated, for 3 months minimum. Risks of infection and adverse medication effects should be discussed prior to starting a trial.

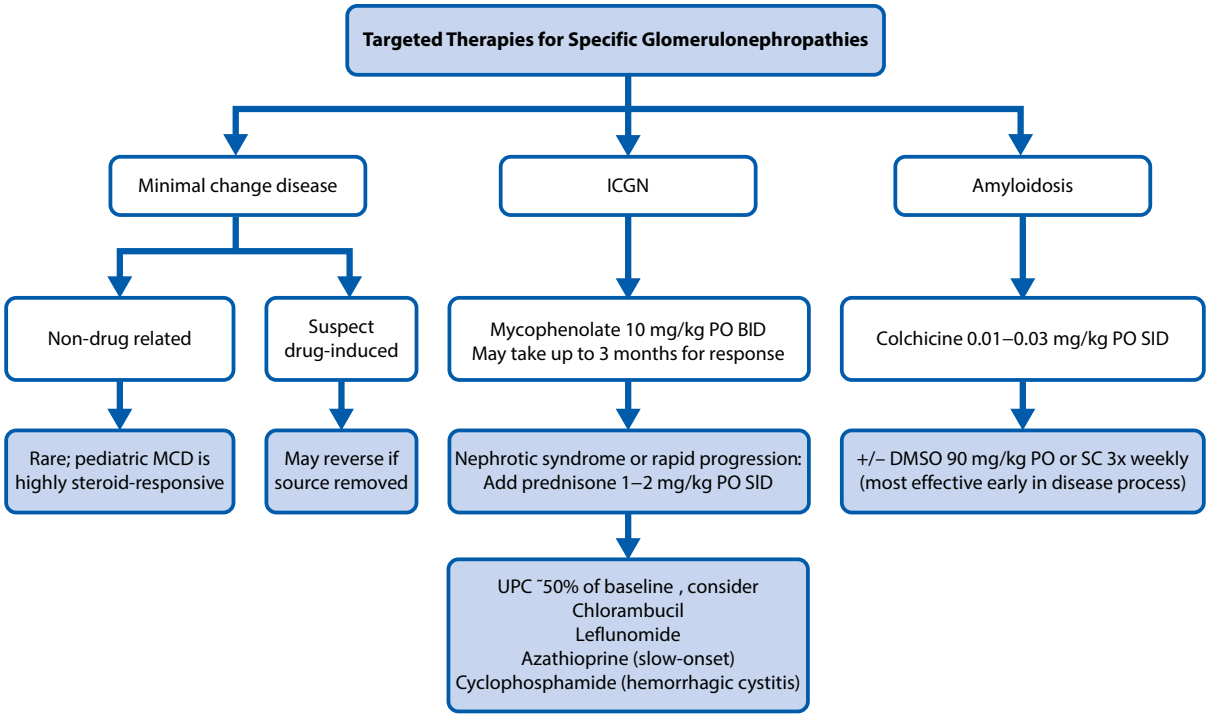


FIGURE 2.13.3 Targeted therapies for specific glomerulonephropathies.

THERAPEUTIC RECOMMENDATIONS

Symptomatic therapies for renal proteinuria are presented in Figure 2.13.2. Proteinuria can be reduced via inhibition of the renin-angiotensin-aldosterone system (RAAS), but controversy exists regarding the use of ACE inhibitors (e.g., enalapril, benazepril) versus angiotensin receptor blockers (ARBs; telmisartan). This author prefers ARBs due to anecdotal increased efficacy over ACEs but starting with either is reasonable. Combination therapy can be cautiously attempted in refractory animals but has not been scientifically evaluated. Goals of therapy include reduction in UPC to < 50% of baseline without significant hyperkalemia, worsening of azotemia, GI effects, or hypotension. Any animal receiving RAAS inhibition for proteinuria or hypertension should be evaluated for these adverse effects every 2–4 weeks during dose titration, then every 3–4 months once an optimal dose is determined. Additionally, management of sequelae such as hypercoagulability, hypertension, hyperphosphatemia, and dysrexia/hyporexia should be implemented (Figure 2.13.2).

Targeted therapy (Figure 2.13.3) should be initiated simultaneously when symptomatic if the specific underlying disease is known or strongly suspected (i.e., amyloidosis in a Shar Pei). If trialing an immunosuppressant without a pathologic diagnosis of ICGN, mycophenolate is recommended due to the relatively low risk of adverse effects. However, evidence to support one medication over another is lacking. For animals with a biopsy diagnosis of ICGN, chlorambucil or azathioprine could be considered alternatively to mycophenolate for animals with stable disease. In severely affected animals, a rapidly tapered course of immunosuppressive glucocorticoids in addition to slower-acting immune suppressants can be considered. However, glucocorticoids may increase UPC, so they are not recommended for long-term management. If the pet responds to immune suppressive, tapering to the lowest-effective dose is controversial, and life-long immunosuppression may be needed.

PROGNOSIS

Prognosis varies from fair to grave depending on underlying disease, severity of disease at diagnosis, and response to treatment.

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CHAPTER 2

Common Clinical Problems
CHAPTER 2.14 Regurgitation

Roman Husnik

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INTRODUCTION

Regurgitation is a passive oral evacuation of esophageal or pharyngeal content. It is almost always misinterpreted as vomiting by pet owners. Therefore, the first diagnostic step is to not only distinguish regurgitation from vomiting (Table 2.14.1) but also distinguish regurgitation from expectoration and dysphagia.

ETIOPATHOGENESIS

The esophagus is a tubular organ connecting the pharynx to the stomach. There is an important species difference between dogs and cats in the esophageal muscular is layers. In dogs, the esophagus is composed entirely of striated muscle, whereas in cats, only the distal half of the esophagus is composed of smooth muscle.

TABLE 2.14.1 Differentiation of regurgitation from vomiting

Clinical sign	Regurgitation	Vomiting
Abdominal contractions	Usually absent	Typically present
Evacuated content re-eaten	Often (not in cases of GER and esophagitis)	Absent
Prodromal signs (nausea, licking of the lips, salivation, excessive swallowing, hiding and depression)	Absent (excessive salivation and swallowing attempts due to dysphagia can imitate nausea in cases with pharyngeal disorder)	Typically present
Cervical esophageal distension	May be present	Absent
Time after eating	Variable	Variable
Character of ejected material	Usually undigested (depending on time interval after eating, whether the food is mixed with fluid and presence of GER)	Can be partially digested (depending on time between ingestion and vomiting)
Presence of bile	+/– (Duodenogastric reflux may occur under normal circumstances; bile may be present in regurgitant due to GER of bile from the stomach into the esophagus prior to regurgitation)	+/– (Duodenogastric reflux may occur under normal circumstances)
pH	Variable	Variable
Risk of aspiration pneumonia	High	Moderate

GER, gastroesophageal reflux.

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Regurgitation can be caused by disease of the esophagus, as well as pharyngeal disorders and soft palate anomalies (Table 2.14.2). Regurgitated food can also come from the stomach and the oral cavity. Diseases that result in primary hypomotility, inflammatory/neoplastic infiltration, or obstruction of the esophagus may interrupt normal passage of food/fluid, compromising the normal contractile function of the esophageal wall and possibly result in esophageal dilation. Regurgitation is a passive process with minimum prodromal signs. It occurs mostly based on gravity and passive changes of intrathoracic and intra-abdominal pressures with change of body position, barking, or during activities, without involvement of a reflex arc. Nausea and retching are not usually present; however, terminal retch or gag can occur, which the owners can misinterpret as cough. Regurgitation puts patients at risk for aspiration-related diseases.

TABLE 2.14.2 Most common causes of regurgitation

Esophageal disease (most common cause)
Obstructive disorders
- Foreign bodies
- Stricture
- Vascular ring anomalies
- Peri-esophageal masses (external compression)
- Intraluminal neoplasia

Esophagitis (including reflux esophagitis)

Infectious
- *Spirocerca lupi*
- *Pythium insidiosum*

Neuromuscular disorders
- Megaesophagus (congenital, acquired – idiopathic or secondary [many possible causes])
- Motility abnormalities

Hiatal disorders

Esophageal diverticulum

Gastrointestinal disorders
Disease processes associated with frequent and severe vomiting, GER, reflux esophagitis, and secondary dysmotility
Gastric distension (e.g., pyloric obstruction)
Gastric hypomotility and functional ileus (e.g., CIRMD [e.g., severe acute pancreatitis, gastroenteritis, and peritonitis] and POI)

Pharyngeal disorders (usually accompanied by dysphagia)
Obstructive disorders
- Foreign bodies
- Pharyngeal, tonsillar neoplasia
- Retropharyngeal lymphadenopathy

Neuromuscular disorders
- Myasthenia gravis
- Cricopharyngeal achalasia
- CNS lesions (cerebellar disorders, brainstem lesions)
- Neuropathies of cranial nerves IX and X
- Rabies
- Botulism

Palate disorders
- Congenitally short or cleft palate

CIRMD, critical illness-related GI motility disorders; GER, gastroesophageal reflux; POI, postoperative ileus.

DIAGNOSTIC APPROACH

Signalment, history, and physical examination can be useful in prioritizing differential diagnoses and detecting underlying disorder. The detailed clinical approach is shown in Figure 2.14.1.

HISTORY

It is important to ask questions about potential foreign body (FB), caustics, recent carrion (botulism) ingestion, or general anesthesia. Regurgitation starting a few weeks after anesthesia can be caused by stricture as a consequence of severe reflux esophagitis. Rabies vaccination status and current medication should be assessed. Combination of opioids with recent anesthesia, abdominal surgery, electrolyte abnormalities, and stress of hospitalization increases the risk of critical illness-related GI motility disorders/postoperative ileus (CIRMD/POI) and contributes to the higher incidence of gastroesophageal reflux (GER) and regurgitation in hospitalized animals. The owner should be questioned about the presence of muscular weakness that might reflect a neuromuscular disorder such as myasthenia gravis.

The sudden onset of clinical signs indicates the possibility of ingestion of a FB or caustics. Gradual onset and progressive course are often related to megaesophagus, stricture, neuromuscular disease, or neoplasia. An intermittent course can be seen in cases of reflux esophagitis or hiatal disorders. Onset of problems during weaning and switching to solid food indicates congenital origin (megaesophagus, vascular ring anomaly [VRA], stricture, cricopharyngeal achalasia). Regurgitation immediately after feeding usually indicates a complete obstruction or involvement of the proximal esophagus, while regurgitation several hours after feeding is likely caused by megaesophagus or distal obstruction. Regurgitation of dry food but not liquids usually indicates stricture or partial obstruction. Normal appetite or polyphagia is most often seen in animals with benign stricture or megaesophagus, while esophagitis is accompanied by anorexia. Weight loss may occur due to malnutrition.

In adult dogs with confirmed megaesophagus, it is important to look for manifestations of its potential causes and complications. Cough and dyspnea accompanying regurgitation are usually a manifestation of aspiration pneumonia, less commonly bronchoesophageal fistula or rarely pressure of dilated esophagus. Especially in young animals, regurgitation can escape the attention of the owner, and they are presented for respiratory abnormalities.

PHYSICAL EXAMINATION

It is important to observe the patient while eating/drinking, as well as a thorough examination of the oropharynx, masticatory muscles, and neck, especially the thoracic inlet. Atrophy of the masticatory muscles (e.g., myasthenia gravis, chronic myositis) and FB can

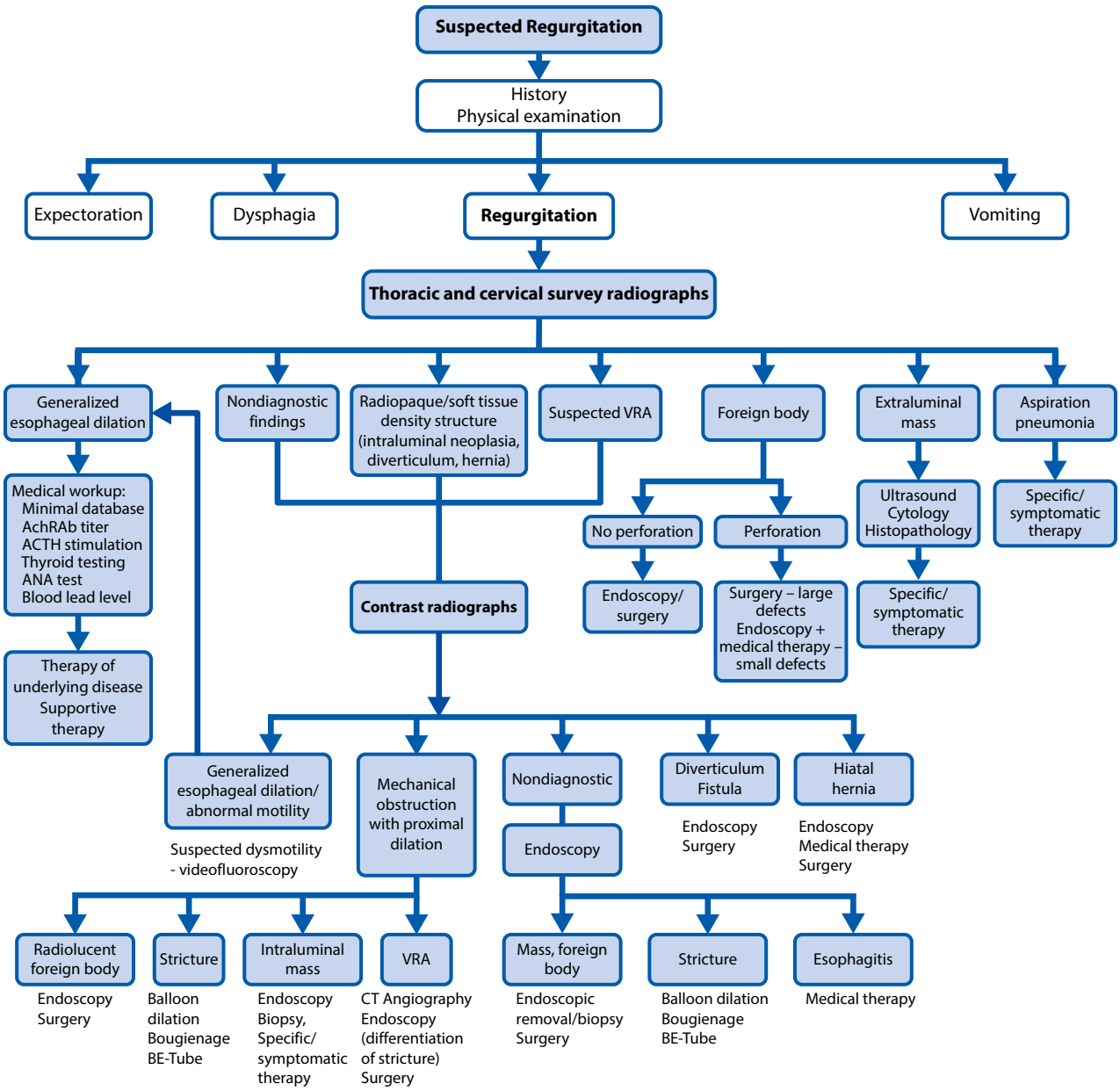


FIGURE 2.14.1 Algorithm for the clinical approach to regurgitation in dogs and cats. AchRAb, acetylcholine receptor antibody; ACTH, adrenocorticotropic hormone; ANA, antinuclear antibody; BE, balloon-esophageal; VRA, vascular ring anomaly.

be detected. In some cases, dilation of the cervical esophagus may be apparent on the left side of the neck (Figure 2.14.2). Examination of the respiratory system can reveal complicating aspiration pneumonia. With suspected secondary megaesophagus, attention should be paid to thorough examination of skin, mucous membranes, and mucocutaneous junctions (systemic lupus erythematosus), muscles (myopathy, botulism, myasthenia gravis, hypoadrenocorticism), exclusion of canine distemper and dysautonomia. In cases of mediastinitis due to esophageal perforation, a stiff posture, lethargy, and fever can be detected, and Horner syndrome may be present. Mediastinal masses in cats can be palpated during gentle compression of the anterior thorax. A neurological examination should be performed to evaluate for deficits consistent with generalized neuromuscular dysfunction. The blink reflex fatiguing over time increases the suspicion for myasthenia gravis.

PARACLINICAL DIAGNOSTIC TESTS

Survey radiography (SR), contrast radiography, fluoroscopy, ultrasonography, endoscopy, and computed tomography are diagnostic imaging methods often available in modern veterinary practice. In a patient presented with a history of regurgitation, initial diagnostic evaluation includes cervical, left/right lateral, and ventrodorsal thoracic radiographs (including cranial abdomen). Generalized (megaesophagus) or focal (VRA, stricture)



FIGURE 2.14.2 Two-year-old female spayed Pitbull. Dilation of the cervical esophagus is apparent on the left side of the neck. Histopathology of endoscopic biopsies confirmed diagnosis of fungal esophagitis (suggestive of *Pythium* spp.).

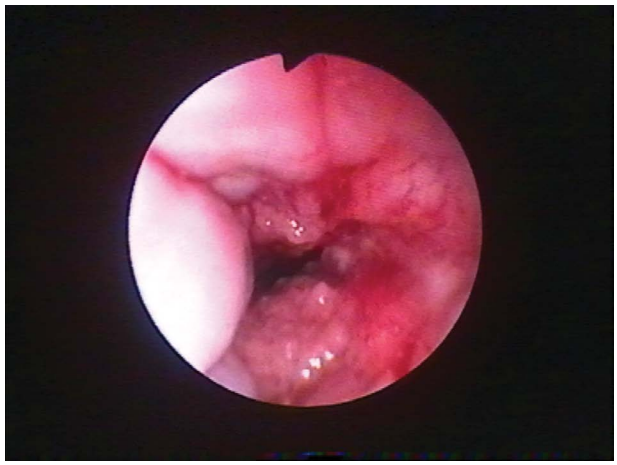


FIGURE 2.14.4 Nine-year-old male intact Belgian Shepherd. Esophageal undifferentiated carcinoma viewed via esophagoscopy. The mass was causing partial obstruction of the lower esophagus and subsequent regurgitation following ingestion of meals.

esophageal dilation, FB, masses, and aspiration pneumonia can be detected. Contrast radiography may be helpful if SRs are non-diagnostic. Disorders not readily diagnosed by SR include esophagitis, radiolucent FB, strictures, esophagobronchial fistula, and diverticulum. Video fluoroscopy is beneficial for better assessment of esophageal motility or for confirmation of hiatal hernia. In unclear cases, endoscopy and biopsy are useful in diagnosing stricture, esophagitis (**Figure 2.14.3**), intraluminal mass (**Figure 2.14.4**), FB, and diverticulum (**Figure 2.14.5**). Endoscopy may also be used therapeutically to remove an FB (**Figure 2.14.6**), to dilate a stricture, or to place a gastrostomy feeding tube. Computed tomographic angiography allows differentiation of VRA from other causes of esophageal obstruction and provides information to determine amenability of surgical correction. Ultrasonography can be used to further specify compressive masses and can guide fine-needle aspiration/biopsy. Scintigraphy and esophageal pH/impedance testing have been used to diagnose esophageal motility disorders, GER, unexplained esophagitis, or hiatal hernias. A minimal database consisting of CBC, serum chemistry (including serum creatinine kinase [CK]), and urinalysis is recommended to screen for underlying diseases in patients with systemic illness or secondary megaesophagus. Acetylcholine receptor antibody test, adrenocorticotropic hormone stimulation, thyroid tests, antinuclear antibody test, and blood lead assay should be considered in cases with megaesophagus or esophageal hypomotility. Edrophonium (if available) challenge test can support the diagnosis of myasthenia gravis. Electrodiagnostics and/or muscle and nerve biopsy can help to detect some neuromuscular disorders. In cases of POI and CIRMD, a minimal

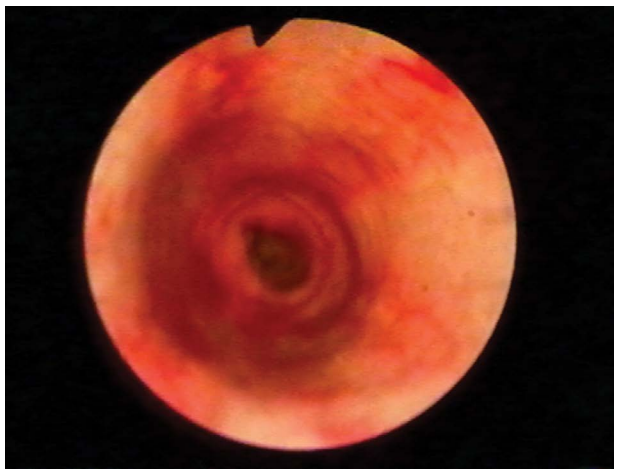


FIGURE 2.14.3 Four-year-old female spayed Yorkshire Terrier. Esophagoscopy is showing inflamed esophageal mucosa of distal third of the esophagus due to severe vomiting and gastroesophageal reflux caused by gastric foreign body retention and intermittent gastric outlet obstruction.

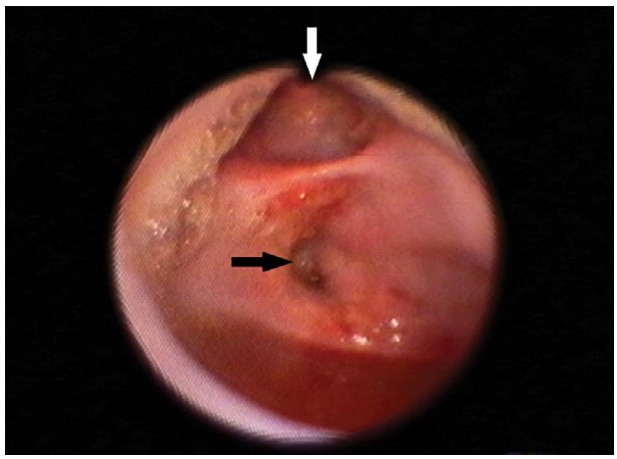


FIGURE 2.14.5 Three-year-old male neutered West Highland White Terrier. Caudal thoracic esophageal diverticulum (pulsion form, white arrow) as a consequence of increased esophageal luminal pressure caused by esophageal foreign body retention is shown. Cardia is also visible (black arrow).

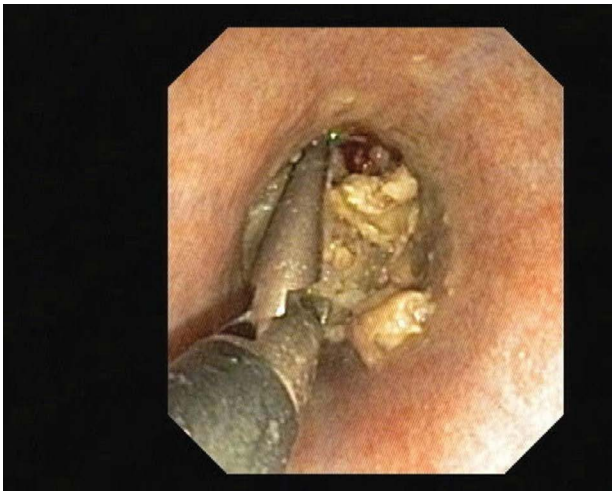


FIGURE 2.14.6 One-year-old female intact West Highland White Terrier. Esophageal foreign body (bone coated with connective tissue) was detected in the thoracic portion of the esophagus. Rigid grasping forceps were passed along the side of the flexible endoscope to grasp the object and remove it from the esophagus.

database and abdominal ultrasound are recommended to screen for underlying disease and monitor for metabolic consequences. Additionally, more targeted tests can be performed based on the list of differential diagnoses applying to each particular patient.

TREATMENT AND PREVENTION

Proper diagnosis and treatment of underlying disease as well as complications such as aspiration pneumonia are an essential premise. When primary disease is not identified or does not respond to therapy, strategies to reduce frequency and severity of regurgitation are used. Dietary modifications include small, frequent meals and feeding in upright position or through a gastrostomy tube. Keeping the patient in an upright position for 10–15 minutes after feeding (e.g., in Bailey chair) and between feedings may allow gravity to help with esophageal transit and evacuation. Some animals do better with a gruel consistency of the food, while others regurgitate less with canned food formed into a meatball shape or dry food (depending on the type of esophageal disease). If GER is present, judicious use of prokinetics and gastric acid suppressants may reduce the risk of esophagitis and regurgitation.

Preanesthetic administration of esomeprazole and cisapride significantly increases gastric pH and decreases the number of reflux events in anesthetized dogs. Therefore, administration of proton pump inhibitor and prokinetic agent may be beneficial for prevention of esophagitis secondary to GER.

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CHAPTER 2

Common Clinical Problems
CHAPTER 2.15 Seizures

Gabriel A. Garcia

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INTRODUCTION

Seizures are one of the most common neurological problems in veterinary medicine. Successful long-term management is dependent upon initially controlling clinical signs while trying to identify the underlying cause. Client education, setting realistic expectations, and working together with the primary veterinarian are essential. One can strive to eliminate seizures altogether, but this is an unrealistic goal, as approximately 15% of epileptics become seizure-free. Seizure events can be emotionally devastating for owners due to the peracute nature, frequency, and unpredictability.

PATHOPHYSIOLOGY

A seizure is the clinical manifestation of excessive, hypersynchronous electrical activity in the forebrain. It is the result of an imbalance of neuronal excitation from excitatory neurotransmitters (glutamate and aspartate) and neuronal inhibition from inhibitory neurotransmitters (gamma-aminobutyric acid [GABA] and glycine).

STAGES OF A SEIZURE

Identifying the different stages is helpful when trying to differentiate a seizure from other episodes. Owners commonly witness the final stages, ictus and postictal, but occasionally they may identify others. Thorough descriptions and videos of the events may help veterinarians characterize the episodes and assist in identifying seizure activity.

Stages include:

- *Prodrome:* Abnormal behavior, such as hiding, anxiousness, restlessness, or fearfulness. Occurs hours to days before the seizure.
- *Aura:* Difficult to identify in animals. Manifests as subtle behavioral changes.
- *Ictus:* Actual seizure event. Usually lasts less than 1–2 minutes. Commonly occurs at rest or sleep. Owners may overestimate the length of an episode due to its dramatic nature and their emotional response.

Cluster seizures refers to more than one seizure in a 24-hour period. Seizure events lasting longer than 5 minutes are termed status epilepticus (SE).

Seizures can be categorized as generalized or partial (focal). A partial seizure may progress to secondary generalization.

- *Generalized seizures:* Both cerebral hemispheres are involved. Motor manifestations are typically bilateral. Consciousness is impaired. Can include one or all of the following:
  - *Tonic:* Sustained muscle contractions resulting in recumbency (**Figure 2.15.1**)
  - *Myoclonic:* Brief, jerking, involuntary muscle contractions
  - *Clonic:* Repetitive, rhythmic, and prolonged muscle contractions
  - *Atonic:* Transient, sudden loss of muscle tone
- *Partial seizures:* Seizure focus in one cerebral hemisphere. The portion of the body involved is dependent on which portion of the forebrain is involved. If awareness is altered, it is referred to as a complex partial seizure (**Figure 2.15.2a, b**).
- *Partial motor seizures:* Disturbance of motor function with normal responsiveness.

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FIGURE 2.15.1 Generalized seizure activity in a young puppy due to hypoglycemia. Generalized motor seizure with tonic (rigid) and clonic (contraction) manifestation resulting in lateral recumbency. The mostly tonic rigid extension is intermittently interrupted by the clonic contractions, resulting in the paddling or running appearance of generalized seizures. (*Courtesy of M. Schaer.*)

- *Partial sensory seizures:* Involves the limbic system. Behavioral seizures presenting as rage, aggression, fly biting, running fits, tail chasing, or vocalization.

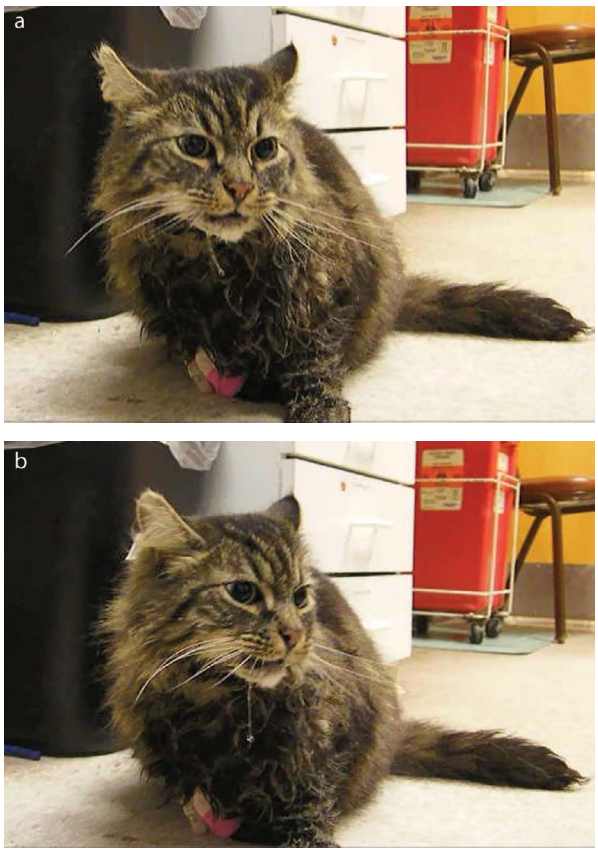


FIGURE 2.15.2 a, b Cats can commonly display partial to partial complex seizures where they may display altered consciousness, ataxia, hypersalivation, twitching of the ears and/or tail, and vocalization or growling. (*Courtesy of S. Carrera-Justiz.*)

- *Autonomic seizures:* Uncommon, predominantly autonomic signs (i.e., vomiting, diarrhea, or abdominal discomfort).
- *Postictal period:* Immediately follows the seizure and may last several hours. It is characterized by abnormal behavior such as aggression, restlessness, anxiety, lethargy, confusion, increased thirst, and appetite. Patients may display transient neurological deficits such as vision loss, obtundation, ataxia, and proprioceptive deficits.

- **Distinguishing signs of seizure:**
  - Peracute onset
  - Parasympathetic signs—hypersalivation, urination, or defecation
  - Tonic–clonic movements or rhythmic contracture of facial or appendicular muscles
  - Altered mentation—decreased responsiveness to stimuli
  - Postictal period

EPILEPSY CLASSIFICATION

The term epileptic describes a patient that experiences more than one seizure due to a forebrain abnormality. Certain breeds (Table 2.15.1) have a higher incidence of epilepsy. If inadequately treated, epilepsy can worsen over time, known as the "kindling effect."

Epilepsy is categorized by etiology – idiopathic epilepsy, symptomatic epilepsy, cryptogenic epilepsy, or reactive seizures. Regardless of the underlying cause, seizures are a clinical sign of forebrain dysfunction (Figure 2.15.3).

- *Idiopathic epilepsy:* Also known as primary or familial, is suspected to have a genetic basis. There are no structural forebrain abnormalities identified. Age of onset is typically 6 months to 6 years with an incidence of 0.5%–5% of the canine population. As many as 25%

TABLE 2.15.1 Breeds with predisposition to epilepsy

– Beagle	– Golden Retriever
– Belgian Shepherd	– Irish Setter
– Bernese Mountain Dog	– Irish Wolfhound
– Border Collie	– Keeshond
– Boxer	– Labrador Retriever
– Cocker Spaniel	– Lagotto Romagnolo
– Collie	– Miniature Schnauzer
– Dachshund	– Nova Scotia Duck Tolling Retriever
– Dalmatian	– Saint Bernard
– English Springer Spaniel	– Siberian Husky
– Finnish Spitz	– Standard Poodle
– German Shepherd Dog	– Vizsla

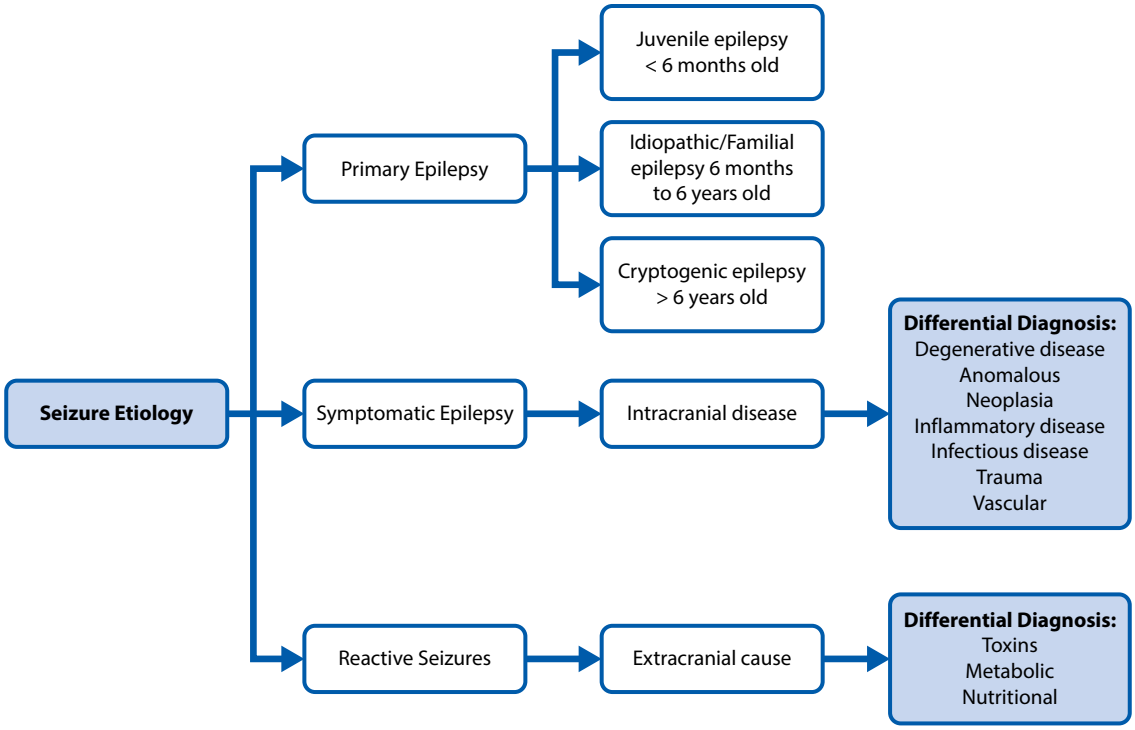


FIGURE 2.15.3 Seizure etiologies and differential diagnoses.

of epileptics are of the refractory type, whereby there is inadequate seizure control despite appropriate medication regimens.

- *Symptomatic epilepsy:* Seizures resulting from damage to the forebrain due to a structural lesion, such as inflammation (encephalitis), neoplasia, or congenital abnormalities (i.e., hydrocephalus).
- *Cryptogenic epilepsy:* Seizure focus is not compatible with idiopathic epilepsy, but no structural abnormalities are identified in the forebrain. These animals are typically older than 6 years of age.
- *Reactive seizures:* Describe recurrent seizures resulting from an extracranial cause, such as toxins and metabolic causes interfering with cerebral metabolism (a neurologic manifestation of systemic disease). There are no structural abnormalities noted in the forebrain, and the neurologic dysfunction will persist as long as the underlying cause is present.

CLINICAL APPROACH TO THE SEIZURE PATIENT

History

A thorough history is vital to differentiate seizures from other seizure-like episodes. Relevant questions include:

- When was first seizure and how many have occurred subsequently?
- Does the owner notice any atypical behavior prior to or after seizures?
- Describe the episode. Ask for videos.
- How long did the episode last?
- Is the pet normal in between episodes or is there abnormal behavior or motor deficits noted?
- Any precipitating factors prior to episodes such as feeding, sleep, or rest?
- Is the pet currently on any medications?
- Is the pet current on vaccines?
- Any exposure to toxins or human medications?

Exam Findings

A meticulous physical and neurological examination is essential for identifying any abnormalities and to appropriately localize lesions. Neurolocalization, signalment, and history allow for an accurate list of differential diagnoses (Table 2.15.2). Referral to a veterinary neurologist is recommended in patients with abnormal interictal exams, difficult or refractory epileptics, or in order to rule out any underlying intracranial pathology.

Diagnosis

Minimum database includes complete blood count (CBC), serum chemistry profile, urinalysis, blood pressure, and, when indicated, bile acids. It is important to initially rule out metabolic disease. Magnetic resonance imaging (MRI) and cerebrospinal fluid analysis are required to rule out structural or inflammatory forebrain disease. An electroencephalogram (EEG) can be helpful in confirming seizure activity; however, this diagnostic test requires specialized equipment and expertise in interpretation (Figure 2.15.4).

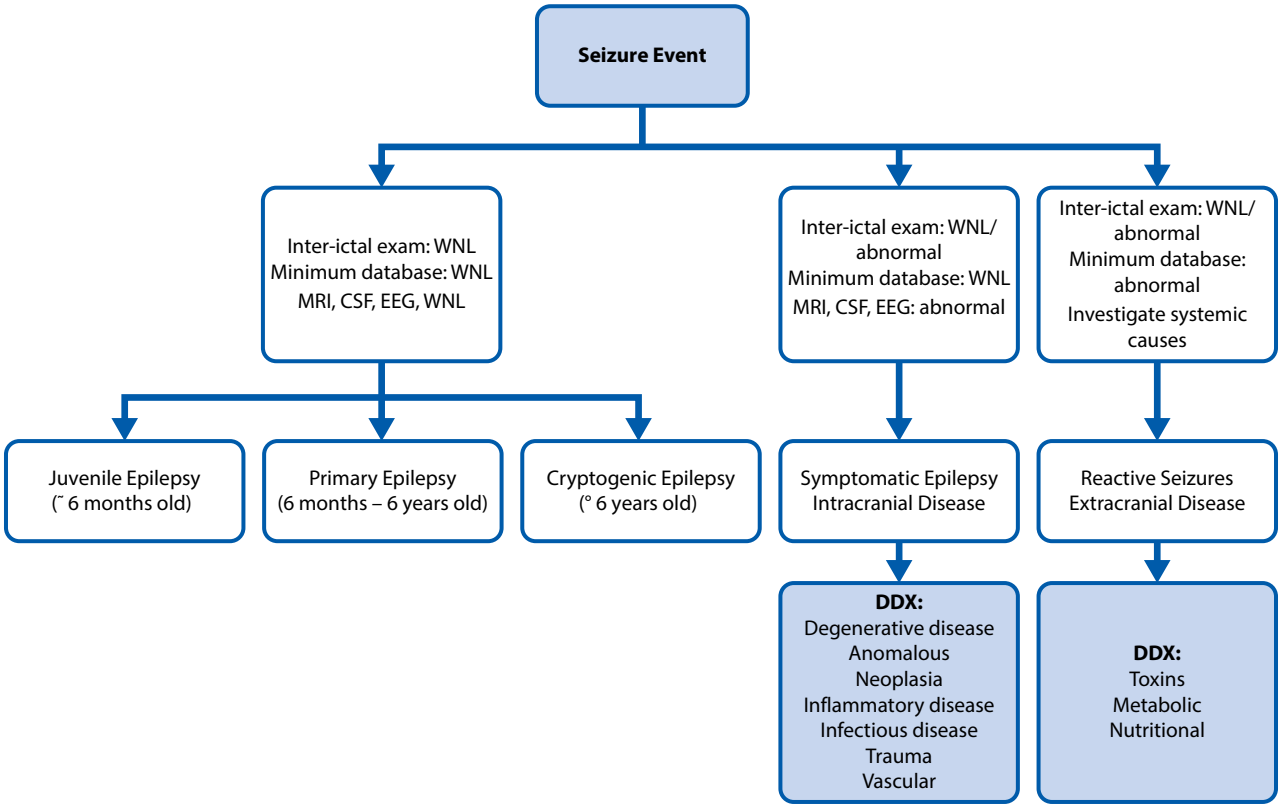


FIGURE 2.15.4 Diagnostic investigation and seizure etiology. WNL, within normal limits; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid analysis; EEG, electroencephalogram; NSF, no significant findings; DDX, differential diagnosis.

Maintenance Treatment

The main goal of therapy is to decrease the frequency and the severity of the seizures, while maintaining a good quality of life for both the pet and the owner. There is a balance between medication side effects and seizure frequency. The first therapeutic objective is to maximize the benefits of one anticonvulsant medication before adding a new medication. The most commonly used anticonvulsants are phenobarbital, potassium bromide, zonisamide, and levetiracetam (Table 2.15.3). Monitor medication serum levels when indicated. It is important to discuss the potential of continued seizure activity despite treatment. There is some debate on when to initiate therapy.

The following guidelines provide indications for the commencement of treatment:

- Frequency ≥1 seizure every 6 weeks
- Cluster seizures or SE
- Seizures increasing in frequency or severity
- Postictal periods are prolonged or difficult for the owner to deal with

A positive response to therapy is shown by at least a 50% reduction in seizure frequency.

Treatment for Cluster Seizures and Status Epilepticus (SE)

The goal is to stop the prolonged seizure event. This may be achieved with either a bolus or a continuous rate infusion (CRI) of a benzodiazepine (diazepam versus midazolam), ketamine, dexmedetomidine, or propofol. Providing the animal with a loading dose of medication (i.e., phenobarbital or potassium bromide) might be necessary before providing for maintenance anticonvulsant treatment.

MISCELLANEOUS

Although a number of nonpharmacological alternatives such as vagal nerve stimulation, dietary alteration, acupuncture, cannabinoid nutraceuticals, and homeopathy have become increasingly available and investigated, no single one has shown enough response to replace standard of care with anticonvulsant medications. These can be considered as supplemental modalities.

TABLE 2.15.2 Common differential diagnoses

Degenerative	– Storage diseases – Leukodystrophy

Anomalous	– Hydrocephalus
	  – Congenital
	  – Acquired (obstructive)
	– Lissencephaly
	– Cysts

Metabolic	– Hepatic encephalopathies, uremia – Hypoglycemia, hyperglycemia – Intoxication – Hypocalcemia – Hypothyroidism – Electrolyte abnormalities – Disturbances in acid–base metabolism – Disturbances in osmolarity – Heat stroke
Nutritional	– Thiamine deficiency

Neoplastic	– Primary
	  – Meningioma
	  – Glioma / astrocytoma
	  – Ependymoma
	  – Choroid plexus tumors
	  – Lymphoma
	  – Histiocytic sarcoma
	  – Peripheral nerve sheath tumor (CN V)
	– Secondary
	  – Frontal sinus tumors
	  – Calvarial tumors
	  – Pituitary tumors
	– Metastatic

Inflammatory/Infectious	– Immune-mediated inflammation (dogs > cats)
	  – Meningoencephalitis of unknown etiology (MUE)
	  – Granulomatous meningoencephalitis (GME)
	  – Necrotizing leukoencephalitis (NLE)
	  – Necrotizing meningoencephalitis (NME)
	– Infectious (cats > dogs)
	  – Bacterial
	  – Protozoan (*Toxoplasma*, *Neospora*)
	  – Viral (rabies, distemper, coronavirus/FIP)
	  – Fungal (*Cryptococcus*)
	  – Rickettsia (*Ehrlichia canis*, *Rickettsia rickettsii*)
	  – Parasitic (aberrant migrations – *Dirofilaria*, *Cuterebra*, *Taenia*, *Baylisascaris*)

Idiopathic	– Idiopathic / primary / familial epilepsy – Juvenile epilepsy – Cryptogenic epilepsy
Traumatic	– Acute – Chronic (gliosis or scar)

Vascular	– Infarct
	  – Ischemic
	  – Hemorrhagic
	– Commonly there is an underlying systemic cause – hypertension
	  – Pheochromocytoma, cardiac disease, renal disease
	– Hypercoagulable states
	  – Hyperadrenocorticism

CN, cranial nerve; GME, granulomatous meningoencephalitis; MUE, meningoencephalitis of unknown etiology; NLE, necrotizing leukoencephalitis; NME, necrotizing meningoencephalitis.

TABLE 2.15.3 Common anticonvulsant medications

Medication	Recommended dosing	Serum level therapeutic ranges	Steady state	Monitoring	Side effects
Levetiracetam (Keppra®)	20–60 µg/kg t.i.d. p.o., IV	N/A	2–3 days	Levels not established in veterinary medicine	Sedation, ataxia
Levetiracetam extended release (Keppra XR®)	30–60 µg/kg b.i.d. p.o.	N/A	2–3 days	Levels not established in veterinary medicine	Sedation, ataxia May find empty extended-release capsules in feces
Phenobarbital (PB)	2–4 µg/kg b.i.d. p.o., IV, SQ Loading dose: 8–16 µg/kg	25–35 µg/mL	10–14 days	CBC, chemistry, serum level at 2 and 6 weeks Monitor levels every 6 months or 2 weeks after a dose change	Sedation, ataxia, polyphagia, polydipsia, polyuria, hepatotoxicity, bone marrow dyscrasias Induces P450 system
Potassium bromide (KBr)	40–60 µg/kg s.i.d. or split dose b.i.d. p.o.	Monotherapy = 1,000–3,000 µg/L With PB = 1,500–2,500 µg/L	3 months	CBC, chemistry, serum level at 1 and 3 months Monitor levels every 6 months or 1 month after a dose change	Sedation, ataxia, paresis, polyphagia, polydipsia, polyuria, behavioral changes, pancreatitis, pruritis Do not use in cats – pneumonitis can be fatal
Zonisamide (Za)	5–10 µg/kg b.i.d. p.o.	10–40 µg/mL	3–4 days	CBC, chemistry, serum level at 2 and 6 weeks Monitor levels every 6 months or 2 weeks after a dose change	Sedation, ataxia, hepatotoxicity, blood dyscrasias Induces P450 system
Benzodiazepines Emergency dosing	Diazepam –0.5 µg/kg IV, per rectum Midazolam – 0.5 µg/kg IV 0.25–0.5 µg/kg intranasal	N/A	N/A		Sedation, ataxia, prolong postictal period Oral diazepam hepatotoxic to cats Do not store diazepam in plastic syringe

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CHAPTER 2

Common Clinical Problems
CHAPTER 2.16 Syncope, Episodic Weakness, and Collapse

Boyd R. Jones

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INTRODUCTION

Syncope, episodic weakness, and collapse are clinical signs that are often easily recognized, but sometimes confirmation of their cause may be difficult. Owner descriptions of what they see may be confusing, or what they have seen may be misinterpreted. Syncope, weakness, or collapse may occur at rest but occur more frequently with exercise and activity.

Syncope (fainting) refers to the sudden loss of consciousness resulting from paroxysmal episodes of impaired cerebral blood flow, which deprives the brain of energy substrates, oxygen, and glucose. True syncope is most often related to cardiac disease but can be associated with coughing (cough syncope), hypoglycemia, severe anemia, polycythemia acid–base imbalance, and other causes.

Episodic weakness or exercise intolerance is weakness that occurs with activity and exercise and improves after rest. There is weakness and fatigue after mild exercise, but occasionally, more prolonged exercise is needed to cause clinical signs. The degree of weakness may vary from mild hindlimb ataxia to complete collapse. Most animals are normal in between episodes. Collapse may be acute with seizures, narcolepsy, cataplexy, or syncope but also may be a component of more chronic and progressive metabolic or neurologic disorders.

CLINICAL SIGNS

Syncope is characterized by a short period of flaccid collapse and loss of consciousness. Most dogs are motionless with relaxed skeletal muscles. Sometimes there is involuntary urination and vocalization. Recovery is rapid, but there may be confusion for a short time afterwards.

Signs of episodic weakness are often intermittent and include a degree of weakness, stiff stilted walk, ventroflexion of the neck and head, and reluctance to continue walking or exercising. Animals may lie down and refuse to move or collapse when they attempt to get up and walk. They may be alert or obtunded and sometimes pant as they appear to be, and are, apprehensive. Muscle strength improves after rest, and between episodes, the animal may appear normal. There may be key events that precipitate the clinical signs, such as exercise, feeding, or excitement; these triggers must be identified by careful and complete questioning of the owner.

Relying on the owner's description of clinical signs can be misleading. Their description of what they see may not give a true indication of the clinical signs. Most digital cameras and smart phones have movie capacity so that owners can be asked to record the event to confirm what they see. The clinician can then view the event to determine its true nature and have an accurate record of the clinical signs, which is essential to aid differential diagnosis and direct the next investigations. Furthermore, the video can be sent to a specialist clinician for interpretation and specialist advice if that is required.

A complete history and clinical examination are also essential to help localize the cause to a body system and, in the case of a neurologic disease, to localize the lesion(s). Some of the important questions to ask the owner of an animal with syncope, collapse, or weakness are included in Table 2.16.1, along with the object of the questioning. Clinical experience, the history, and findings from a physical examination may enable the clinician to characterize the condition so that the diagnosis only needs to be confirmed. However, especially with episodic weakness, the animal may be examined when it is, or appears to be, normal, making further investigation essential. A plethora of diagnostic tests and procedures may be considered; therefore, it is best to delay full investigation until an episode is viewed. For additional investigation, there needs to be a high index

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TABLE 2.16.1 Questions for clients and their object, with specific outcomes related to syncope, episodic weakness, and collapse

History	Object and outcome
What did you see?	Try to determine from the description of the clinical signs if they are cardiac or neurologic in origin
How often have the signs occurred?	Increased frequency may suggest a progressive disease
Are the clinical signs always the same?	Episodic conditions usually show repeatable clinical signs
Is the animal normal immediately after an episode?	With syncopal causes and neuromuscular diseases, there are often no significant signs, in contrast to seizures
Is the animal normal in between episodes?	There may be no signs, but with some neuromuscular diseases, clinical signs can be detected
Is there anything that initiates an episode?	Exercise / coughing may induce syncope Feeding may induce narcolepsy; exercise is a trigger for weakness and collapse with neuromuscular diseases (e.g., myasthenia gravis)
Is there vomiting / regurgitation?	Regurgitation frequently occurs with metabolic and neuromuscular disease (e.g., myasthenia gravis, Addison's disease)
Have you seen the dog vomit or regurgitate?	Try to establish if esophageal signs are present suggesting muscle disease
Are litter mates affected?	Breed-related conditions that result in weakness and syncope are well known
Is the animal stiff or floppy during an episode?	Stiffness may be present with seizures or some myopathies but often not with cardiac and metabolic causes
What color are the tongue / gums?	Pale or cyanotic mucous membranes may indicate cardiovascular disease
What are the heart / pulse rates?	Detection of arrhythmias indicates cardiac disease

of suspicion as to whether the condition is neuromuscular, metabolic, or cardiovascular in origin. The investigation required for each is different. An approach to working up a case with syncope or episodic weakness is shown in Figures 2.16.1 and 2.16.2 and in Table 2.16.2. More information about each condition can be sought from other chapters in this book.

DIAGNOSTIC INVESTIGATION

Minimum Database

Hematology, biochemistry, including values for all electrolytes (sodium, potassium, calcium, phosphate), and urinalysis are the minimum required for most cases, and the results may provide a diagnosis or give an indication for further diagnostic tests (e.g., adrenocortical function, thyroid function, fasting blood glucose/insulin). Serum creatine kinase elevation is suggestive of muscle disease.

An electrocardiogram (ECG) should be performed if cardiac disease (especially an arrhythmia) is suspected. Owners can be taught how to check and determine the heart rate and rhythm during an attack if the animal is normal at the time of examination. An ECG is often normal, and, therefore, ambulatory ECG (Holter) monitoring may be required. Blood pressure should be determined if cardiac disease and/or hypertension is suspected.

Lactate and pyruvate analysis can assist with some rare metabolic muscle diseases that are classified as mitochondrial myopathies. These disorders are genetic in nature and are characterized by accumulation of vacuoles of lipid, glycogen, and other metabolites within certain muscle fibers, abnormal urine organic acid and blood amino acid profiles, lactate and pyruvate elevations, and abnormal lactate and pyruvate ratios.

Endocrine

Adrenal and thyroid function tests may be indicated in some cases. Measurement of insulin (with glucose) after fasting or at the time of an event is required if insulinoma or another hypoglycemia-causing tumor (e.g., gastric leiomyoma) is suspected.

Serology

Measurement of acetylcholine receptor antibodies is essential in dogs with suspected myasthenia gravis (MG) or in those with acquired megaesophagus. Serology may also be of value if specific infectious diseases are suspected.

Cerebrospinal Fluid Analysis

Cerebrospinal fluid (CSF) analysis is of limited value unless there is a high index of suspicion of a neurologic disease. CSF analysis rarely contributes unless there is a diffuse infectious or inflammatory disease of the central nervous system.

Electrophysiology

If neuromuscular disease is suspected, electrophysiologic investigation may help confirm the suspicion. Electromyogram (EMG) insertion activity can help confirm muscle or nerve disease and help differentiate muscular from axonal disease. Nerve conduction velocity might provide more definitive information with neuropathies.

Imaging

Dogs with suspected cardiac disease require echocardiography; plain radiographs of the thorax can help

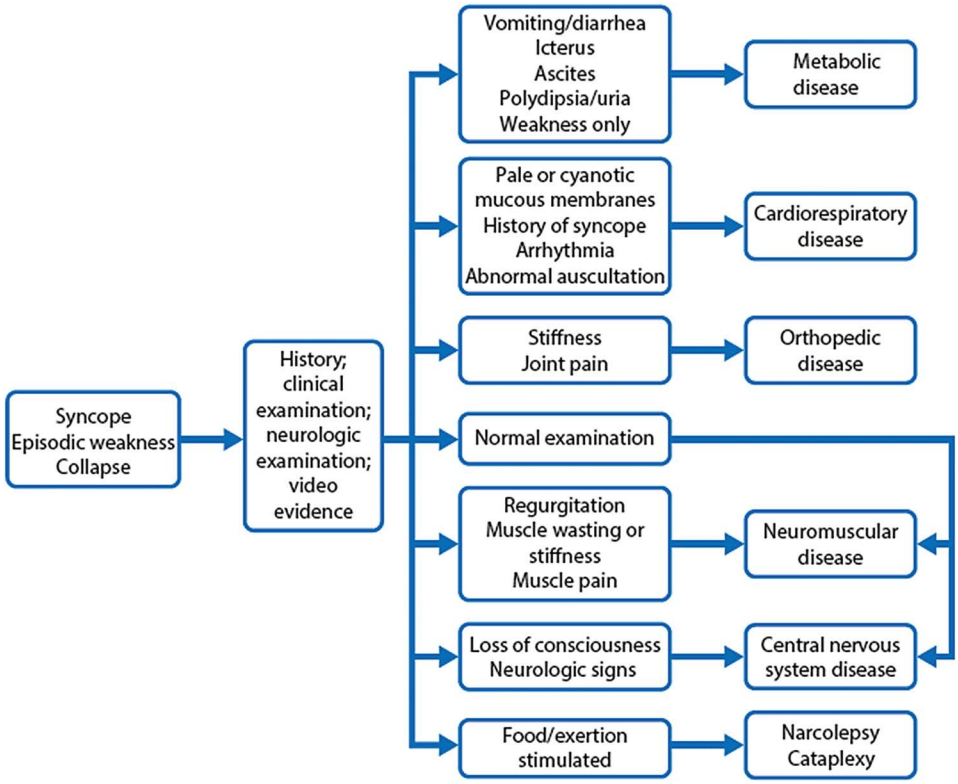


FIGURE 2.16.1 Algorithm for the general approach to the differential diagnosis of syncope, episodic weakness, and collapse.

if cardiorespiratory disease or megaesophagus is suspected. Contrast radiography or fluoroscopy can determine esophageal dilatation/function. Individual cases may have indication for CT/MRI investigation.

Muscle/Nerve Biopsy

Muscle biopsy is of particular value for the diagnosis of the inherited myopathies. Nerve biopsy can confirm axonal degeneration/regeneration, demyelination, and

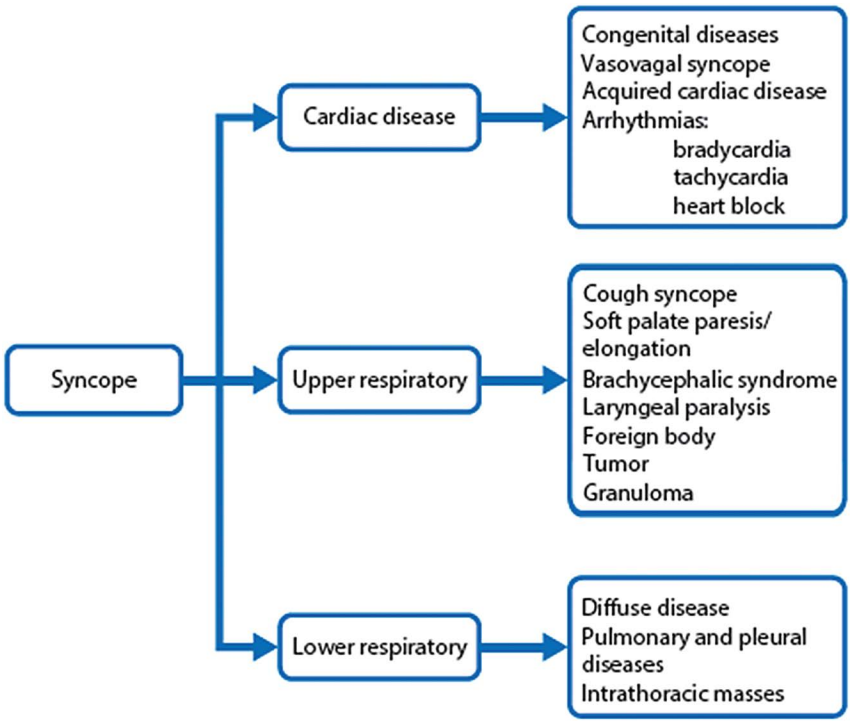


FIGURE 2.16.2 Algorithm for syncope.

TABLE 2.16.2 Differential diagnosis of weakness

Endocrine diseases	– Insulinoma – Hypoadrenocorticism – Hyperadrenocorticism (Cushing's myopathy) – Hypothyroidism (myopathy, neuropathy) – Hypoparathyroidism – Pheochromocytoma – Diabetes mellitus / ketoacidosis
Orthopedic diseases	– Degenerative joint disease (hips, stifles, spondylosis) – Polyarthritis – various types
Hematologic diseases	– Anemia – all causes – Myeloproliferative disease – Polycythemia – Hemoglobinopathies
Metabolic diseases	– Uremia – encephalopathy – Hyperglycemia / hypoglycemia – Hypernatremia / hyponatremia – Hypokalemia / hyperkalemia – Hypercalcemia / hypocalcemia – Acidosis – Hyperthermia – Hypoxia

Myopathies	– Inherited
	  – Labrador Retriever myopathy
	  – Sex-linked muscular dystrophies (dystrophin defects): Golden Retriever, Japanese Spitz
	  – Devon Rex cat myopathy
	  – Burmese cat hypokalemic myopathy
	  – Metabolic myopathies (e.g., pyruvate dehydrogenase deficiency)
	  – Myotonia
	  – Muscular dystrophies
	– Polymyositis
	  – *Infection:* Protozoan, viral, etc.
	  – Immune-mediated
	– Exertional myopathy
	– Malignant hyperthermia
	– Paraneoplastic (Lambert–Eaton syndrome associated with myasthenia gravis)
	– Nutritional
	– Endocrine–steroid, hypothyroid, hyperthyroid (cats)
	– Lipid storage myopathy
	– Miscellaneous
	  – Exercise-induced collapse (Labrador Retrievers)
	  – Ischemic myopathy (cat thromboembolism)

Neuromuscular junction	– Myasthenia gravis–acquired, congenital – Organophosphate toxicity – Tick paralysis – Snake bite (*Elapidae* and pit viper) – Botulism
Neurologic	– Episodic falling (Cavalier King Charles Spaniel) – Scottie cramp (also other breeds: Jack Russell, Norwich Terrier) – Narcolepsy / cataplexy (breed association) – Polyradiculoneuritis (Coonhound paralysis) – Inherited breed specific neuropathies – Motor neuron diseases – Endocrine (hypothyroid, insulinoma/ hypoglycemia, hyperlipidemia) – Neoplastic / paraneoplastic diseases – Distal denervating diseases – Lysosomal storage diseases – Axonopathies (e.g., Boxer)

fibrosis, findings that have diagnostic and/or prognostic significance.

Edrophonium Response

Slow intravenous administration of an ultrashort-acting anticholinesterase (0.1–1.0 mg edrophonium hydrochloride [Tensilon®]; note that this drug is no longer available in the United States and many other countries) is used for the diagnosis of MG. In dogs and cats with MG, there is a rapid improvement in the ability to exercise for several minutes.

Blood Gas Analysis

Blood gas analysis can assist with some cardiorespiratory diseases (hypoxemia) and some metabolic myopathies (metabolic acidosis with exercise).

Genetic Tests

Molecular (DNA) diagnostic testing is available for some inherited diseases (e.g., Burmese cat hypokalemic polymyopathy, Labrador Retriever myopathy, Japanese Spitz myopathy, narcolepsy). Your diagnostic laboratory should be consulted, or an internet search made for information on what diagnostic tests are available for that breed if you suspect a familial link.

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CHAPTER 2

Common Clinical Problems
CHAPTER 2.17 Vomiting

Frédéric Gaschen

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INTRODUCTION

Vomiting is characterized by the forceful oral ejection of gastric content with or without addition of small intestinal content.

The vomiting response can be divided into three sequential phases. The prodromal phase is characterized by nausea with licking of the lips, yawning, hiding, and depression and occurs with hypersalivation and excessive swallowing. This is associated with relaxation of the lower esophageal sphincter and proximal part of the stomach. The second phase is retching, with retrograde giant small intestinal contractions that bring jejunal and duodenal chyme (and bile) back into the gastric lumen if the pylorus is patent, followed by rhythmic retching, inhibition of salivation, activation of the intercostal muscles, protection of the airways by laryngeal elevation, and increased upper esophageal sphincter tone. Finally, during the final expulsion phase, the cervical esophageal and pharyngeal tones decrease, the lower esophageal sphincter relaxes, the rectus abdominis muscle contracts, and the diaphragm squeezes the stomach. Breathing is momentarily inhibited, and the glottis is closed while the gastric content is propelled into the esophagus and ultimately out of the mouth.

Regurgitation, dysphagia (associated with oral and pharyngeal diseases), and coughing/gagging may be misinterpreted as vomiting by pet owners. Regurgitation is the passive oral evacuation of esophageal content associated with esophageal dysmotility, obstruction, and/or dilation (see Chapter 2.14 on Regurgitation). Typically, retching does not occur with regurgitation. Moreover, overall, regurgitation is less commonly observed because esophageal diseases are less common than disorders that trigger vomiting.

PATHOPHYSIOLOGY

The vomiting or emetic center is a conglomerate of nuclei located in the medulla oblongata. Vomiting can be elicited by activation of neural or humoral pathways. The emetic center is closely associated with the chemoreceptor trigger zone (CRTZ), an area lacking a blood–brain barrier where receptors are in direct contact with circulating blood. Stimulation of the CRTZ by blood-borne emetogenic substances (e.g., uremic toxins, endotoxins, drugs) is the basis of the humoral pathway of emesis. The emetic center may also be stimulated by the vestibulocochlear nucleus (e.g., motion sickness) and cortical centers. Additionally, it receives direct input from the peritoneum and abdominal organs via nerve fibers traveling with the vagus nerve, which constitutes the neural pathway of vomiting (Figure 2.17.1). The emetic center is responsible for the coordination of the vomiting

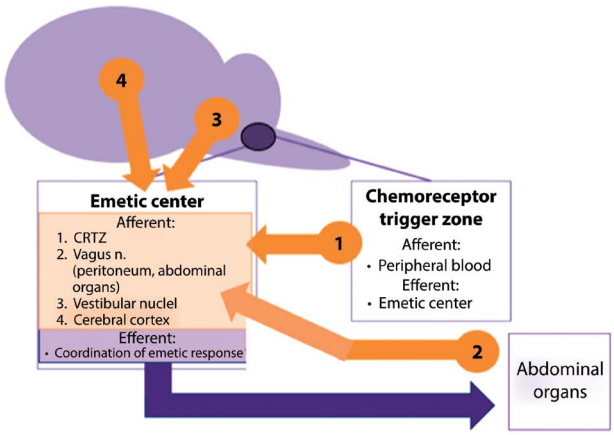


FIGURE 2.17.1 Afferent and efferent pathways to and from the emetic center and chemoreceptor trigger zone.

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TABLE 2.17.1 Antiemetic drugs most commonly used in dogs and cats and their target receptors

Antiemetic drug	Target/antagonism	Dose and route	Other effects
Maropitant	NK1 receptors: Substance P antagonist	1 mg/kg per day SC or slowly IV (over 1–2 minutes)	
Metoclopramide	Dopamine2 receptor (D)	0.3–0.5 mg/kg SC q.8h. or 1–2 mg/kg CRI q.24h. (D)	Prokinetic effects on gastric antrum
Ondansetron	5-HT3 receptors in the CRTZ and afferent nerves	0.5–1 mg/kg slowly IV, p.o. q.8–12h. (D); 0.1–1 mg/kg slowly IV, IM, SC, p.o. q.6–12h. (C)	

C, cat; CRI, constant rate infusion; D, dog. If not specified, applies to both dogs and cats.

effort through efferent pathways. Numerous receptors are involved in the stimulation of vomiting, and some are the targets of antiemetic drugs (Table 2.17.1).

DIFFERENTIAL DIAGNOSES

A wide range of diseases may cause vomiting in dogs and cats through direct stimulation of the emetic center via afferent vagal branches or indirectly via stimulation of the CRTZ (Table 2.17.2). Diseases of the gastrointestinal (GI) tract generally act directly on the vomiting center through the neural pathway, while systemic disorders such as kidney diseases often stimulate the CRTZ via the humoral pathway.

CLINICAL APPROACH

Acute Vomiting

It is likely that many dogs and cats that experience a few episodes of acute vomiting are not presented for veterinary examination because the problem is self-limiting. If presenting to a veterinarian, acutely vomiting animals should be assessed for the severity of disease. A few episodes of vomiting in the absence of complications such as dehydration in an otherwise healthy animal may not require any further investigations or treatment, even though a bland diet and possible empirical prescription of antiemetics may be of benefit. However, dogs and cats that are ill need to undergo more detailed examination and investigations.

The most relevant differential diagnoses may differ on the basis of the animal's signalment. Younger animals are more prone to infectious diseases, such as parvovirus infection in dogs, and to ingestion of foreign objects.

A detailed history should be obtained. Important questions include diet, environment, duration and frequency of vomiting, relationship to eating, description of the vomiting process, appearance of the vomitus (e.g., presence of bile [Figure 2.17.2], hairballs [Figure 2.17.3], hematemesis (see Chapter 9, Digestive Diseases, Figure 9.26) frank blood, behavioral changes, and coexisting clinical signs, as well as previous illnesses, deworming history, and current medications. This information helps confirm the existence of vomiting, assess the disease severity, and may yield valuable data about any underlying disease(s).

TABLE 2.17.2 Common causes of vomiting in dogs and cats and their anatomic origin

Gastrointestinal	Outside gastrointestinal tract
Stomach – *Obstructive:* Gastric foreign body, space-occupying lesion in pylorus – Adverse reaction to food, including dietary indiscretion – *Infectious:* Viral, bacterial, parasitic – *Toxic:* Drugs, plants, chemicals – Chronic gastritis – Gastric neoplasia – Gastric ulcer – Gastric motility disorder	**Abdominal** – Acute and chronic recurring pancreatitis – Diseases of liver and biliary tree – Peritonitis – Diaphragmatic hernia – Neoplasia – Pyometra
Small bowel – *Infectious:* Viral, bacterial, parasitic – *Obstructive:* Foreign body, intussusception, space-occupying lesion – Adverse reaction to food, including dietary indiscretion – *Toxic:* Drugs, plants, chemicals – Inflammatory disease – Intestinal neoplasia – Paralytic ileus	**Metabolic** – Uremic syndrome – Electrolyte disorders – Acid–base disorders – Endocrine diseases – Hyperthyroidism (C), diabetic ketoacidosis, hypoadrenocorticism (D) – *Toxins:* Drugs, plants, chemicals – Sepsis, endotoxemia
Colon – Colitis – Severe constipation	**Neurologic** – Motion sickness – Vestibular disorders – Encephalitis/meningitis – Increased intracranial pressure – Psychogenic (excitation, fear, pain) – Dysautonomia

C, cat; D, dog. If not specified, applies to both dogs and cats.

A thorough physical examination should be performed. In cats particularly, it is important to visualize the sublingual frenulum by applying gentle dorsal pressure in the intermandibular space with a finger, searching for a piece of string looping around the base of the tongue at the origin of a linear foreign

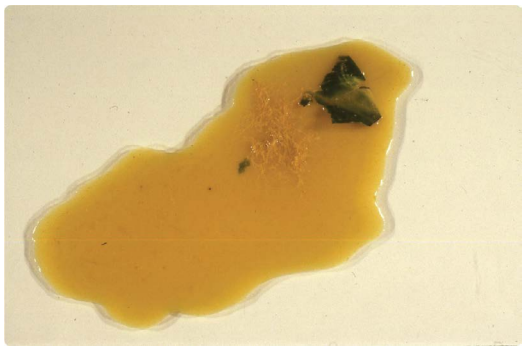


FIGURE 2.17.2 Canine vomit admixed with bile. (*Courtesy of M. Schaer.*)



FIGURE 2.17.3 Hairball vomited by a cat. (*Courtesy of M. Schaer.*)



FIGURE 2.17.4 A piece of thread (arrow) looped around the base of the tongue in a vomiting cat with a radiographic diagnosis of a linear foreign body. (*Courtesy of M. Schaer.*)

body (Figure 2.17.4). Abdominal palpation may reveal discomfort or pain (gastroenteritis, pancreatitis), or abdominal masses (foreign body, intussusception, granuloma, neoplasia). Hydration and cardiovascular status are important to guide the planning of fluid therapy.

In dogs presenting with acute vomiting, dietary indiscretion, GI foreign body, ingestion of toxic substances, and acute pancreatitis are the top four differential diagnoses and should be the focus of the initial diagnostic investigations (Figure 2.17.5). Gastric

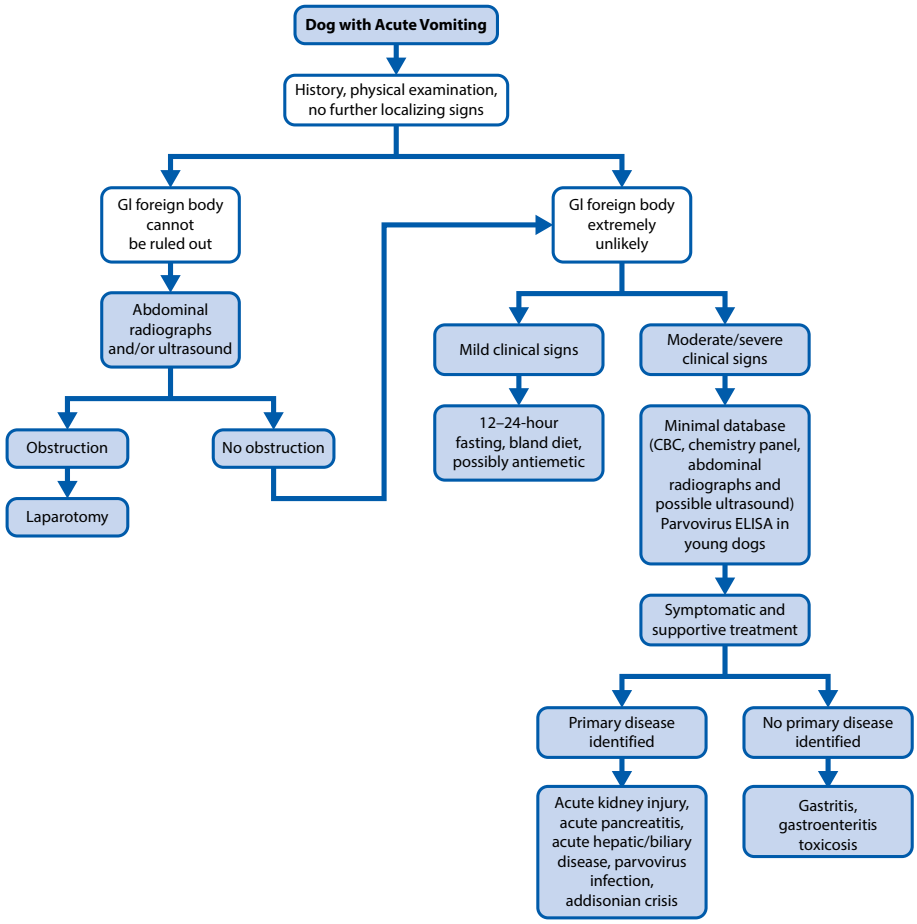


FIGURE 2.17.5 Algorithm for the clinical approach to acute vomiting in the dog after gastric dilatation-volvulus has been initially ruled out.

dilatation-volvulus (GDV) may be associated with vomiting, although the efforts are often unproductive. Moreover, abdominal distension with gastric tympany is often present and easily noticed. Abdominal radiographs are useful to evaluate gastric position and confirm the diagnosis of GDV. They are also necessary to rule out GI obstruction (two lateral views and a ventrodorsal view). Cats may ingest foreign bodies or chew on toxic plants; however, dietary indiscretion is less prevalent in this species, and pancreatitis is less commonly associated with significant vomiting.

Chronic Vomiting

Animals with chronic or chronic intermittent vomiting commonly have diseases affecting the digestive tract (including stomach, intestine, liver, and pancreas) or other organ systems such as the kidneys or the endocrine system. Sometimes, GI obstruction may take a more protracted course and should be ruled out by abdominal radiographs when supported by history and physical exam. Chronic vomiting is a more common presentation in cats (Figure 2.17.6). The search for an underlying cause is best started with a minimal database consisting of bloodwork (complete blood count [CBC], chemistry panel) and urinalysis to assess the function of various organ systems. A serum thyroxine level should be obtained in cats greater than 5 years old. Abdominal imaging (radiographs and/or ultrasound) can be carried out to assess the appearance of abdominal organs, including gastric and intestinal wall, kidneys, liver, and pancreas. If the primary problem cannot be identified based on the information obtained from the initial database, additional more specific tests can be performed in order to identify the primary problem. Cats may vomit chronically in the absence of any other problems (healthy chronic vomiters); this is sometimes associated with hairballs (Figure 2.17.3), but the cause often remains unknown. However, cats vomiting once weekly or more frequently should be examined to rule out an underlying disease. Moreover, increases in the vomiting frequency and onset of additional clinical signs such as hyporexia or weight loss also justify further investigations.

Treatment

Treatment of vomiting dogs and cats needs to focus on three points: (1) Stopping the vomiting process with judicious use of antiemetics (Table 2.17.1), particularly when vomiting is acute or frequent with debilitating consequences, (2) correcting the fluid and electrolyte deficits resulting from vomiting, and (3) addressing the underlying disease at the origin of vomiting.

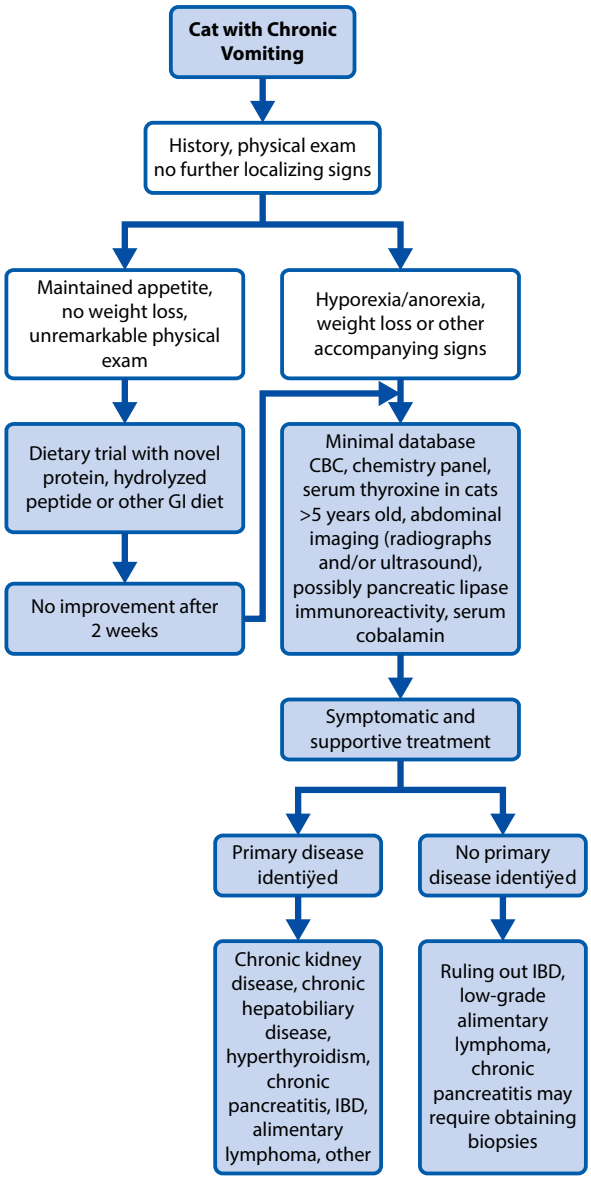


FIGURE 2.17.6 Algorithm for the clinical approach to chronic vomiting in the cat. IBD, inflammatory bowel disease.

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SECTION

II

DIAGNOSTIC TECHNIQUES



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CHAPTER 3

Approach to Thoracic Radiographs

L. Abbigail Granger

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BASICS OF THORACIC RADIOGRAPHY

Technique and Positioning

Choosing Thoracic Views

The effect of recumbency on lesion conspicuity requires consideration when selecting appropriate views to obtain of the thorax. The views chosen to complete a thoracic study impact visibility of pulmonary lesions due to recumbency-associated atelectasis. Given that most pulmonary lesions result in an increase in pulmonary opacity, requiring adjacent aerated lung to recognize, the effect of recumbency on lesion conspicuity is especially evident when clinical suspicion is present for aspiration or bronchopneumonia, pulmonary bullae, any unilateral or focal pulmonary disease, or when radiographs are obtained as a screening for metastasis (Figure 3.1a–c). As exact diagnosis is often unknown at the time of imaging due to overlapping clinical signs, many radiologists advocate 3- or 4-view thoracic studies, to include both lateral views and an orthogonal view as standard of care.

Positioning

To obtain a lateral view, position the animal in right or left recumbency and extend forelimbs as far as possible to remove superimposition over the cranial thorax. To avoid obliquity, a radiolucent positioning device such as a foam wedge is often needed at the level of the sternum, especially in deep-chested dogs. Rely on palpable

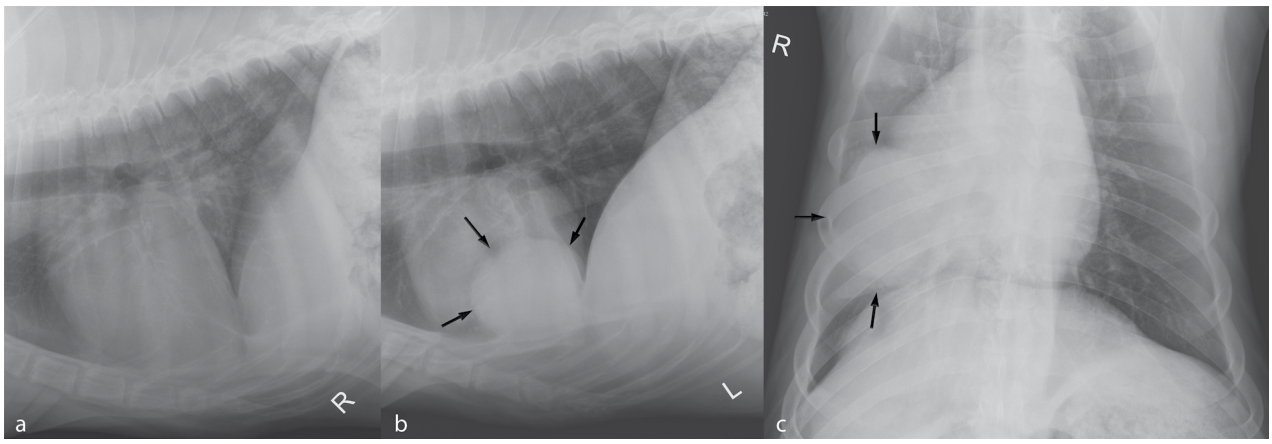


FIGURE 3.1 Right lateral (a), left lateral (b), and ventrodorsal (c) thoracic radiographs of a dog having a pulmonary mass. In spite of the large size of the mass (b and c, black arrows), it is nearly invisible on the right lateral view, while being well identified on the left lateral view. This variation in visibility of the mass with recumbency is due to poor aeration in gravity-dependent lungs when the dog is positioned on its right side, indicating that the mass is also right-sided. The mass is highlighted by adjacent aerated lung when the dog is positioned on its left side, making the mass clearly visible. The location of the mass as being right-sided is confirmed on the ventrodorsal view.

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landmarks to appropriately center and collimate each view. Easily palpable landmarks include the thoracic inlet cranially and the proximal aspect of the 13th ribs caudally. The collimated beam should be centered at the caudal angle of the scapula, which is typically in the same plane as the central heart when forelimbs are extended (Figure 3.2a–c). The ventrodorsal or dorsoventral views should also be obtained with forelimbs extended with a radiolucent trough being an option to assist with positioning (Figure 3.3a–d). Sandbags, tape, and radiolucent wedges should be used to properly position patients and avoid personnel exposure. The entire thorax should be included each view, including the spine and the sternum. In some cases, patients are too large to fit onto one field of view and will require a cranial and caudal view. In such cases, it is also useful to obtain a view centered at the heart, especially when cardiac disease is a concern.

Exposure and Timing

Thoracic views should routinely be exposed on peak inspiration in order to maximize inherent contrast, using a low milliampere-seconds (mAs)/high kilovoltage peak (kVp) technique to reduce respiratory motion. Motion can also be limited by use of sedation. If full anesthesia is required, the patient must be intubated and the views obtained under positive pressure in order to avoid confounding results created by atelectasis, which can occur within 5 minutes when 100% inspired oxygen is used.

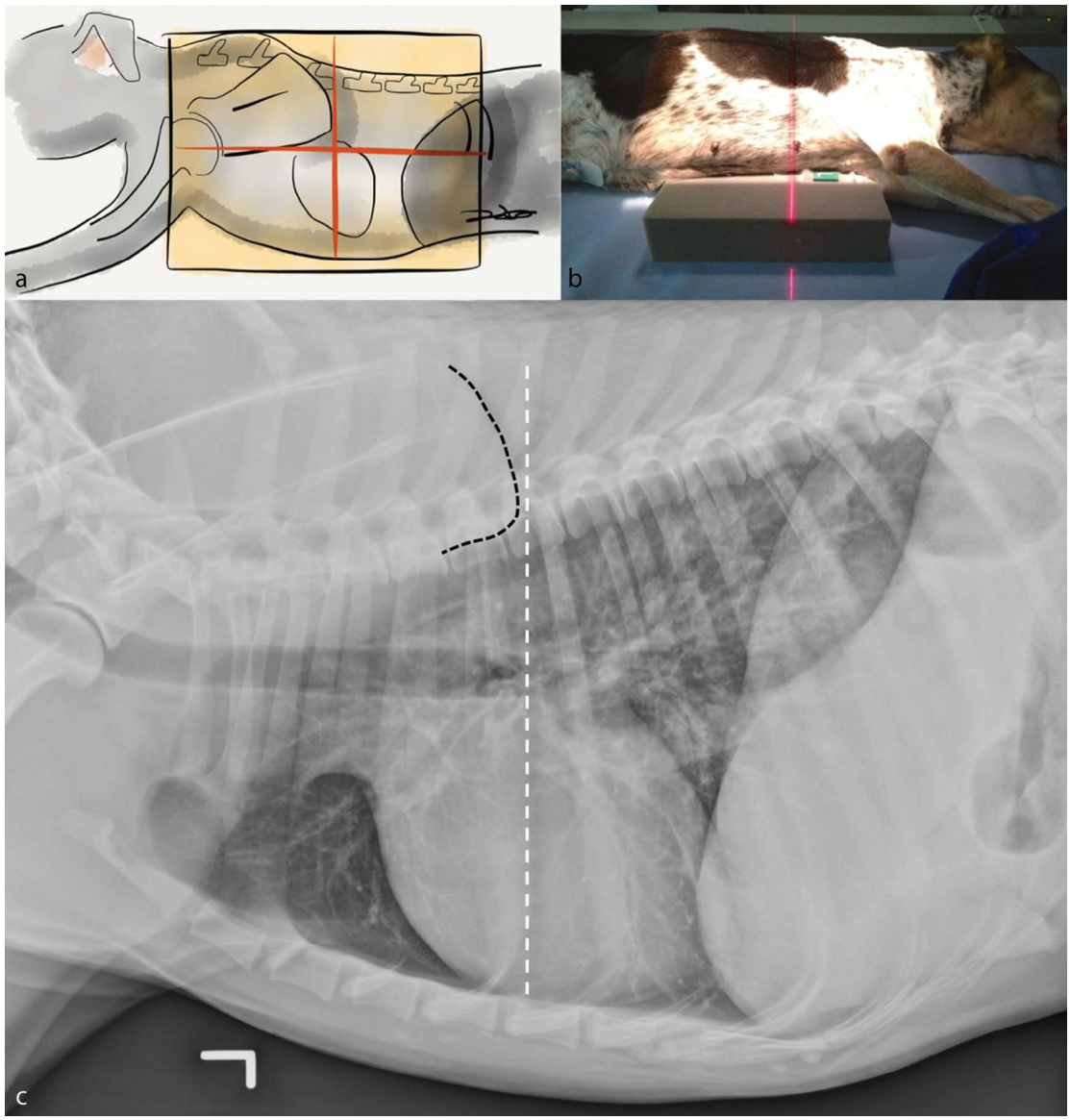


FIGURE 3.2 Palpable landmarks and positioning for a lateral thoracic view. The caudal angle of the scapula is a reliable landmark for centering the beam over the heart, as shown in (a) and (b). To correctly use this landmark and to limit superimposition over the cranial lungs, the forelimbs must be extended, as shown in part (c). A foam wedge is essential to preventing obliquity, in most cases. Radiographically the caudal angle of the scapula (dashed black line) is superimposed near the center of the heart (dashed white line).

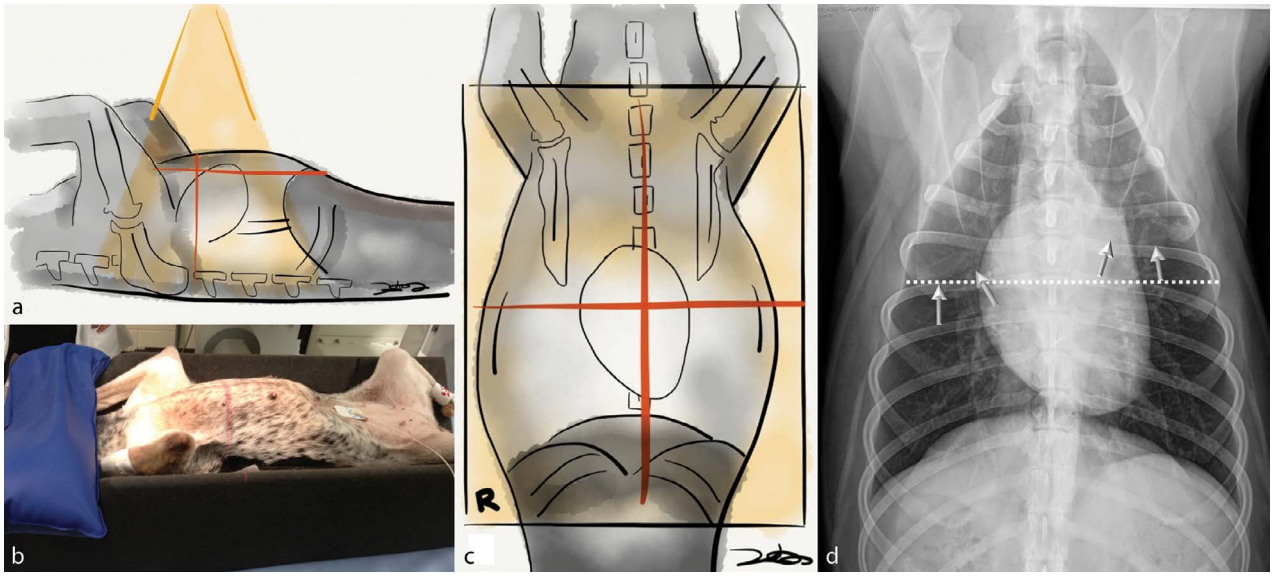


FIGURE 3.3 Positioning **(a–c)** to obtain a ventrodorsal view **(d)**. The thoracic inlet and the proximal aspect of the caudal ribs should be included to ensure all lungs are in the field of view. The view should be centered at the caudal angle of the scapula, a palpable landmark for the heart when forelimbs are extended. To avoid obliquity, a trough may be used, as shown in part (b). Sandbags can be used to avoid personnel exposure. On the ventrodorsal radiograph (d), the caudal margin of the scapulae (arrows) is superimposed near the plane of the center of the heart when the view is appropriately collimated and centered (dotted white line).

READING THE THORACIC RADIOGRAPH

Systematic Approach

Some indications for obtaining thoracic radiographs are listed in Table 3.1, and the influence of recumbency on the appearance of thoracic structures is detailed in Table 3.2. A systematic approach to interpreting thoracic radiographs will prevent the interpreter from seeking only an answer for the specific indication of the study and is essential to preventing abnormalities going undetected that may or may not relate to the presenting clinical complaint. A systematic approach also increases comfort level for interpretation of radiographic studies. A standardized protocol of thoracic views with each view being oriented and reviewed the same way each time allows the benefit of repetition to form a method that is thorough and more rapid than an approach that is haphazard and steered only towards viewing organs specifically associated with the indication for the study. All radiographic studies must be approached in the same way, analogous to completing a checklist of anatomical structures, as shown in Box 3.1.

Description

When an abnormality is detected during systematic evaluation of an imaging study, it must be described. The classic approach to radiographic description uses a list of signs: Size, shape, location, number, margination, and opacity. These can be used to prompt the interpreter of characteristics to consider when describing apparent lesions. Evaluating a lesion with respect to these descriptors ensures that the interpreter processes the abnormality thoroughly and has a starting point for researching causes of any lesions. These morphological descriptions are essential to recognizing abnormalities and differentiating their causes.

INTERPRETATION OF THORACIC ABNORMALITIES

1. Extrathoracic Structures

Extrathoracic structures should be evaluated early during interpretation, as the complexity of interpreting anatomy within the thorax can distract from investigating extrathoracic structures. The presence or lack of symmetry of the thoracic wall should be noted on the ventrodorsal/dorsoventral view. Oftentimes, enough of the abdomen is included to determine presence of cranial organomegaly or loss of detail. Regardless of whether lesions located in extrathoracic structures are related to clinical signs, they can influence appearance of structures within the thorax and should be noted prior to assessment of intrathoracic abnormalities.

Superficial Soft Tissues and Skeleton

Thoracic boundaries include the intercostal and paraspinal muscles, ribs, spine, diaphragm, and thoracic inlet. Opacities comprising the thoracic wall include soft tissue, fat, and mineral, and their appearance can vary based on conformation and body condition score. Lesions within the thoracic wall can be categorized as congenital or acquired. Additionally, acquired

TABLE 3.1 Indications for thoracic radiography

Indication	Associated clinical signs or history	Some common differential diagnoses

Thoracic barrier abnormality	– Palpable or visible defect
	– Thoracic wall pain
	– Known trauma
		– Rib or soft tissue thoracic wall mass
		  – Neoplasia
		  – Lipoma
		  – Sarcoma
		  – Abscess/cellulitis
		  – Trauma
		  – Migrating foreign body
		– Trauma
		  – Rib fracture
		  – Hematoma
		– Congenital malformation

Respiratory disease	– Cough
	– Dyspnea/tachypnea
	– Cyanosis
	– Exercise intolerance
	– Syncope
	– Altered respiratory sounds
		– Tracheobronchitis
		  – Inflammatory/allergic
		  – Infectious (viral, bacterial, parasitic)
		– Tracheomalacia/bronchomalacia
		– Bronchopneumonia/aspiration
		– Bronchiectasis
		– Tracheal hypoplasia
		– Cardiogenic edema
		– Noncardiogenic edema
		  – Near drowning
		  – Strangulation
		  – Electrocution
		  – Toxicity/drug reaction
		  – Neurogenic
		  – Barotrauma
		  – Acute lung injury (ALI) or acute respiratory distress syndrome (ARDS)
		  – Re-expansion pulmonary edema
		  – Aspiration of irritant
		  – Overhydration
		  – Vasculitis
		  – Uremic pneumonitis
		– Upper airway obstruction
		  – Tracheal/bronchial foreign body
		  – Mural abnormality
		  – Extramural compression by mass or cardiac enlargement
		– Interstitial infiltration
		  – Pneumonitis
		  – Inflammatory/allergic
		  – Infectious
		  – Neoplasia (e.g., lymphoma)
		– Pulmonary mass(es)
		  – Neoplasia
		  – Abscess
		  – Granuloma
		  – Cyst
		  – Hematoma
		– Pulmonary fibrosis
		– Hemorrhage
		– Lung lobe torsion
		– Anomaly
		  – Kartagener's syndrome or ciliary dyskinesia
		  – Surfactant deficiency

Cardiovascular disease	– Audible murmur
	– Dyspnea/tachypnea
	– Exercise intolerance
	– Syncope
	– Cough
	– Altered respiratory sounds
	– Cyanosis
	– Arrhythmia
		– Acquired cardiac diseases
		  – Endocardiosis
		  – Cardiomyopathy
		  – Heartworm infection
		– Congenital cardiac diseases
		  – Intra- and extracardiac shunts (L → R or R → L)
		  – Valvular malformations
		– Pericardial disease/effusion
		– Cor pulmonale

(*Continued*)

TABLE 3.1 Indications for thoracic radiography (*Continued*)

Indication	Associated clinical signs or history	Some common differential diagnoses

Pleural disease	– Dyspnea/tachypnea
	– Exercise intolerance
	– Altered respiratory sounds (decreased)
	– Decreased audibility of heart
		– Pleural effusion
		  – Transudates
		  – Exudates
		  – Hemorrhage
		  – Chyle
		– Pneumothorax
		– Diaphragmatic rupture
		– Pleural mass

Mediastinal disease (noncardiac)	– Regurgitation/dysphagia
	– Dyspnea/tachypnea
	– Exercise intolerance
	– Altered respiratory sounds
		– Megaesophagus – generalized
		  – Metabolic
		  – Congenital
		  – Esophagitis
		– Focal esophageal dilation – esophageal obstruction
		  – Luminal foreign body
		  – Mural lesion
		  – Extraluminal compression
		  – Vascular ring anomaly
		  – Hiatal herniations
		– Mediastinal mass
		  – Lymph node (lymphoma)
		  – Thymus
		– Tracheal compression/obstruction
		– Pneumomediastinum
		– Mediastinitis

Trauma	– Dyspnea/tachypnea – Altered respiratory sounds – Thoracic wall pain – Palpable or visible thoracic wall defect	– Pulmonary contusions – Rib fractures – Pneumomediastinum – Pneumothorax and/or pleural hemorrhage – Shock – Diaphragmatic rupture
Systemic disease	– Fever – Lethargy – Weight loss – Neoplasia	– Numerous potential causes
Screening test	– Geriatric patient – Pre-anesthetic	– Maybe none
Monitor response to treatment	– Improved or worsened clinical signs	

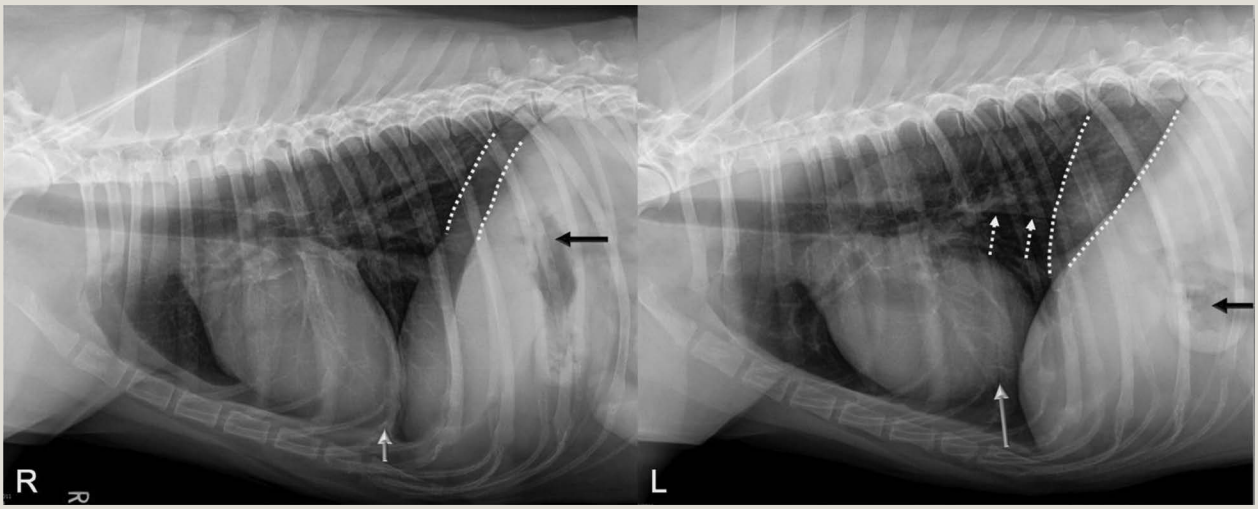
abnormalities can be further categorized as traumatic or nontraumatic and as originating from skeleton versus soft tissue.

Congenital thoracic wall abnormalities include vertebral body malformations, transitional vertebrae, and sternal anomalies, such as pectus excavatum or carinatum. Most of these abnormalities do not create clinical signs requiring correction but can affect the overall appearance of intrathoracic structures, especially if the abnormality alters cardiac position or pulmonary inflation potential.

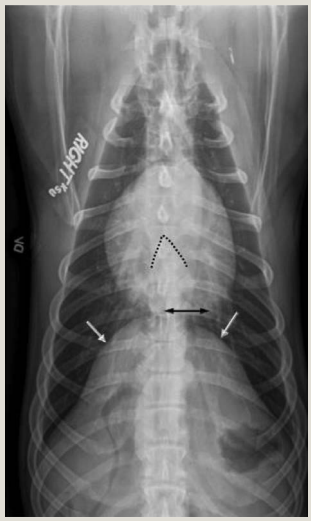
Differential diagnoses for thoracic wall mass are typical of a mass at any location and include neoplasia (skeletal or soft tissue), abscess/cellulitis, hematoma, granuloma, and cyst. Ranking of these differential diagnoses is based on full description of the abnormality along with clinical history. Neoplasia, cellulitis/abscess, and hemorrhage/hematoma formation are the three most likely causes of a thoracic wall mass.

Lipomas are the most common thoracic wall neoplasms. Most often, these are benign, slow-growing, well-demarcated nodules or masses that are located in the subcutaneous soft tissues, recognized by their fat opacity rather than soft tissue opacity. Nonlipomatous, focal, acquired nodules or masses associated with the thoracic wall may be soft tissue or mineral opaque. They may be broad-based (sessile) or have a stalk-like attachment to the thoracic wall (pedunculated). Neoplastic thoracic wall lesions are most often sarcomas originating from ribs, with primary osteosarcoma and chondrosarcoma being the most common. Radiographically visible rib lysis or periosteal proliferation are indicators of aggression (Figure 3.4a–c). Care must be taken to correctly categorize a lesion as originating within

TABLE 3.2 Influence of recumbency on the appearance of thoracic structures

Lateral view	
Right	**Left**
	

– Heart more elongated (apex contacts sternum, white arrow)
– Diaphragmatic crura parallel (dotted line)
  – Right crus more cranial
– Gas located in gastric fundus (black arrow)
– Esophagus often not visible
– Assess left-sided lungs
	– Heart more rounded (apex can appear elevated, white arrow)
	– Diaphragmatic crura diverge (dotted line)
	  – Left crus more cranial
	– Gas located in pylorus (black arrow)
	– Esophagus more readily seen (dotted arrow)
	– Assess right-sided lungs

Ventrodorsal/dorsoventral view	
Ventrodorsal	**Dorsoventral**
	
– Diaphragmatic crura seen (white arrows) in addition to the central cupola – Increased distance between cardiac apex and diaphragm – Heart elongated – Apex closer to midline (black double arrow) – Increased apparent divergence of principle bronchi (dotted line) – Accessory lung lobe better aerated and better assessed – Caudal vena cava better seen	– Only the cupola of the diaphragm is seen, creating a dome shape (white arrows) – Contact between diaphragm and cardiac apex – Heart rounded – Apex positioned further to left (black double arrow) – Position of principle bronchi less divergent (dotted line) – Caudal lung lobes better aerated and better assessed – Caudal lobar vessels better seen

Box 3.1 Systematic evaluation of the thorax

- Extrathoracic structures
  - Superficial soft tissues (skin, fat, muscle)
  - Skeleton (spine, sternum, ribs, visible forelimbs)
  - Diaphragm
  - Visible abdomen
- Pleural space
- Noncardiac mediastinum
  - Mediastinal reflections
  - Trachea
  - Esophagus*
  - Vascular structures (aorta, caudal vena cava, azygous*, etc.)
  - Thymus†
  - Sternal, cranial mediastinal, and tracheobronchial lymph nodes*
  - Lymphatics*
- Heart, great vessels, and pericardium
- Lungs
  - Airway (bronchi, bronchioles*, and alveoli*)
  - Pulmonary arteries and veins
  - Interstitium (elastic fibers, collagen, fibroblasts, smooth muscle, mast cells, mononuclear cells)

* Structures not radiographically visible in a normal animal.
† Structure not normally visible in a mature animal.

the thoracic wall rather than within lung, as differential diagnoses appropriate to the organ of origin must be assigned. Lesions extending into the thorax may be mistaken as having a pulmonary organ of origin. Lysis or periosteal proliferation of the skeleton of the thoracic wall is evidence of a thoracic wall lesion. Also, the presence of an extrapleural sign can differentiate mass lesions as being associated with thoracic wall rather than pulmonary. An extrapleural sign occurs when the margin of a thoracic wall lesion has a broad-based contact with the wall, and an obtuse angle is formed between the lesion and the normal pleural surface. This localizes a lesion to the extrapleural space, to include any structure superficial to the parietal pleura. A lung lesion would be expected to have a narrower point of contact, creating an acute angle between the mass and the thoracic wall. An extrapleural mass not located on tangent with the thoracic wall can create an apparent acute angle, falsely appearing pulmonary rather than extrapleural in origin (Figure 3.4a–c).

Most thoracic wall masses associated with neoplasia or infection are palpable on physical examination. The benefit of radiographic examination is to determine opacity and, therefore, potential tissue type of the mass, involvement of bone, or presence of intrathoracic extension.

In cases of trauma, hematoma formation may result in a soft tissue mass of the thoracic wall. The presence of concurrent rib fractures can also deform the thoracic wall, with serial and segmental rib fractures being most apt to create an alteration in thoracic shape on physical exam and radiographically, potentially resulting in paradoxical chest wall movement indicative of flail chest.

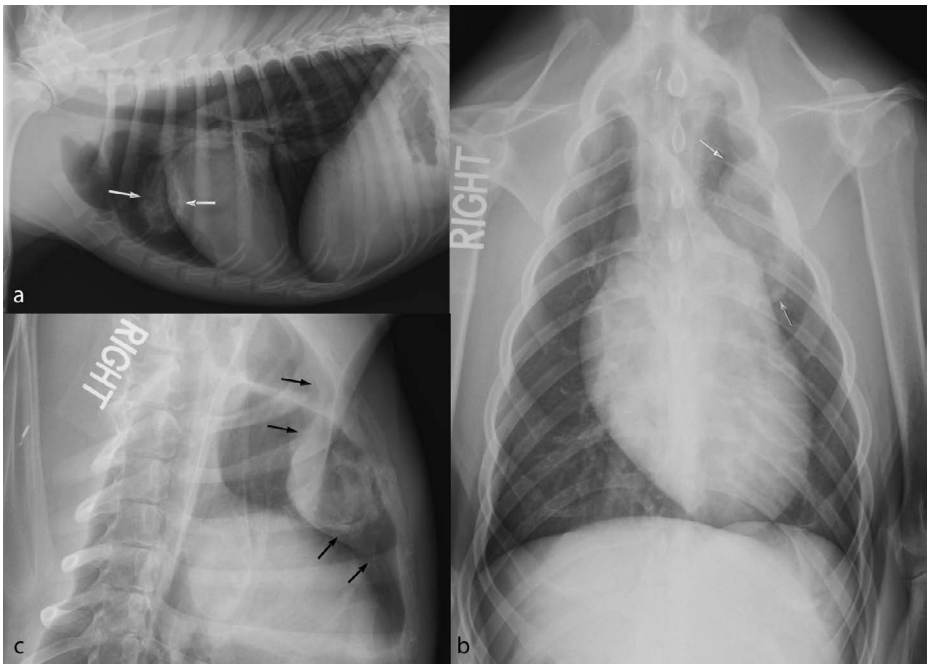


FIGURE 3.4 Extrapleural sign in a dog having chondrosarcoma of the left 3rd rib. A focal region of expansile rib lysis and surrounding mass are present within the left cranial thoracic wall (a and b, white arrows). On lateral and humanoid ventrodorsal projections **(a** and **b)**, the mass appears to have a narrow-based point of contact and creates an acute angle with the thoracic wall. On an oblique image obtained to view the lesion at its junction with the thoracic wall **(c)**, the soft tissue component of the mass is clearly broad-based, creating an obtuse angle between it and the thoracic wall (black arrows). The broad-based point of contact combined with the visible rib lysis confirms an extrapleural origin for the mass.

Diaphragm and Cranial Abdomen

The diaphragm defines the caudal thoracic boundary. On a normal thoracic study, the diaphragm should be positioned near the 11th or 12th thoracic vertebra on full inspiration. A diaphragmatic position cranial to this may indicate a technical failure to expose the view on inspiration and should be corrected, if so. If not due to technical factors, a cranially positioned diaphragm may be categorized as a primary disturbance of the diaphragm itself or secondary to abdominal or thoracic abnormalities. Primary diaphragmatic pathology is rare and includes unilateral or bilateral paralysis and malformation of the muscle itself (diaphragmatic eventration). Secondary causes may be related to increased abdominal mass or abnormalities within the lungs or pleural space. A caudally positioned diaphragm is typically not associated with any technical error, although extreme inspiration can result in a diaphragm that is positioned at T13 or caudally. Additional causes of a cranially or caudally positioned diaphragm are shown in Table 3.3. Diaphragmatic malpositioning may be unilateral or bilateral.

Loss of distinction of diaphragmatic margins is most often due to border effacement associated with pleural or pulmonary disease. If the diaphragm is effaced, its integrity should be questioned.

2. Pleural Space

The thoracic boundaries (thoracic wall and diaphragm) are lined by parietal pleura. The parietal pleura reflects onto itself dorsally to surround the right and left lungs forming a continuation, called the visceral pleura, that is tightly adhered to the lung surface. The two layers of pleura surrounding the right and left lungs form the pleural sacs. The pleural sacs each create boundaries of the mediastinum, which lies primarily on midline. The visceral pleura surrounding each lung lobe extends between each lobe as the lungs exit the hilus, creating fissures between each lobe that can be radiographically evident in cases of pleural disease.

Soft Tissue Opacity in the Pleural Space – Pleural Effusion

Pleural effusion is the accumulation of fluid within the pleural space. As the fluid volume exceeds 100 mL, it becomes radiographically evident in most dogs and cats. Several radiographic signs indicate the presence of pleural effusion as shown in Box 3.2 and Figure 3.5a, b. Oftentimes, multiples of these signs are present on each thoracic view, increasing support for diagnosis of pleural effusion. The visibility of each radiographic sign is more pronounced with increasing fluid volumes.

The position of the animal has an influence on the visibility of each of the radiographic signs presented in Box 3.2. First, pleural fissure lines are less prominently seen on the dorsoventral view than the ventrodorsal view. Also, the visibility of the cardiac silhouette varies with sternal or dorsal recumbency, as shown in Figure 3.6a, b. The heart is a soft tissue opaque, ventrally located structure. When the animal is placed in sternal recumbency, fluid within the pleural space moves ventrally and will surround the heart, causing border effacement of its margins. Oftentimes, the margins of the cardiac silhouette are readily visible when animals having pleural fluid are positioned in dorsal recumbency and a ventrodorsal view is obtained.

TABLE 3.3 Pathologic causes of unilateral or bilateral abnormal diaphragmatic positioning

Cranially positioned diaphragm	Caudally positioned diaphragm

– Study exposed on expiration
– Obese patient
– Abdominal mass effect
– Pulmonary atelectasis
– Upper airway obstruction
– Pain with inspiration
– Diaphragmatic paralysis (rare)
– Diaphragmatic eventration (rare)
	– Exaggerated inspiration
	– Air trapping (lower airway obstruction)
	– Pulmonary emphysema
	– Increased intrapleural/intrathoracic volume
	  – Pneumothorax
	  – Pleural effusion
	  – Thoracic mass(es)

Box 3.2 Radiographic signs indicating pleural effusion

- Separation of lungs from the thoracic wall by fluid opacity
  - Secondary decreased lung volume creating interstitial or alveolar pulmonary patterns
- Presence of pleural fissure lines that widen at the periphery seen on lateral and ventrodorsal views
- Blunting of the right and left costophrenic angles seen on the ventrodorsal view
- Scalloping of ventral lung margins on the lateral view(s)
- Border effacement of the mediastinum, heart, thoracic wall, and diaphragm
  - A hallmark of pleural effusion is effacement of the heart on the DV view and visibility of the heart on the VD view
- Increased thoracic diameter with severe fluid accumulations

Causes of Pleural Effusion

Pleural effusion could be due to primary pleural pathology or secondary to a systemic disease process. Since the causes of pleural effusion are numerous, categorizing differentials based on potential fluid type (transudates including modified transudates, exudates, hemorrhage, and chyle) can assist with considering differential diagnoses that can be a source of each. Causes for each of these types are shown in Table 3.4. The most common causes of pleural effusion in both dogs and cats are pyothorax, neoplasia, and cardiac failure. In many cases, the identification of the underlying cause of pleural effusion requires fluid analysis, systematic clinical workup, and advanced imaging such as thoracic ultrasound or computed tomography.

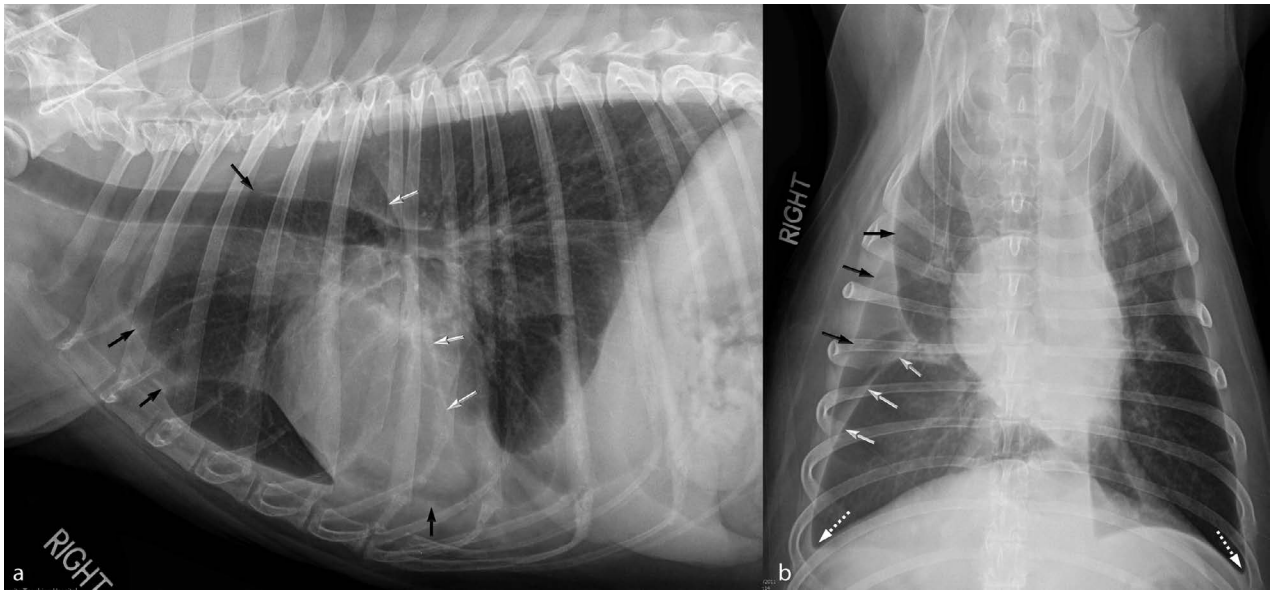


FIGURE 3.5 Right lateral **(a)** and ventrodorsal **(b)** views of a dog having moderate pleural effusion. There is separation of the lungs from the thoracic wall by fluid opacity (black arrows). Pleural fissure lines are present that widen at the peripheral aspect of the thorax further from the hilus (white arrows). The right and left costophrenic angles are blunted (dotted white arrows). Additionally, there is border effacement of the cardiac apex and ventral diaphragm on the lateral view (a). The presence of each of these findings will be more pronounced with increased fluid volumes.

Keys to Interpreting Cases with Pleural Effusion

Interpretation of thoracic studies having pleural effusion can be a challenge. Especially with moderate-to-severe fluid volumes, the visibility of soft tissue thoracic structures such as the heart, mediastinum, and pleural margins can be effaced, leaving many structures uninterpretable. In such cases, rely on clues that are visible in order to diagnose or at least rule out sources of pleural effusion, keeping in mind that pleural effusion is typically a secondary process, and nonpleural disease is often the cause of pleural effusion. Steps that can be used to investigate causes of pleural effusion are shown in Box 3.3.

Mediastinal masses often result in concurrent pleural effusion that can effectively efface the margins of the mass. An alteration in tracheal positioning, which remains readily distinct due to its being aerated, can be

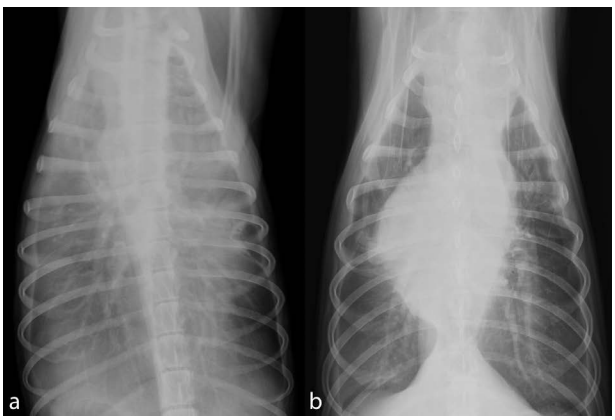


FIGURE 3.6 The mobility of fluid in the pleural space in sternal **(a)** and dorsal **(b)** recumbency. When an animal is positioned in sternal recumbency (a), gravity-dependent fluid accumulates ventrally and surrounds the ventrally located heart. Because the heart and fluid are of identical opacity and are in direct contact with each other, margins become effaced. When an animal is positioned in dorsal recumbency (b), the fluid accumulates dorsally. Lungs rise to the nongravity-dependent part of the thorax, which is ventral and surrounds the heart, making its margins evident.

TABLE 3.4 Causes of pleural effusion

Fluid type	Underlying causes
Transudates and modified transudates	– Congestive heart failure or systemic venous obstruction – Hypoproteinemia – Diaphragmatic translocation of peritoneal effusion – Diaphragmatic rupture – Neoplasia – Vasculitis – Lung lobe torsion – Pleuritis, mediastinitis
Exudates (septic/pyothorax or nonseptic inflammatory)	– Primary lung disease (pulmonary abscess or pneumonia) – Pleuritis, mediastinitis – Foreign body migration (grass awn)
Hemorrhage (hemothorax)	– Coagulation deficit – Trauma – Neoplasia
Chyle (chylothorax)	– Obstruction of lymphatic return (congestive heart failure, neoplasia) – Ruptured lymphatics (trauma, neoplasia)

Box 3.3 Next steps in analysis of cases with pleural effusion

- Obtain all four radiographic projections so that all lung fields, the mediastinum, and the cardiac silhouette can be best assessed
  - Ensure that the entire thoracic wall, including all ribs, are visible in the study
- When evaluating the radiographic study, pay close attention to the following:
  - Cardiac size and shape (need VD view)
  - Tracheal positioning for evidence of a cranial mediastinal mass
  - Ribs, sternum, and spine for evidence of an extrapleural lesion
  - Lungs for evidence of masses or nodules (all four views may be needed)
  - Bronchi for alterations in position or blunting, possibly indicating lung lobe torsion
  - Presence of a mediastinal shift in the face of bilateral pleural effusion indicating a thoracic mass or diaphragmatic rupture
  - Presence of abdominal disease at the edge of the study
  - Lung margination as being sharp or rounded
- Tap the fluid and repeat radiographic views
- Perform analysis of tapped fluid
- Perform thoracic ultrasonography or computed tomography

an indicator of a mass effect, regardless of the visibility of a mass itself. Marked deviation or compression of the trachea are indicators of potential underlying mediastinal mass effect, as shown in Figure 3.7a, b. In cases of pleural effusion, the trachea will elevate to some degree, but its path should remain straight with no focal changes in direction. Also, the tracheal hilus should be located at the 5th or 6th intercostal space in a normal animal or an animal having only pleural effusion. If a mediastinal mass is large enough, caudal displacement of the hilus may result. The cranial mediastinum is best assessed on the ventrodorsal view in cases of pleural effusion, as most masses are ventrally located and are effaced by any fluid located ventrally.

Primary or metastatic neoplasms resulting in pulmonary masses or nodules can be obscured by pleural effusion. In cases of moderate-to-severe pleural effusion, the lung volume will be decreased. This results in a secondary atelectasis and an increase in pulmonary opacity that is typically most severe in the cranial or right middle lung lobes. When atelectasis is severe, interpretation of lungs as normal or abnormal is impossible and can preclude visibility of masses and nodules. Additionally, border effacement of the heart, mediastinum, and thoracic wall by fluid can prevent interpretation of these structures. Removal of fluid and repeat radiographic examination can increase visibility of mass(es) within the thorax, as shown in Figure 3.8a, b. As with removal of any tissue, unless a diagnosis is known, the fluid sample should be analyzed for evidence of its underlying cause.

Soft Tissue Opacity in the Pleural Space – Diaphragmatic Rupture

Separation of the lungs from the thoracic wall by soft tissue opacity and border effacement of the diaphragm are most often caused by pleural fluid; however, these signs may be due to soft tissue rather than fluid. Diaphragmatic rupture must always be considered in thoracic studies where pleural soft tissue opacity is present and the diaphragmatic margins are effaced such that its integrity cannot be confirmed. In many cases

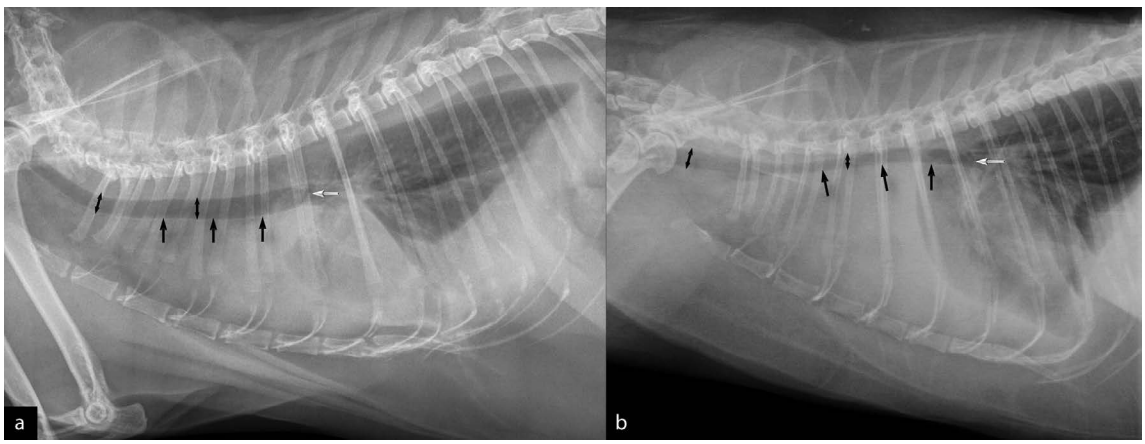


FIGURE 3.7 Lateral thoracic radiographs of a cat having only pleural effusion (a) and a cat having a mediastinal mass with concurrent pleural effusion (b). In the cat with pleural effusion, the trachea is mildly uniformly elevated (a, black arrows) due to the pleural fluid and the influence it has on lung and, subsequently, tracheal positioning. The tracheal hilus is in a normal position located at the junction between the 5th and 6th intercostal spaces (a, white arrow). Additionally, the tracheal lumen remains similar in diameter throughout its length (a, double-headed arrows). In the cat having concurrent pleural effusion and a cranial mediastinal mass, the trachea is markedly elevated and focally deviated in the region of the cranial mediastinum (b, black arrows). The trachea is compressed, as seen by a decrease in diameter at the level of the tracheal deviation (b, double-headed arrows). The tracheal hilus is also caudally displaced and is located at the center of the 7th intercostal space (b, white arrow).

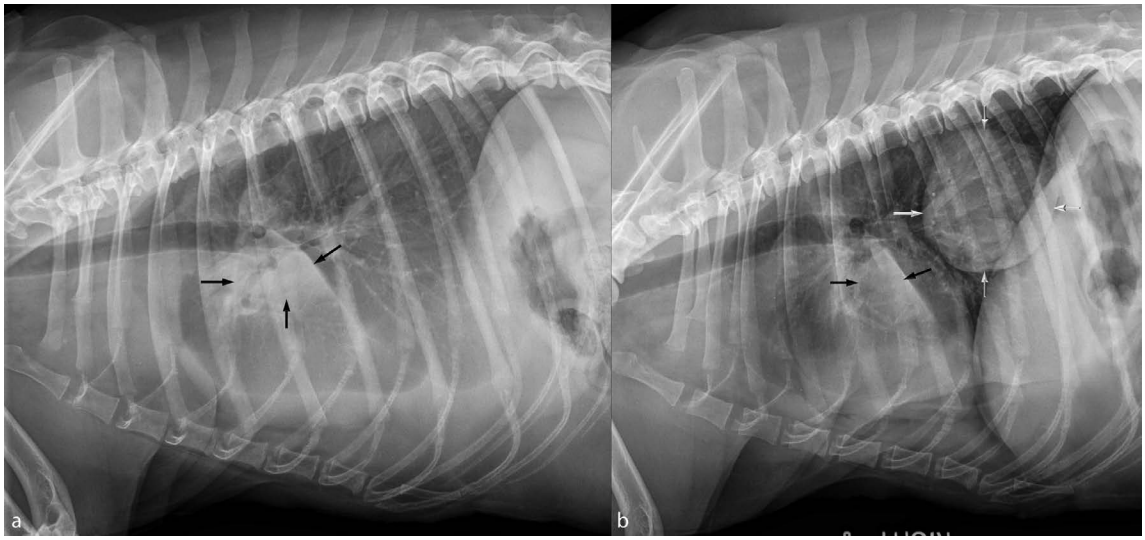


FIGURE 3.8 Right lateral views of the same dog before (a) and after tapping (b) pleural effusion that was secondary to a primary pulmonary carcinoma of the right caudal lung lobe. Prior to tapping (a), a pulmonary mass is not visible due to the presence of marked pleural effusion. A general increase in pulmonary opacity is present that is most severe near the tracheal hilus, where an alveolar pulmonary pattern is seen (a, black arrows). This is typical of the location for atelectasis when complete lung expansion is prevented by pleural fluid. After tapping the fluid, a well-defined, round mass within the caudal lung is clearly evident (b, white arrows). Cytologic fluid analysis was consistent with carcinoma. The region of atelectasis, though not completely resolved, is diminished (b, black arrows).

of diaphragmatic rupture, concurrent pleural effusion is present along with herniated abdominal organs, complicating radiographic confirmation of herniation. Several radiographic signs shown in Box 3.4 and Figure 3.9a, b raise suspicion of diaphragmatic rupture above that of pleural fluid occurring alone.

Soft Tissue Opacity in the Pleural Space – Pleural Masses

In addition to herniated abdominal organs, neoplasia or severe pleuritis can be responsible for pleural mass lesions. Oftentimes, concurrent, mobile pleural fluid is also present, resulting in border effacement of the pleural mass, rendering the soft tissue component invisible. Similar to diaphragmatic rupture with abdominal organ herniation, pleural masses due to neoplasia or pyogranulomatous pleuritis can be large enough to create a thoracic mass effect recognized as a deviation of the heart, trachea, or lungs away from the lesion (contralateral mediastinal shift). Again, the mediastinal shift may be the only indication of a pleural mass versus mobile pleural effusion that tends to distribute evenly.

Box 3.4 Radiographic signs indicating diaphragmatic rupture

- Partial border effacement of the diaphragm that is more prominent on one side versus the other
- Separation of lungs from the thoracic wall by soft tissue/fluid opacity that is more prominent in one hemithorax versus the other
- Contained tubular or round gas opacities within the thorax or crossing the diaphragm
- Decreased abdominal contents within peritoneal space
  - Absence of visible organs
  - Wasp-waist appearance to abdominal wall
- Cranially displaced gastric axis
- Evidence of pleural mass effect
  - Contralateral mediastinal shift with displaced heart and trachea away from the hemithorax having the most pleural opacity

Gas Opacity in the Pleural Space – Pneumothorax

Pneumothorax is accumulated gas within the pleural space between parietal and visceral pleura. It has multiple potential causes that are categorized as traumatic, spontaneous, or iatrogenic, as shown in Table 3.5. Pneumothorax may also be categorized as open or closed. An open pneumothorax implies a penetrating or perforating trauma with extension of air from the environment into the pleural space. Closed pneumothorax occurs when the respiratory system is the source of gas within the pleural space. Trauma is the most common underlying cause of pneumothorax and is the only category that can result both closed and/or open configurations.

Spontaneous pneumothorax is always closed and results from some extension of air from the respiratory system. It can be primary or secondary. Primary spontaneous pneumothorax occurs when there is no evidence of underlying pulmonary disease. In reality, most cases are assumed to be the result of a ruptured pulmonary bulla or bleb, which, of course, implies underlying

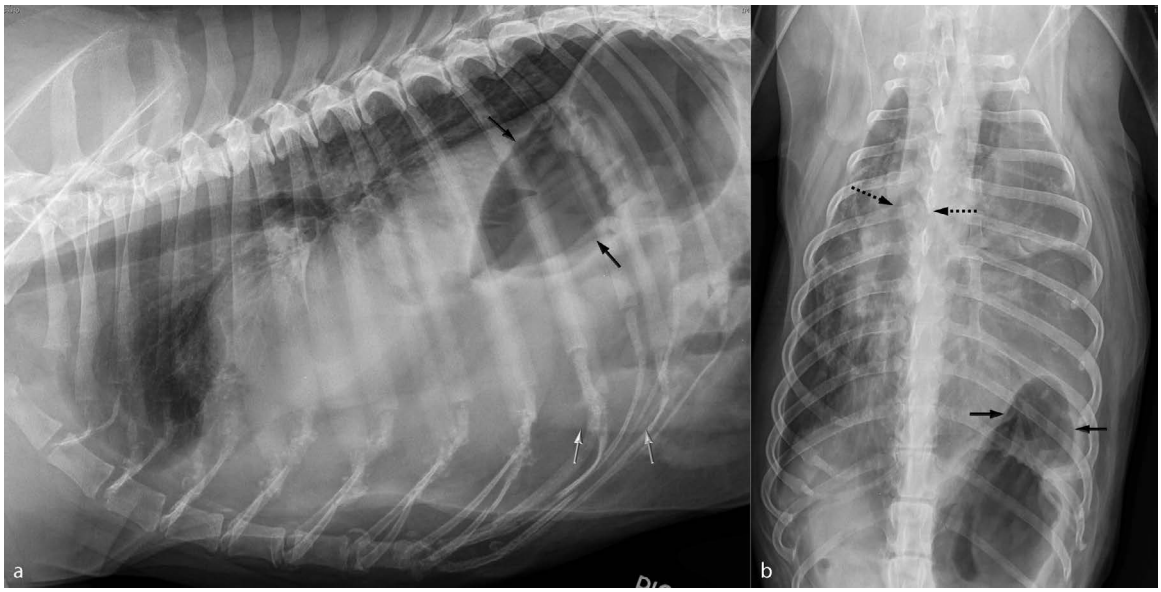


FIGURE 3.9 Lateral **(a)** and dorsoventral **(b)** views of a dog presented for increased respiratory effort after vehicular trauma. A marked increase in soft tissue opacity is present within the caudoventral thorax that is notably located on the left side. There is border effacement of most of the cardiac silhouette and the diaphragm. The left diaphragmatic margin is effaced on the dorsoventral view. The tracheal hilus is deviated to the right hemithorax (b, dotted black arrows) consistent with a mediastinal shift away from the hemithorax containing most of the increased soft tissue opacity. The normal caudoventral liver margin is not identified, and the tail of the spleen (a, white arrows) is cranially displaced. These findings support the diagnosis of diaphragmatic rupture with herniated abdominal organs. Finally, a gas-filled structure with visible rugal folds consistent with stomach is seen crossing from the abdomen to the thorax (black arrows), confirming diagnosis of herniation.

pulmonary pathology. Secondary spontaneous pneumothorax is associated with known underlying lung disease (except pulmonary bullae or blebs). Dogs most commonly have primary spontaneous pneumothorax; cats typically have secondary spontaneous pneumothorax.

TABLE 3.5 Categories and causes of pneumothorax

Category	Underlying cause(s)
Traumatic	**Open** – Penetrating or perforating wound **Closed** – Blunt force trauma
Spontaneous	**Primary** – Idiopathic – Presumed rupture of bulla or bleb **Secondary** – Rupture of necrotic or cavitary lung lesions (not bullae or blebs) – Pneumonia – Parasitic infection – Pulmonary abscess – Cavitary neoplasm – Congenital lobar emphysema – Bronchopulmonary dysplasia – Grass awn migration – Interstitial pneumonitis or fibrosis – Pulmonary thromboembolism
Iatrogenic	– Extreme positive pressure ventilation – Thoracocentesis

Radiographic signs of pneumothorax are summarized in Box 3.5. The right lateral view is the most sensitive view for detection of pneumothorax, where separation of the heart from the sternum is often the first sign identified (Figure 3.10a, b). Additionally, identifying separation of the lungs from the thoracic wall by gas opacity indicates pneumothorax. The key to diagnosing pleural gas is recognizing the absence of pulmonary vascular markings in the region suspected of absent lungs. In cases of spontaneous pneumothorax, the underlying pulmonary bulla or bleb is rarely evident radiographically. When

Box 3.5 Radiographic signs indicating pneumothorax

- Separation of the heart from the sternum (earliest visible sign seen on lateral view)
  - Absence of pulmonary vascular markings at the region of separation
- Retraction of lungs from the thoracic wall by gas opacity
  - Absence of pulmonary vascular markings at the region of retraction
- General increased pulmonary lung opacity
  - More evident with increasing pleural volume of gas
- Evidence of tension (only with severe gas accumulations)
  - Flattened or tented diaphragm
  - Mediastinal shift away from pleural space containing most gas
  - Barrel-shaped chest

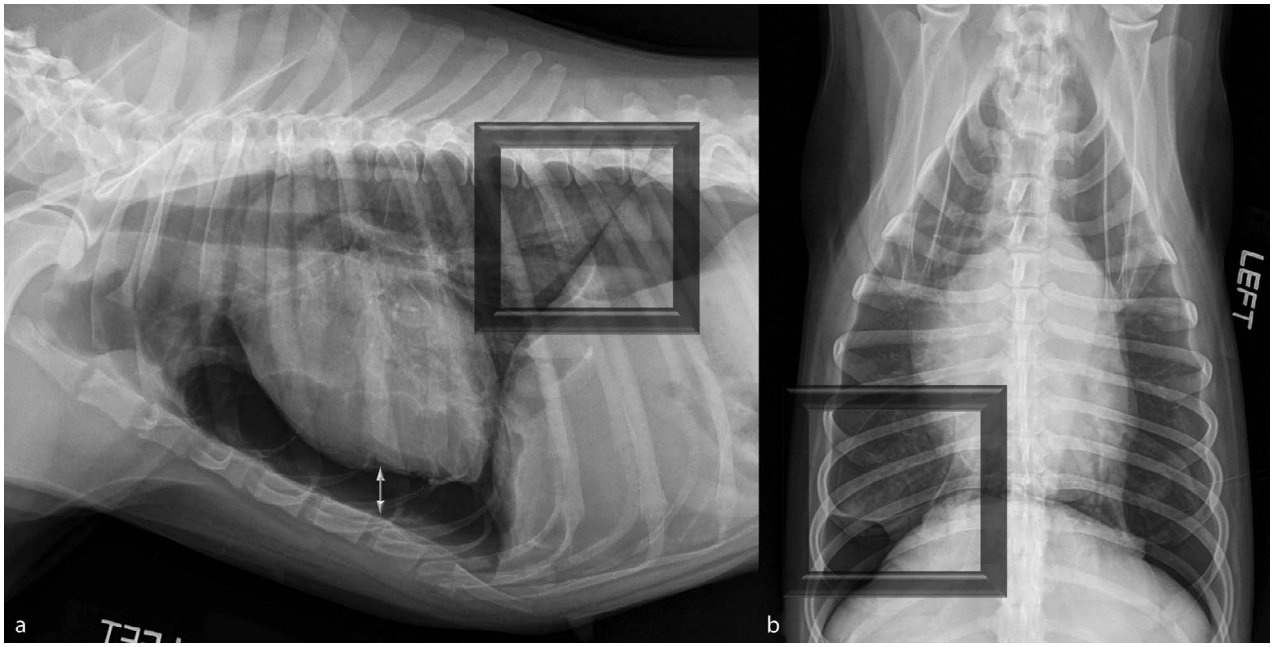


FIGURE 3.10 Lateral **(a)** and ventrodorsal **(b)** view of a dog having moderate pneumothorax with accompanying magnified views of the indicated regions. Moderate separation of the heart from the sternum with interposed gas opacity is present on the lateral view (white double arrow). Additionally, separation of the lungs from the thoracic wall is visible on both views (black boxes). The lungs are mildly, diffusely increased in opacity consistent with atelectasis due to increased pleural volume.

compared to radiographs, computed tomography is able to detect the underlying bullae with greater sensitivity, but the exact cause of pneumothorax often remains unidentified even with advanced imaging.

3. Noncardiac Mediastinum

As an entry point into the central thorax and evaluation of the mediastinum, the extrathoracic trachea should be followed, evaluating its margins until the bifurcation is reached. From this point, the mediastinum can be evaluated. Abnormalities would include alterations in margination (decreased visibility due to border effacement), position, size, or opacity of the mediastinum. The mediastinum spans from the thoracic inlet to the diaphragm and the entire dorsal to ventral dimension of the thorax. The mediastinal compartment communicates with fascial planes of the neck cranially and with the retroperitoneal space caudally (through the aortic hiatus). This communication is an important consideration when determining the underlying cause of pneumomediastinum, as discussed later. The mediastinum includes many structures that are not normally visible on thoracic radiographs due to border effacement, including sternal, cranial mediastinal, and tracheobronchial lymph nodes, thymus, esophagus, vessels (brachiocephalic trunk, left subclavian, azygous vein, etc.), nerves, and lymphatics. In the diseased state, these structures may become visible due to altered size or opacity. The main visible mediastinal structures are the trachea, heart, and great vessels. Cardiovascular mediastinal structures will be discussed in more detail in the next section. The thymus is visible only in young animals.

Mediastinal Gas – Pneumomediastinum

Mediastinal gas or pneumomediastinum can be seen independently or concurrent with pneumothorax. Radiographically, mediastinal gas is readily distinguished from pleural gas because it acts as a contrast, increasing visibility of soft tissue opaque from margins within the cranial mediastinum that are not normally seen (Figure 3.11). The most commonly seen

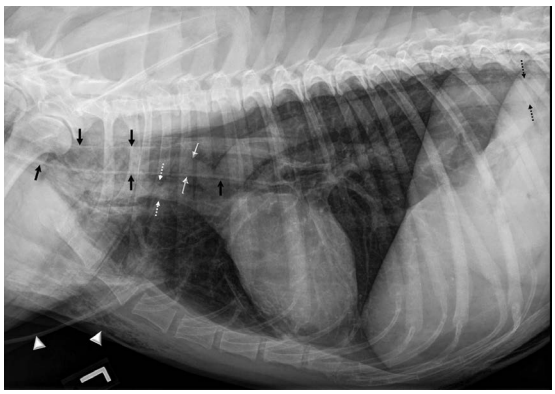


FIGURE 3.11 Pneumomediastinum in a dog having received multiple bite wounds. Subcutaneous emphysema is present superimposed over the thorax and located ventrally (white arrowheads). The outer margin of the trachea is visible (black arrows) due to adjacent gas creating contrast. The margins of the brachiocephalic trunk (dotted white arrows) and left subclavian (white arrows) are no longer effaced by surrounding soft tissue structures due to interposed gas highlighting their margins. The cranial abdominal aorta is visible (dotted black arrows) because it is surrounded by gas extending into the retroperitoneal space through the aortic hiatus.

Box 3.6 Causes of pneumomediastinum

- Cervical trauma
  - Penetrating wounds (e.g., bites) introducing gas into deep cervical soft tissues
- Tracheal or laryngeal rupture
- Alveolar rupture causing tracking of gas through interstitium
  - Blunt force thoracic trauma
  - Iatrogenic pulmonary hyperinflation
- Esophageal rupture (concurrent effusion is expected)
- Extension from the retroperitoneal space (uncommon)
- Mediastinitis due to gas-producing bacteria (concurrent effusion is expected)

radiographic sign of pneumomediastinum is increased delineation of the outer tracheal wall as it is highlighted by gas. The lateral view is typically the only view that is diagnostic, as superimposition precludes visibility of mediastinal gas on the orthogonal view. Pneumomediastinum has several potential causes, as shown in Box 3.6. In many cases, clinical history provides a clue as to the underlying cause. Trauma is the most commonly reported cause of pneumomediastinum. Given the potential causes of pneumomediastinum, it is recommended that radiographs be obtained of the entire neck in order to assess the larynx, trachea, and other cervical structures that may be the cause of mediastinal gas. In many cases of tracheal rupture, a lesion is not identified on radiographs, and tracheoscopy may be needed to assess the integrity of the trachea and esophagus. Typically, when esophageal rupture occurs, the leakage of fluid is far greater than gas, resulting in mediastinal and, therefore, pleural effusion that is in higher volume than any concurrent gas.

Regardless of the cause of pneumomediastinum, gas within the mediastinal space can leak into the pleural space due to fenestrations. However, gas within the pleural space will never leak into the mediastinum, as excess pleural pressure due to the pneumothorax collapses the mediastinum, effectively protecting gas from entering the mediastinum. Also, as previously mentioned, the mediastinum communicates with the cervical fascial planes cranially and the retroperitoneal space caudally through the aortic hiatus. Therefore, gas within the mediastinum can extend to these spaces, and gas within these spaces can extend to the mediastinum. Pneumomediastinum that is in such severity as to cause subcutaneous emphysema after tracking through the cervical soft tissues can be assumed to occur from tracheal rupture.

Mediastinal Shift

Mediastinal structures such as the trachea and heart can be displaced from their midline locations due to disease in the pleural or pulmonary space. A mediastinal shift can be categorized as contralateral or ipsilateral.

TABLE 3.6 Categorization and causes of a mediastinal shift

Ipsilateral
– Mediastinum is pulled *toward* the abnormality
	Pleural disease
	– Adhesions between mediastinal and thoracic wall pleura (uncommon)
	– Atelectasis caused by fibrotic pleura constricting lung(s) (uncommon)
	Pulmonary disease
	– Remaining causes of atelectasis (common)
	  – Positional/recumbency/anesthesia associated
	  – Bronchial obstruction

Contralateral – Mediastinum is pushed *away* from the abnormality	**Pleural disease** – Unilateral pleural effusion or pneumothorax (common) – Pleural mass (uncommon) – Diaphragmatic rupture with herniated abdominal organs (common) **Pulmonary disease** – Lung mass (common)

A contralateral mediastinal shift follows disease present in the right or left hemithorax that causes a *push* of the mediastinum *away* from the diseased side. An ipsilateral mediastinal shift occurs when disease within the thorax causes a *pull* of the mediastinum *toward* the diseased side, caused by a decrease in volume or a physical tethering of the mediastinum toward the lesion. Some diseases that may cause a mediastinal shift have been mentioned previously in the discussion on pleural diseases. Additional causes are shown in Table 3.6. Recognition of a mediastinal shift can be key to differentiating causes of pulmonary or pleural lesions seen but is almost never associated with mediastinal lesions alone, so its presence typically indicates disease outside the mediastinum.

Mediastinal Masses

Recognition of the position of the trachea is key to differentiating the most likely organ of origin for many mediastinal masses. As previously mentioned, many of the structures within the mediastinum, especially within the cranial mediastinum, are not visible in the normal animal. However, when mediastinal structures become enlarged, they create masses characteristic to their location within the mediastinum, assisting with distinguishing organ of origin for the mass. The location of mediastinal masses associated with specific organs is shown in Table 3.7. The effect that these masses have on the tracheal positioning is essential to distinguish likely organs of origin and, therefore, differential diagnoses for the mass effect.

Mediastinal Structures – Trachea

In most small animals, the normal tracheal path diverges from the thoracic spine from the thoracic inlet to the tracheal bifurcation. The normal tracheal diameter should be consistent throughout and should be slightly less than the diameter of the larynx. Ratios of the tracheal diameter to the thoracic inlet diameter measured on the

TABLE 3.7 Location of masses associated with mediastinal structures and their most common effect on tracheal positioning

Organ of origin	Mediastinal location for mass	Direction of tracheal deviation
Esophagus – Generalized enlargement – Focal enlargement	Dorsal – Cranial, middle, and caudal mediastinum – Craniodorsal or dorsal middle, most typically	Ventral
Sternal lymph nodes	Cranioventral	Dorsal, if severe enlargement
Cranial mediastinal lymph nodes	Cranioventral	Dorsal
Thymus	Cranioventral	Dorsal +/– right
Ectopic thyroid	Cranioventral	Dorsal
Mediastinal (pharyngeal) cyst	Cranioventral	Dorsal
Heart base	Cranial or middle	Dorsal and right
Tracheobronchial lymph nodes	Middle	Ventral
Left atrium	Middle	Dorsal
Hiatal hernia	Caudodorsal	None

lateral view can be used to determine appropriateness of overall tracheal size with variations of the ratio relative to breed listed in Table 3.8.

TABLE 3.8 Method of measurement and normal values for tracheal diameter to thoracic inlet ratios in normal dogs



Breed type	Ratio value
Nonbrachycephalic breeds	0.20 +/– 0.03
Non-Bulldog brachycephalic breeds	0.16 +/– 0.03
Bulldogs	0.13 +/– 0.04

TABLE 3.9 Causes of tracheal narrowing

Length of trachea affected	Differential diagnoses
Diffuse	**Mural abnormalities** – Tracheal hypoplasia – Tracheitis – Mucosal hemorrhage – Severe tracheal collapse
Focal or segmental	**Mural abnormalities** – Tracheal collapse – Tracheal stricture or cicatrix – Neoplasia – Osteochondroma, chondrosarcoma, osteosarcoma, papilloma – Polyp – Granuloma – Parasitic (*Filaroides osleri*) – Previous tracheal irritation or trauma **Extramural abnormalities** – Mediastinal mass – Pulmonary mass (rare) **Luminal abnormalities** – Foreign body

A decrease in tracheal luminal diameter may be diffuse throughout its length or segmental/focal. Also, any tracheal narrowing can be caused by extraluminal, luminal, or mural factors, as shown in Table 3.9. Diffuse narrowing of the tracheal lumen is caused by mural abnormalities, specifically tracheal hypoplasia, severe tracheal collapse (Figure 3.12), or severe thickening of the tracheal mucosa caused by tracheitis or hemorrhage. These causes may be radiographically indistinguishable;

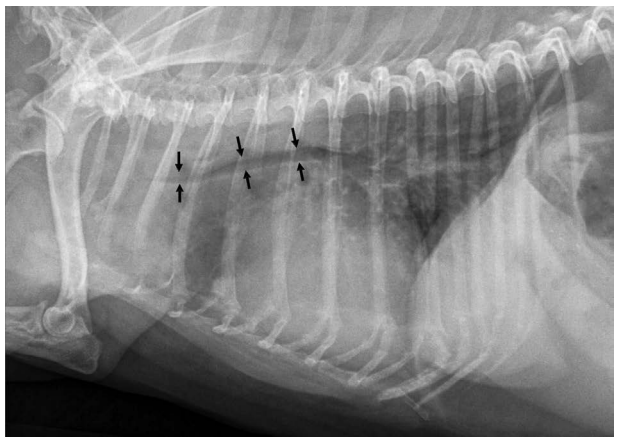


FIGURE 3.12 Lateral thoracic view of a dog having severe tracheal collapse. The view was obtained under attempted inspiration. The trachea at the thoracic inlet and cranial is collapsed and not radiographically visible. The intrathoracic trachea is visible but narrow. The severity of this dog's respiratory signs precluded evaluation of tracheal collapse during cough using fluoroscopy. The diaphragm is cranially positioned, overlapping with the cardiac silhouette. Also, the caudal lungs are mildly increased in opacity and reduced in size due to underaeration. These findings indicate a secondary upper airway obstruction.

Box 3.7 Radiographic signs indicating upper airway obstruction

- Tracheal narrowing at the obstruction
- Increased tracheal diameter cranial to the obstruction
- Decreased lung volume
  - Cranially positioned diaphragm
  - Increased opacity of caudal lungs
- Sternal elevation (most commonly seen in cats)
- Inward deviation of intercostal muscles (most commonly seen in cats)
- Hiatal herniation due to decreased intrathoracic pressure

however, tracheal hypoplasia is congenital, and a sudden decrease in tracheal luminal diameter in an animal with a previously normal tracheal diameter would not be expected with true hypoplasia, as may be seen with acquired tracheitis or hemorrhage. Tracheal hypoplasia that is typically seen in bulldogs is associated with other factors comprising brachycephalic airway syndrome and is often diagnosed in younger animals. The radiographic signs of upper airway obstruction are shown in Box 3.7.

Mediastinal Structures – Esophagus

Because of its dorsal position within the mediastinum, esophageal dilation usually causes ventral displacement of the trachea. A dilated esophagus may contain ingesta, foreign material, fluid, gas, or any combination. The radiographic signs and differential diagnoses for various esophageal diseases are listed in Table 3.10. Radiographic signs indicating esophageal dilation are shown in Box 3.8. Gas-filled esophageal dilation is sometimes more challenging to recognize because the gas within the esophagus creates little contrast with lungs (Figure 3.13a, b). The tracheal stripe sign can be seen when the ventral esophageal wall contacts the dorsal tracheal wall and creates a thick, soft tissue opaque line at the point of contact that is surrounded by luminal tracheal and esophageal gas. Also, in a gas-dilated esophagus, soft tissue opaque

Box 3.8 Radiographic signs of esophageal dilation

- Visibility of the esophagus on plain radiographs
  - Soft tissue opaque tube located dorsally and on midline (fluid or ingesta-filled esophagus)
  - Converging soft tissue opaque lines within the caudal mediastinum (gas-filled esophagus)
- Ventral displacement of the trachea
- Tracheal stripe sign (gas-filled esophagus)
- Secondary abnormalities
  - Aspiration pneumonia
  - Pneumomediastinum, pleural effusion, pneumothorax, gas within cervical soft tissues (esophageal perforation)

TABLE 3.10 Radiographic descriptors and some common differential diagnoses of esophageal disease

Radiographic descriptor	Differential diagnoses
Altered esophageal opacity	**Luminal material (obstructive or nonobstructive)** – Mineral, metal, or soft tissue opaque foreign body or ingesta – Megaesophagus with excess luminal gas or fluid **Mural mass (obstructive or nonobstructive)** – Soft tissue mass (granuloma, abscess, or neoplasia) – Mineralized mass (e.g., malignant transformation of *Spirocerca lupi* granuloma)

Esophageal dilation	**Generalized megaesophagus**
	– Idiopathic
	– Metabolic disease
	  – Hypoadrenocorticism
	  – Hypothyroidism
	– Infection
	  – Botulism
	  – Distemper
	– Toxicity
	  – Lead
	  – Organophosphate
	– Anesthetic induced (transient)
	– Esophagitis
	– Paraneoplastic
	  – Thymoma
	– Lower esophageal obstruction
	  – Hiatal hernia
	  – Lower esophageal mass
	– Neuromuscular diseases
	  – Dysautonomia
	  – Myasthenia gravis
	  – Storage diseases
	– Focal esophageal dilation
	– Obstruction (luminal, extraluminal, or mural causes)
	  – Foreign body
	  – Vascular ring anomaly
	  – Stricture
	  – Esophageal mass
	– Esophageal diverticulum

Pneumomediastinum (+/– pneumothorax) and mediastinal/pleural effusion	– Esophageal perforation

lines are seen within the caudal mediastinum representing the walls of the esophagus as they converge at the esophageal hiatus. These lines are visible in the expected location of the esophagus (within the caudal mediastinum between the aorta and the caudal vena cava on the lateral view and near midline on the orthogonal view). Megaesophagus is a risk factor for aspiration pneumonia. When megaesophagus is positively identified, the lungs should be carefully evaluated.

Focal esophageal dilation may be caused by luminal, extraluminal, or mural obstructions. Luminal causes

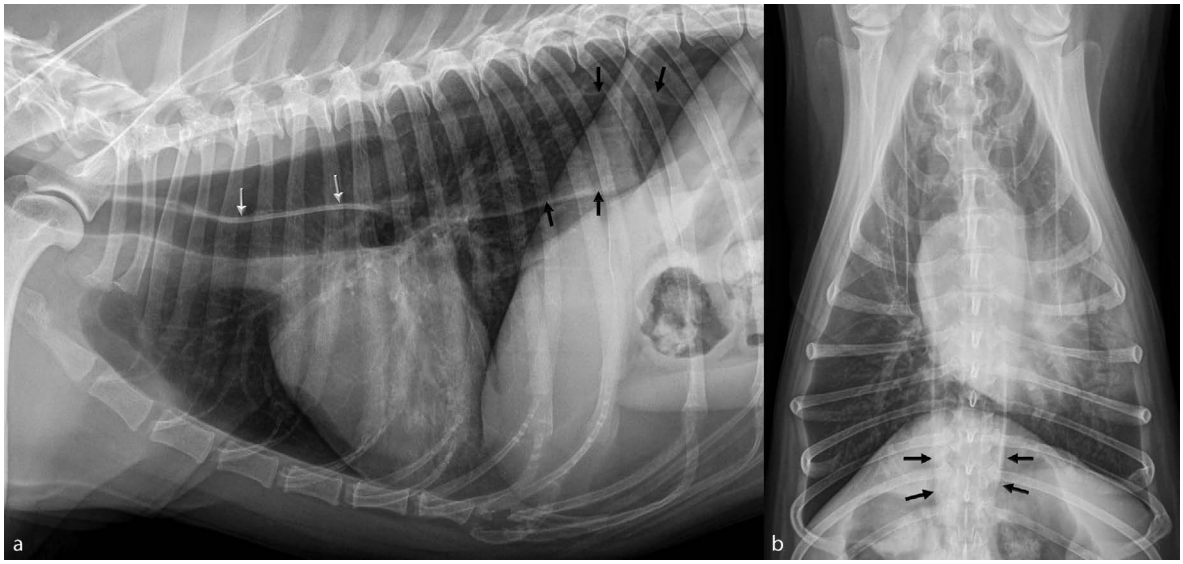


FIGURE 3.13 Lateral **(a)** and ventrodorsal **(b)** thoracic views of a dog having gas-filled megaesophagus. The thoracic trachea is ventrally displaced. A tracheal stripe sign is present (a, white arrows). Additionally, converging soft tissue opaque lines (a and b, black arrows) are visible in the caudal mediastinum between the aorta and the caudal vena cava on the lateral view and on midline on the ventrodorsal view consistent with margins of the esophageal wall, which are separated by excess luminal gas opacity. Increased left-sided pulmonary opacity is causing border effacement of the left cardiac margin consistent with alveolar disease due to secondary aspiration.

of obstruction occur with esophageal foreign bodies. Esophageal foreign bodies are most commonly confined between the heart base and the diaphragm (**Figure 3.14a, b**). Soft tissue opaque foreign bodies, such as rawhide treats, can look similar to esophageal mural masses; however, foreign bodies are more common and present more acutely than mural masses. Extraluminal causes of obstruction resulting in focal esophageal dilation are infrequent. Vascular ring anomalies are the most common cause of extraluminal obstruction. Typically, a vascular ring anomaly will cause the portion of the esophagus cranial to the cardiac base to be dilated along with focal leftward deviation of the esophagus and trachea. On some occasions, the entire esophagus may be dilated with a focal narrowing near the heart base. Mural esophageal masses caused by neoplasia, granuloma, or abscess are rare causes of esophageal obstruction that can appear similar to each other. Hiatal diseases, including sliding hiatal and paraesophageal hernias and gastroesophageal intussusceptions, also cause soft tissue opaque masses associated with the caudal mediastinum. Sliding hiatal hernias are the most common of the hiatal diseases and may be transient from radiographic view to view. The similarity in survey radiographic findings of the various causes of caudal esophageal masses is shown in **Figure 3.15a–c**. The

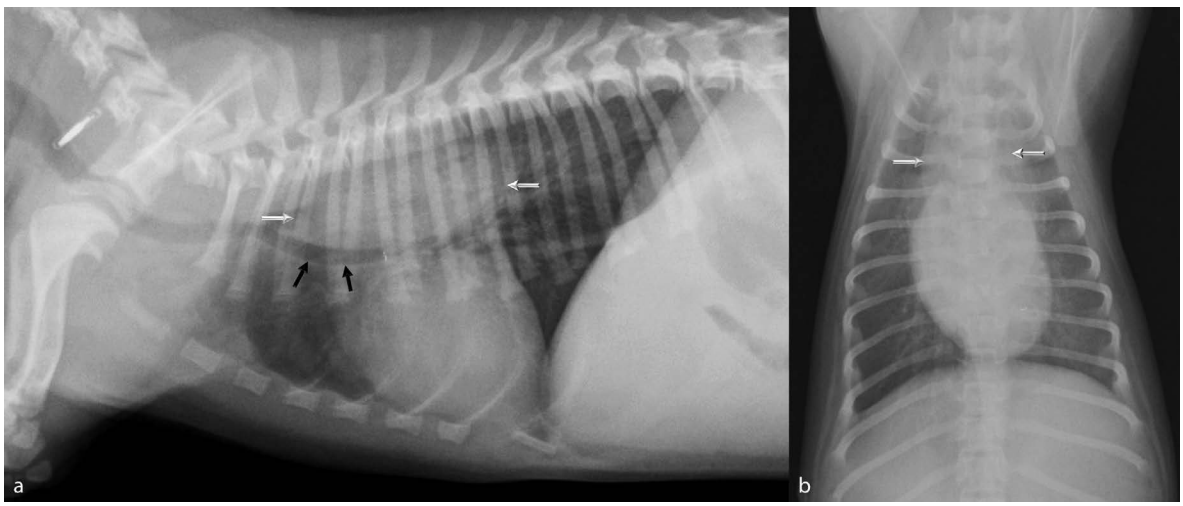


FIGURE 3.14 Lateral **(a)** and ventrodorsal **(b)** thoracic radiographs of a dog presenting for retching and gagging. A poorly defined soft tissue opaque mass is present within the dorsal thorax (a, white arrows). The mass is causing focal ventral deviation of the trachea (a, black arrows), and it is located in midline, causing widening of the mediastinum (b, white arrows). These findings confirm that the mass is mediastinal in origin, most likely originating from the esophagus. A leather belt was removed endoscopically.

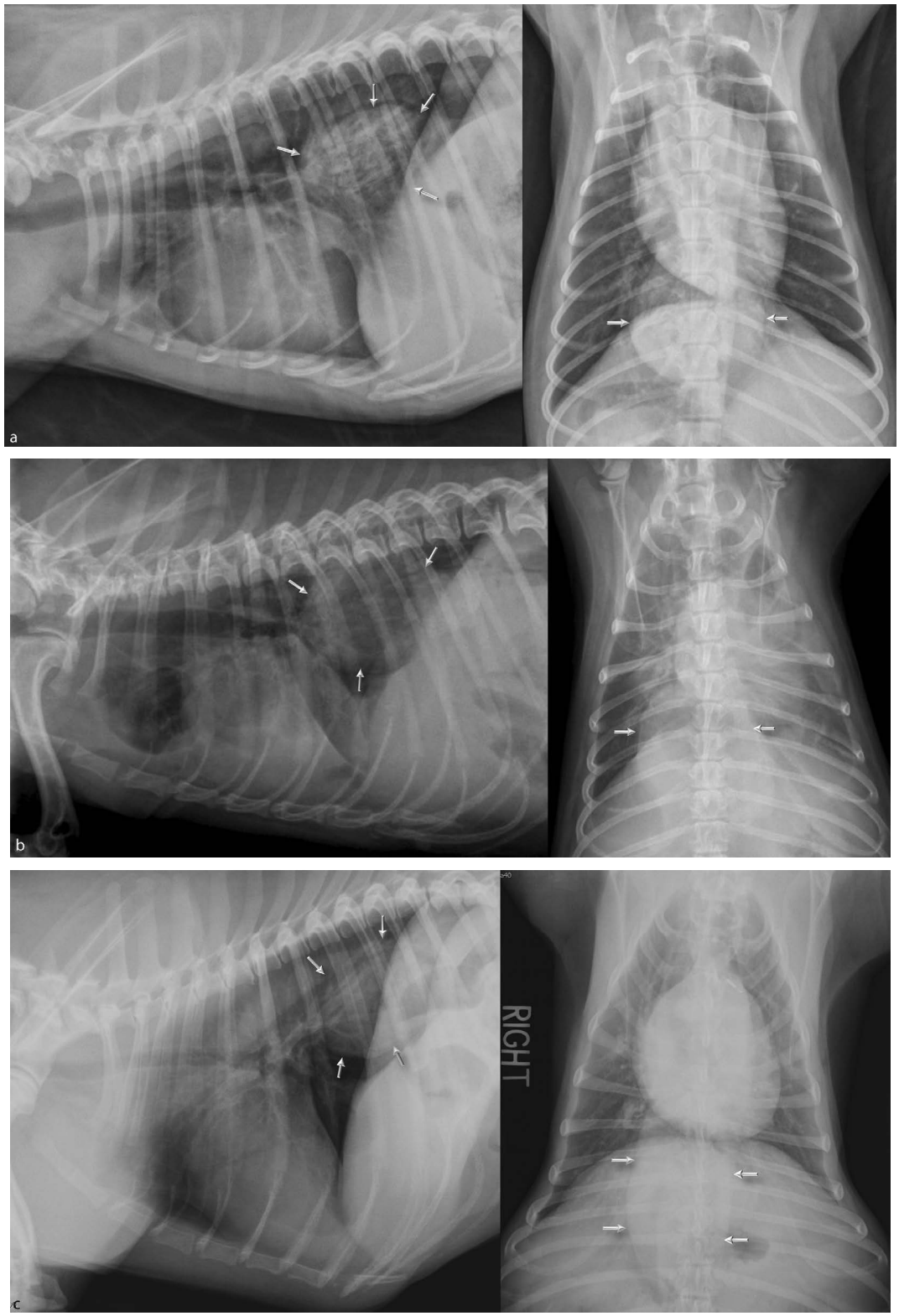


FIGURE 3.15 Lateral and ventrodorsal radiographs of caudal mediastinal masses due to esophageal diseases of different causes. In part **(a)**, a mixed gas and soft tissue opaque mass is seen in the caudal mediastinum (white arrows). Endoscopy confirmed the presence of an esophageal diverticulum. In part **(b)**, a soft tissue opaque mass with a central gas bubble is seen in the caudal mediastinum (white arrows). A rawhide foreign body was diagnosed endoscopically. In part **(c)**, a soft tissue opaque foreign body is present in the caudal mediastinum (white arrows) that has a focal gas bubble at its caudal margin. A sliding hiatal hernia was confirmed and surgically repaired. Oral administration of contrast could be performed to further characterize the lesions; however, barium would be contraindicated in part (b), as concurrent pleural effusion is present, indicating potential for esophageal rupture, which was confirmed during endoscopy.

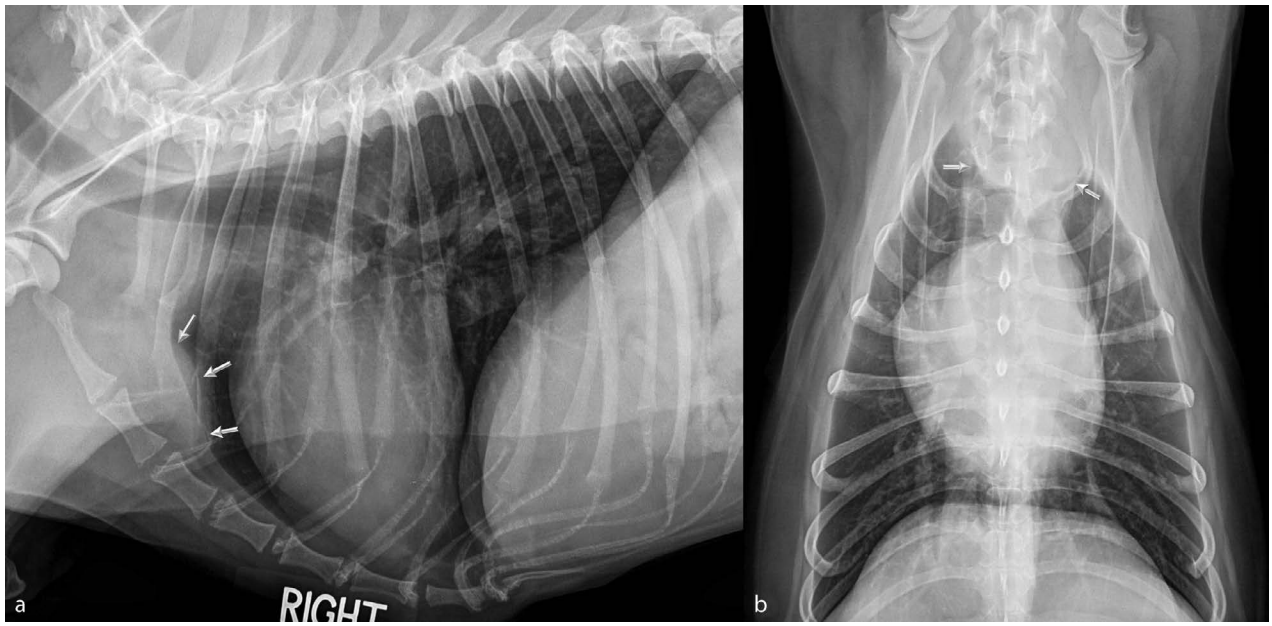


FIGURE 3.16 Lateral **(a)** and ventrodorsal **(b)** thoracic radiograph of a dog having sternal lymphadenopathy due to lymphoma. A broad-based soft tissue opacity is seen within the cranioventral thorax (a, white arrows) that is on midline, creating a widened cranial mediastinum on the ventrodorsal view (b, white arrows), confirming a mediastinal location for the lesion. The cranial mediastinum, in addition to being wide, is nonuniform in its width.

similarities often necessitate use of positive contrast esophagography or endoscopy to differentiate among them, with barium administration being contraindicated when accompanied by radiographic indication of esophageal rupture (e.g., concurrent pleural effusion).

Mediastinal Structures – Lymph Nodes

Three main lymph node centers are present within the mediastinum that can become radiographically visible when enlarged: The sternal (Figure 3.16a, b), cranial mediastinal (Figure 3.17a, b), and tracheobronchial

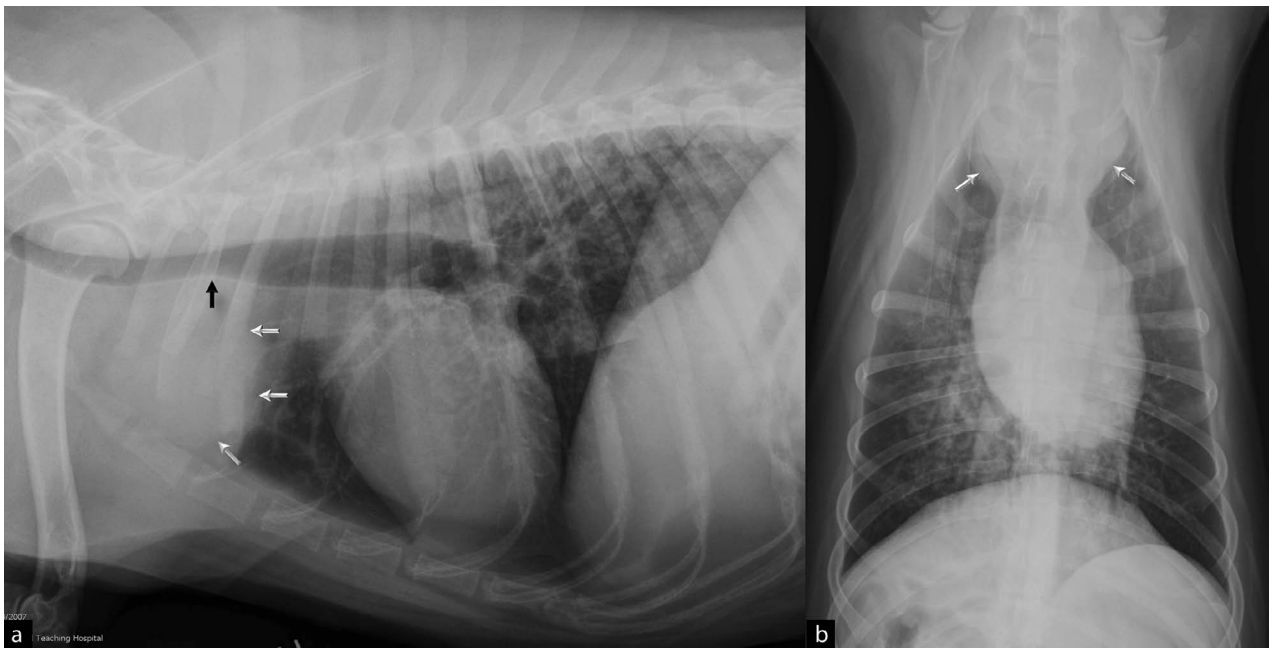


FIGURE 3.17 Lateral **(a)** and ventrodorsal **(b)** thoracic radiographs of a dog having cranial mediastinal lymphadenopathy due to lymphoma. A mass is located in the cranial and ventral aspect of the cranial mediastinum (white arrows) that causes dorsal deviation and compression of the cranial thoracic trachea (a, black arrow) and a widened cranial mediastinum (b, white arrows). An interstitial pattern is present, most evident in caudal lungs, that causes an increase in prominence of bronchi due to pulmonary lymphoma as well.

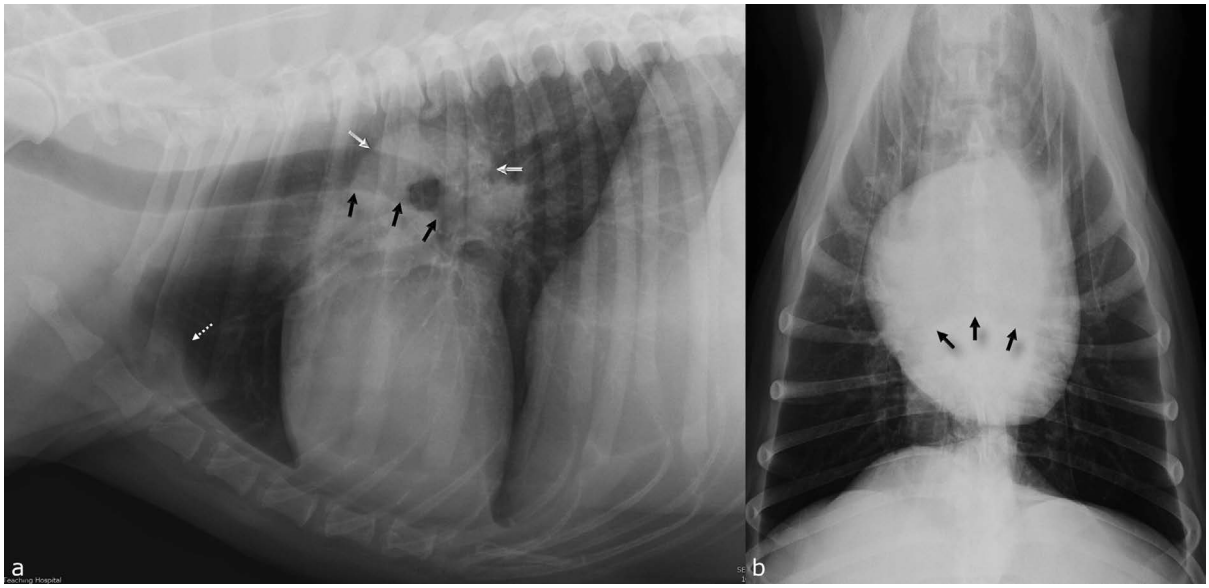


FIGURE 3.18 Lateral **(a)** and ventrodorsal **(b)** thoracic radiographs of a dog having lymphoma and tracheobronchial lymphadenopathy. The distal aspect of the trachea at the hilus and mainstem bronchi are focally ventrally deviated, giving the trachea a "J" shape (a, black arrows). A moderately well-defined soft tissue opacity is present in the region of the hilus on the lateral view (a, white arrows). This opacity is located between mainstem bronchi on the ventrodorsal view and causes widening of the angle between the right and left bronchus (b, black arrows). These findings confirm a mediastinal location for a mass due to tracheobronchial lymphadenopathy. Mild concurrent sternal lymphadenopathy is present that is only visible in the lateral view (a, dotted white arrow).

(Figure 3.18a, b). Both the sternal and cranial mediastinal lymph nodes are located in the cranial mediastinum, and the tracheobronchial lymph nodes are located in the middle mediastinum. In the normal animal, these lymph nodes are invisible. Most often, when lymph nodes become radiographically visible, the underlying cause is neoplastic or granulomatous disease and may be secondary to disease in locations that they drain along the lymphatic system.

Mediastinal Structures – Thymus

The thymus is located in the caudal part of the cranioventral mediastinum within the cranioventral mediastinal reflection. It is not radiographically visible in a normal animal that is greater than 1 year of age due to involution initiating at sexual maturity. In a young animal, the thymus may be visible, creating a soft tissue opacity within the cranioventral mediastinal reflection that is triangular in shape, appearing similar to a sail on the ventrodorsal/dorsoventral view. Thymic enlargement is more ventral in location than cranial mediastinal lymph node enlargement and is more caudal than sternal lymph node enlargement. However, when cranioventral mediastinal lesions approach massive sizes, their organ of origin is often impossible to distinguish with certainty. Masses associated with the thymus are typically caused by thymoma (in dogs) or thymic lymphoma (in cats). Additional potential causes of thymic enlargement include thymic cysts, hemorrhage, and amyloidosis. Thymic masses, especially those caused by thymomas, can be quite immense, causing dyspnea due to tracheal compression and decreased lung volume, as shown in Figure 3.19a, b.

4. Heart, Great Vessels, and Pericardium

Cardiac Radiographic Anatomy

Heart size can be evaluated by subjective assessment or objectively using a ratio of cardiac size to vertebral length, called a vertebral heart score. Cardiac shape is equally important in determining the presence of abnormalities, with alterations in cardiac shape not necessarily affecting cardiac size. Of important consideration is the alteration in apparent cardiac shape that can occur from poorly positioned radiographs that are not centered on the heart. The indications for cardiac imaging are listed in Box 3.9. Though variations in cardiac appearance can be particularly prominent among varying dog breeds, a general description of subjective cardiac assessment is shown in Box 3.10.

The vertebral heart score (VHS) is a method to objectively measure cardiac size that does not require a high experience level (detailed in Figure 3.20). The vertebral heart score can also be used to evaluate increasing size over time, especially useful in repeat evaluation of dogs having mitral valvular insufficiency in predicting onset of cardiac failure. Most normal dogs (98%) have a VHS less than 10.6. Some normal dogs regularly fall above this value. To address this, several breed-specific VHS values have been published in several barrel-chested small breed dogs and in Greyhounds. The reported upper limit of the VHS in cats (performed the same way as in dogs) is 8.0. Regardless of the VHS obtained, the cardiac silhouette must be examined for alterations in shape, which can be detected in hearts having a normal VHS.

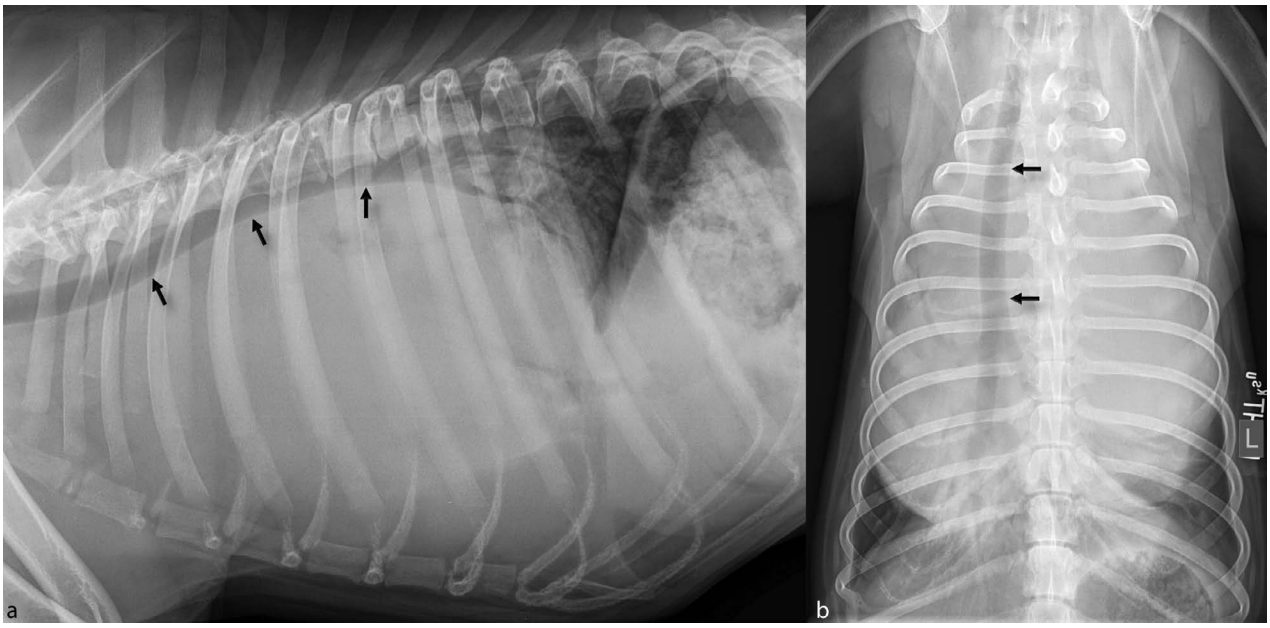


FIGURE 3.19 Lateral **(a)** and ventrodorsal **(b)** thoracic radiographs of a 2-year-old lab presenting for tachypnea and dyspnea. A large cranial mediastinal mass is present that is causing marked dorsal displacement of the trachea (a, black arrows) and caudal displacement of the tracheal hilus to the level of the 7th intercostal space. A mild rightward mediastinal shift is present, as shown by the position of the trachea on the ventrodorsal view (b, black arrows). The margins of the heart are effaced, and there is a marked decrease in lung volume due to the size of the mass. Thymoma was diagnosed histopathologically.

Box 3.9 Indications for cardiac imaging

- Audible murmur
- Exercise intolerance
- Coughing
- Dyspnea
- Increased lung sounds
- Cyanosis
- Syncope
- Abdominal distension/jugular pulses
- Heartworm infection
- Re-evaluation of previously diagnosed cardiac disease

In order to arrive at an appropriate differential list, specific chamber enlargement should be identified when cardiomegaly or altered cardiac shape is identified. Bulges seen within the cardiac silhouette must be anatomically differentiated within the overall shape of the heart. This can be accomplished by way of the clock-face analogy shown in Table 3.11. Chambers of the heart are located within specific "times" along the clock. The clock-face analogy is similar in cats, except that the left atrium is located more peripherally along the left aspect of the cardiac silhouette rather than dorsally at the caudal cardiac base.

Box 3.10 Cardiac size relative to thoracic cavity

Canine

Lateral View
- Length of the heart is less than two-thirds the dorsoventral diameter of the thorax
- Width of the heart is 2.5–3.5 intercostal spaces (deep-chested breeds narrower than barrel chested)
- Two-thirds of the width of the heart is cranial to the carina, and one-third is caudal
- Trachea nearly parallel to the sternum

Ventrodorsal view
- Left cardiac margin flatter than the right
- Width of the cardiac silhouette less than two-thirds the width of the thorax
- Apex positioned slightly left of midline

Feline

Lateral view
- Length of the heart is less than two-thirds the dorsoventral diameter of the thorax
- Width of the heart is 2–3 intercostal spaces
- Trachea diverges form spine and is nearly parallel to the sternum
  - Increased tracheal divergence from spine with age

Ventrodorsal view
- Left cardiac margin flat
- Width of the cardiac silhouette less than half the width of the thorax
- Apex positioned moderately left of midline

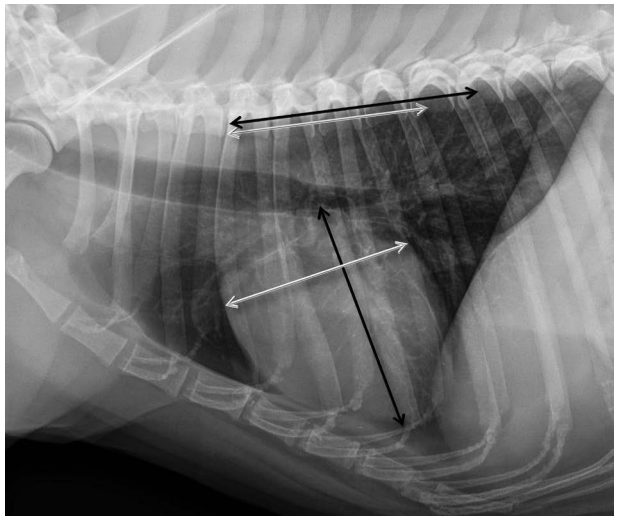


FIGURE 3.20 Technique for performing vertebral heart scale (VHS). A line is drawn along the long axis of the heart from the level of the cardiac base (black) to the cardiac apex. A second line is drawn along the short axis of the heart from the level of the dorsocaudal vena cava margin that extends to the cranial cardiac margin so that the second line is orthogonal to the original line (white). Both of these lines are then transposed onto the thoracic spine from the level of the cranial endplate of T4 extending caudally. The number of vertebrae encompassed within these lines constitutes the VHS, which measures 10 in this case.

Radiographic Appearance of Right-Sided Cardiomegaly

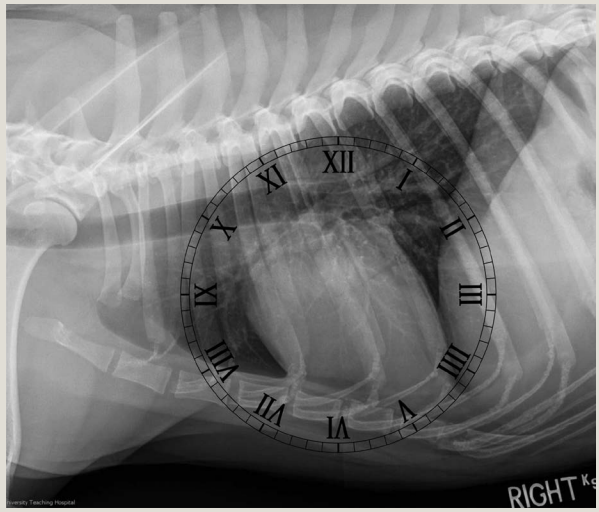
Radiographically, right-sided cardiomegaly causes an increase in width of the cardiac silhouette on the lateral view and increased rounding of the right cardiac margin on the ventrodorsal/dorsoventral views. Bulges in the cardiac silhouette can be seen corresponding to the right atrium, right ventricle, or both according to the clock-face analogy.

Right atrial enlargement will cause an apparent increase in soft tissue opacity between the cranial cardiac base and the cranial mediastinum on the lateral view (8:00–11:00 position). On the orthogonal view, a bulge at the right cranial cardiac margin in the 9:00–11:00 position can be seen. This is shown in Figure 3.21a, b. Secondary to any cardiac enlargement, the trachea will often be elevated, especially cranial to the hilus. On some occasions, especially with concurrent right ventricular enlargement, the cardiac apex will be displaced to the left on the ventrodorsal/ventrodorsal views. In general, right atrial enlargement is more evident on the ventrodorsal view.

Right ventricular enlargement will cause a rounded cranial margin that creates an increase in the apparent width of the cardiac silhouette. The heart will appear to contact an increased length of sternum, though increased sternal contact alone is a poor indicator of cardiomegaly. A "reverse D" shape is often described in reference to right-sided enlargement on the ventrodorsal view. This shape is more specific for right ventricular enlargement rather than atrial enlargement.

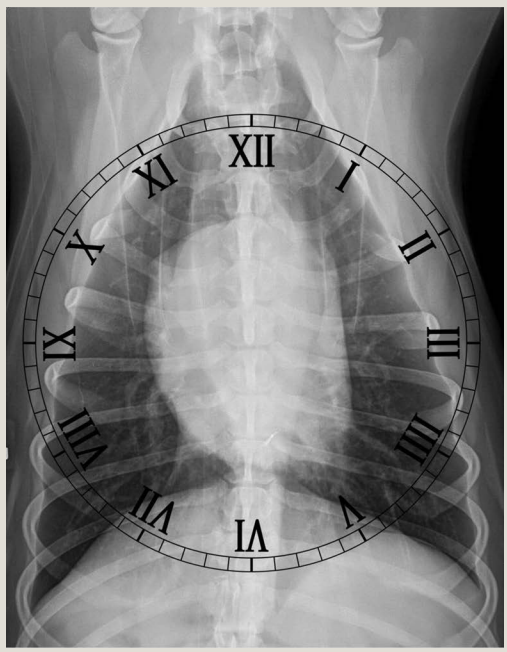
TABLE 3.11 Times corresponding to specific cardiac chambers using the clock-face analogy

Lateral view



Time	Cardiac chamber
12:00–3:00	Left atrium
3:00–5:00	Left ventricle
5:00–8:00	Right ventricle
8:00–11:00	Right atrium, main pulmonary artery, ascending aorta, and arch

Ventrodorsal view



Time	Cardiac chamber
11:00–1:00	Aorta
1:00–2:00	Main pulmonary artery
2:00–3:00	Left auricle
3:00–5:00	Left ventricle
5:00–9:00	Right ventricle
9:00–11:00	Right atrium
Center dial (between mainstem bronchi)	Left atrium

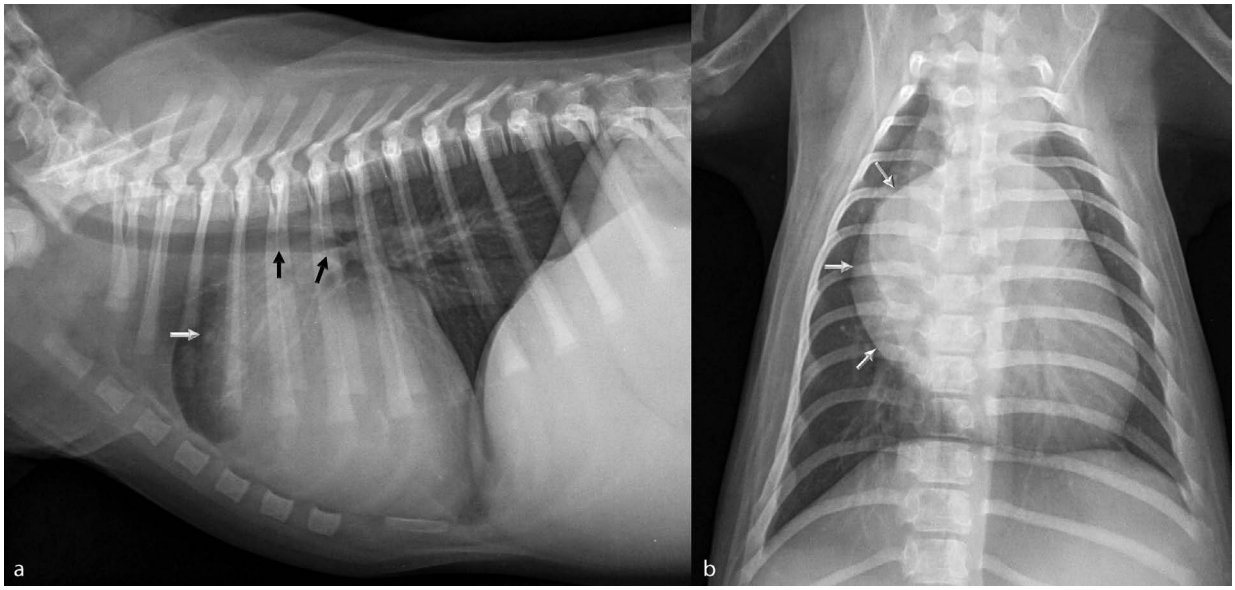


FIGURE 3.21 Lateral **(a)** and ventrodorsal **(b)** views in a puppy having marked right atrial enlargement due to tricuspid insufficiency secondary to a dysplastic tricuspid valve. On the lateral view, the trachea is elevated cranial to its hilus (a, black arrows). A bulge is present at the cranial cardiac base on the lateral view (a, white arrow) in the 8:00–11:00 position and at the right cranial cardiac margin on the ventrodorsal view (b, white arrows) in the 9:00–11:00 position. Also, note the subjective decrease in size of the pulmonary arteries and veins secondary to return flow of vascular volume into the right atrium rather than forward into the main pulmonary artery and lungs.

The reverse D is nonspecific for the underlying cause of right ventricular enlargement. When right ventricular enlargement is severe, the cardiac apex as seen on the lateral view will elevate. The enlarged cardiac silhouette will cause tracheal elevation, similar to that seen with right atrial enlargement. These findings are shown in Figure 3.22 a, b.

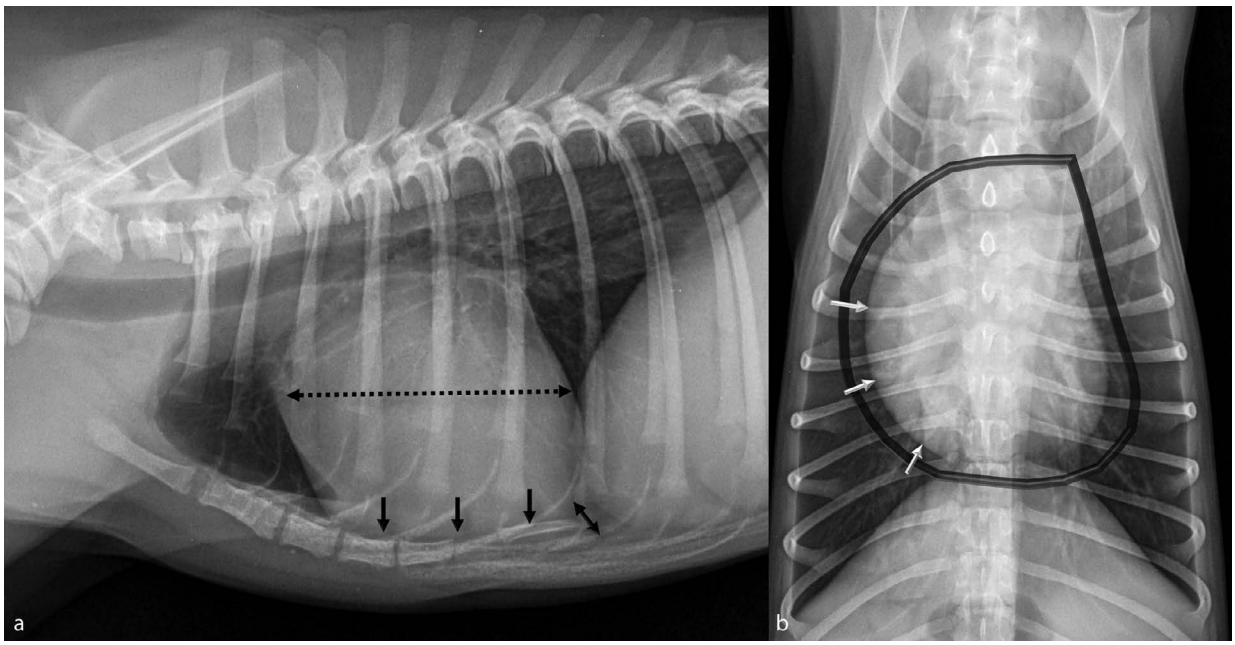


FIGURE 3.22 Lateral **(a)** and ventrodorsal **(b)** views in a dog having marked right ventricular enlargement due to severe pulmonic stenosis. The trachea is elevated being parallel to the spine. The cardiac silhouette is subjectively wide on the lateral view (a, dotted black line) encompassing over four intercostal spaces. Increased sternal contact is present (a, black arrows). The apex of the cardiac silhouette at the junction between the sternum and the diaphragm is mildly elevated (a, double-ended black arrow). The contour of the left margin of the cardiac silhouette is flat. The entire right cardiac margin is rounded with the ventricle (in the 5:00–9:00 position) being more peripheral than the atrium (b, white arrows), creating a silhouette whose outline is reverse D in shape (b, black outline surrounding the heart).

Radiographic Appearance of Left-Sided Cardiomegaly

Left-sided cardiomegaly causes increased height of the cardiac silhouette on the lateral view. Bulges in the cardiac silhouette are seen in the region of the left atrium and/or ventricle. Because of the prevalence of certain diseases in the canine and feline population, left-sided cardiomegaly is more common than right-sided. Additionally, most cardiomyopathies tend to cause left-sided cardiomegaly rather than right-sided in cats and dogs.

With left atrial or left ventricular enlargement, the caudal cardiac margin becomes flattened on the lateral view. This is often the first identifiable indication of mild enlargement. Left atrial enlargement will cause a bulge at the caudal cardiac base (12:00–3:00 position) on the lateral view. On the orthogonal view, the left atrium is not located at the periphery of the cardiac silhouette but is positioned between mainstem bronchi, being superimposed over the cardiac silhouette analogous to the center of the dial using the clock-face analogy. Left atrial enlargement can cause widening of the angle between mainstem bronchi, creating a "U" shape rather than the normal "V" shape, though this appearance can also be created by a thoracic view that is centered on the diaphragm rather than the heart. Sometimes the caudal margin of an enlarged left atrium will create a well-defined rounded margin parallel to the cardiac apex on the ventrodorsal view, referred to as the "double-bubble sign." An enlarged left auricle is peripheral in location along the cardiac silhouette on the ventrodorsal view at the 2:00–3:00 position. Loss of the normal, flat left-sided cardiac margin will be seen due to a bulge created by left auricular enlargement. Secondary to left atrial enlargement, the trachea will be elevated, which is similar to that seen in right-sided cardiomegaly. However, in the case of left atrial enlargement, the caudal mainstem bronchi are additionally elevated, as shown in Figure 3.23a, b.

Given the importance of detecting left atrial enlargement and the recognition that increases in left atrial size may assist in predicting imminent likelihood of left-sided cardiac failure, two objective measurements for left atrial size have been published, called the vertebral left atrial size (VLAS) and the radiographic left atrial dimension (RLAD), though both methods perform better when obtained by more experienced clinicians (Figure 3.24a, b).

Left ventricular enlargement without concurrent left atrial enlargement is uncommon. It is less apparent radiographically than left atrial enlargement and is generally considered the least recognizable chamber enlargement as a sole entity. The caudal cardiac margin may be flat similar to left atrial enlargement; however, with severe enlargement, a pronounced convexity may be seen. The heart may be tall, encompassing greater than two-thirds the dorsoventral diameter of the thorax on the lateral view and elevating the caudal vena cava. The cardiac apex may be rounded and may be displaced toward the left or right on the ventrodorsal view.

Generalized Cardiomegaly

When the cardiac silhouette is generally enlarged (instead of predominantly right-sided or left-sided), pericardial disease must be considered. Most often, if

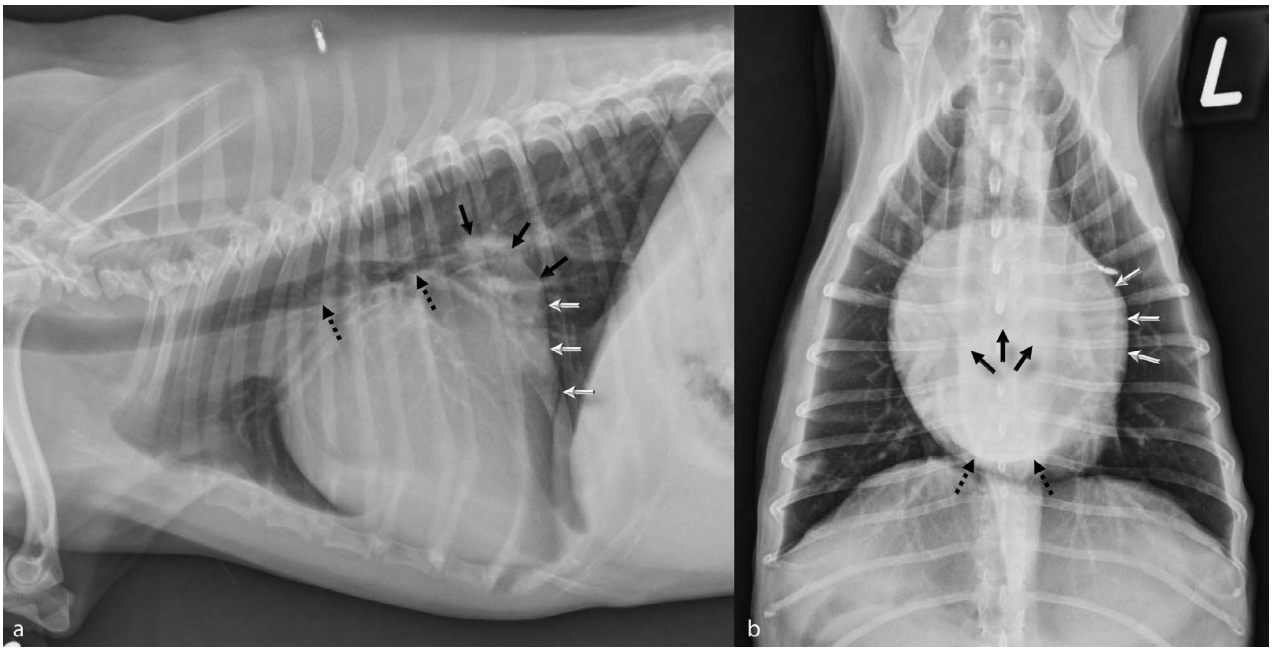


FIGURE 3.23 Lateral (a) and ventrodorsal (b) views in a dog having left atrial enlargement due to mitral valvular degeneration. The heart will often appear tall on the lateral view. The caudal cardiac margin is flat on the lateral view (a, white arrows). A bulge is visible in the caudal cardiac base (a, black arrows). The trachea and mainstem bronchi are elevated (a, black dotted arrows). On the ventrodorsal view, the angle between mainstem bronchi is widened (b, black arrows). The caudal margin of the enlarged left atrium is visible parallel to the cardiac apex (b, dotted black arrows). A left auricular bulge is visible peripherally along the left cardiac margin (b, white arrows).

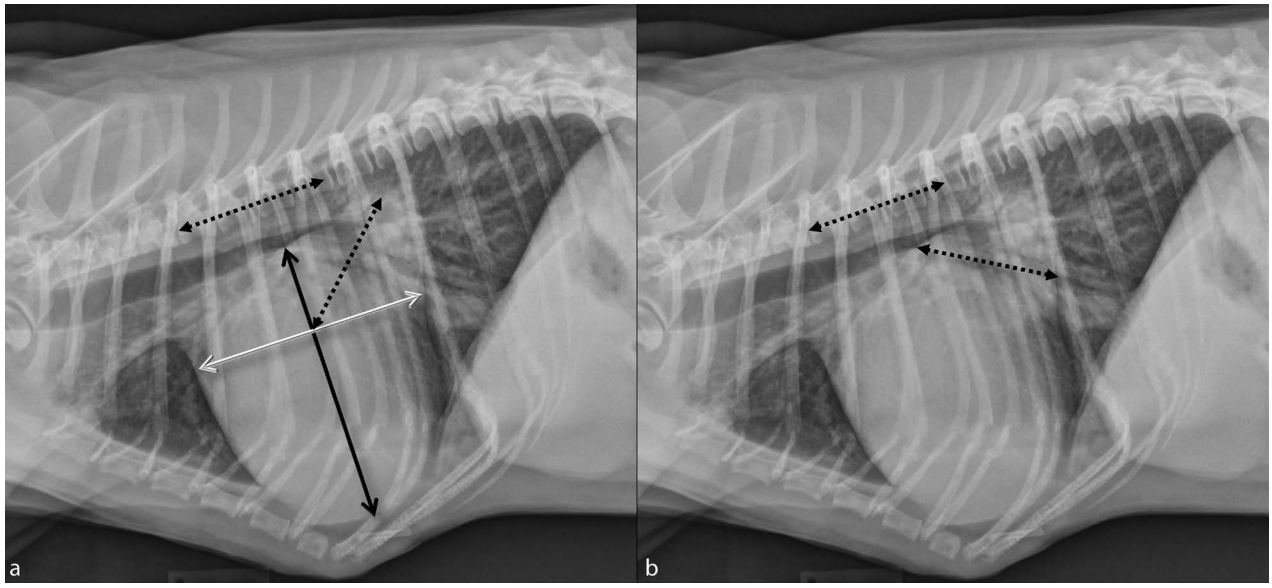


FIGURE 3.24 Right lateral thoracic views (a and b) in the same dog having left atrial enlargement due to degenerative mitral valvular disease and showing the measurement protocol for obtaining the radiographic left atrial dimension (RLAD; a) and the vertebral left atrial size (VLAS; b) intended to detect left atrial enlargement in dogs with mitral valvular insufficiency. To obtain the RLAD (a), intersecting lines are drawn identical to those required to obtain a vertebral heart score (black and white solid arrows). Then, an additional line is drawn bisecting the quadrant encompassed by the left atrium as shown (dotted black arrow). The length of this line is transposed onto the thoracic spine beginning at the cranial endplate of T4. The RLAD in this case measures 3.9 vertebrae. The optimal cutoff to distinguish normal from abnormal is reported to be 1.8 vertebrae, indicating left atrial enlargement in this case. To obtain the VLAS (b), a line is drawn from the most ventral aspect of the tracheal bifurcation to the caudal margin of the cardiac silhouette as it intersects with the dorsal aspect of the caudal vena cava (dotted black arrow). The length of this line is transposed onto the thoracic spine beginning at the cranial endplate of T4. The VLAS in this case measures 3.5 vertebrae. A VLAS > 2.3 vertebrae has been established as a useful predictor for left atrial enlargement in dogs.

the left atrium is detected as enlarged, the cardiomegaly is due to true heart enlargement rather than pericardial disease. If the heart is markedly enlarged and globoid while a dilated left atrium is not seen, pericardial disease/effusion should be ranked first. Keep in mind that severe right-sided cardiomegaly is similar in appearance to pericardial effusion.

Enlarged Great Vessels

Enlargement of the main pulmonary artery or aortic arch can occur due to turbulent blood flow or an increase in pressure downstream in the direction of vascular flow. Findings consistent with enlargement of great vessels should be correlated with additional abnormalities seen within the study (e.g., heart enlargement, peripheral pulmonary vascular size, and signs of failure) to decide on likely differential diagnoses.

An enlarged main pulmonary artery will cause a bulge in the cranial cardiac base (8:00–11:00 position) on the lateral view. This is also the location of the aorta and right atrium. The ventrodorsal view must be used to distinguish these three potential causes of a cardiac bulge in this location. On the ventrodorsal view, an enlarged main pulmonary artery causes a bulge in the left cranial cardiac margin at the 1:00–2:00 position, as shown in Figure 3.25a, b. The two main causes of a dilated main pulmonary artery are turbulent flow (poststenotic dilatation secondary to pulmonic stenosis or patent ductus arteriosus) or congestion due to pulmonary hypertension. All causes of an enlarged main pulmonary artery can result in right-sided cardiomegaly. The main distinguishing factor among the differential diagnoses is the appearance of peripheral pulmonary vasculature, as shown in Table 3.12.

An enlarged aortic arch will cause a bulge in a similar location to that of right atrial and main pulmonary arterial enlargement on the lateral view at the cranial cardiac base (8:00–11:00 position). On the orthogonal view, enlargement of the aortic arch will appear as a bulge in the cranial cardiac margin at the 11:00–1:00 position. Oftentimes, aortic arch enlargement will appear as a widening of the caudal aspect of the cranial mediastinum. Enlargement of the aortic arch is most often caused by turbulent flow and poststenotic dilatation secondary to aortic stenosis, as shown in Figure 3.26a, b.

Aortic enlargement can also occur at the level of the proximal descending aorta. Enlargement in this location is radiographically distinct from enlargement of the aortic arch due to aortic stenosis and nearly pathognomonic for a patent ductus arteriosus (PDA). The enlargement is due to turbulent flow caused by abnormal blood flow between the main pulmonary artery and aorta that occurs at the proximal descending aorta. This finding is most evident on the ventrodorsal view, as shown in Figure 3.27.

The caudal vena cava should be less than 1.5 times the width of the aorta. An enlarged caudal vena cava is

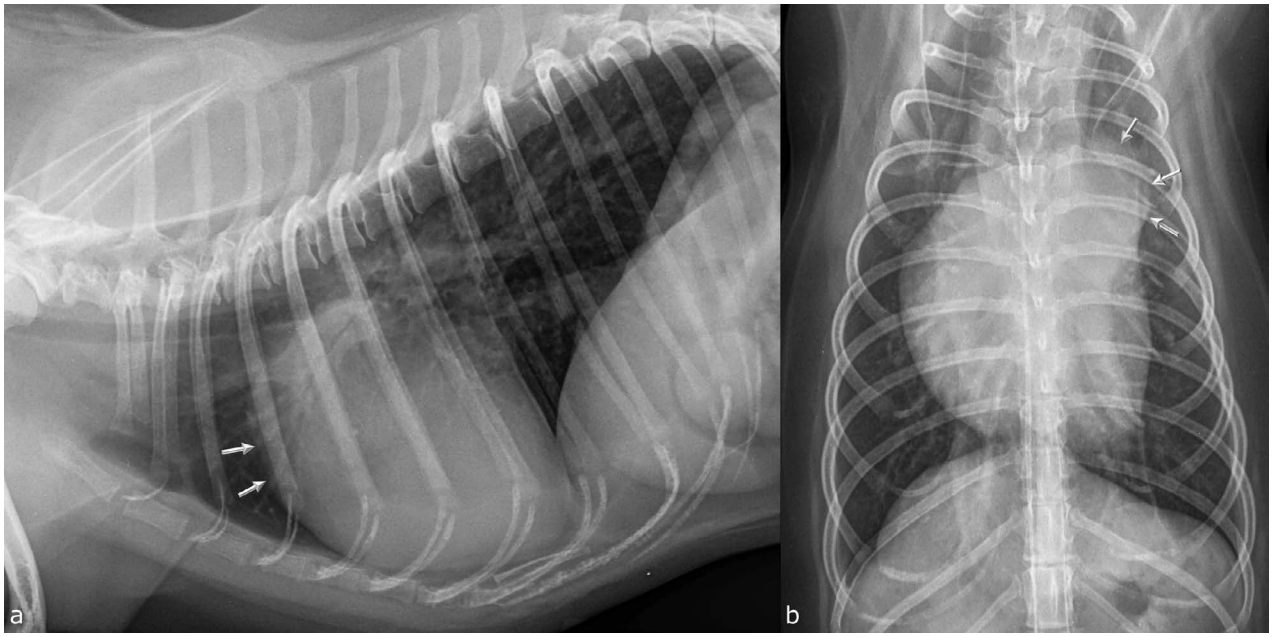


FIGURE 3.25 Lateral **(a)** and ventrodorsal **(b)** radiographs of a dog having radiographically evident main pulmonary arterial enlargement. An increased convexity is present at the cranial cardiac base on the lateral view (a, white arrows). A large focal bulge is present at the left cranial cardiac margin on the ventrodorsal view in the region of the main pulmonary artery (1:00–2:00 position; b, white arrows).

TABLE 3.12 Differential diagnoses and distinguishing factors for main pulmonary arterial (MPA) enlargement

Radiographic findings	Primary differential
Dilated MPA + small peripheral pulmonary vasculature	Pulmonic stenosis
Dilated MPA + dilated peripheral pulmonary arteries	Pulmonary hypertension (primary or secondary to heartworm infection)
Dilated MPA + dilated peripheral arteries and veins	Patent ductus arteriosus

MPA, main pulmonary artery.

most often due to congestion from right-sided heart failure. Radiographic changes consistent with right-sided cardiomegaly may be concurrently evident. The cranial vena cava is not seen as a distinct structure separate from other soft tissue opacities within the cranial mediastinum; therefore, its enlargement is not radiographically visible.

Pulmonary Arteries and Veins

Differentials diagnoses for cardiac enlargements should always be considered in combination with pulmonary vascular appearance. Pulmonary venous enlargement, pulmonary arterial enlargement, and combination pulmonary arterial and venous enlargement or hypovascularity have entirely separate differential diagnoses. Table 3.13 summarizes differential diagnoses for pulmonary arterial and/or venous enlargements.

The pulmonary arteries and veins are paired and surround the lobar bronchi, creating a triad of artery, bronchus, and vein. On the lateral view, the arteries are always located dorsal to the bronchus, and veins are located ventral. The size of the cranial lobar arteries and veins is best assessed on the lateral thoracic radiograph and should be similar in diameter to each other and to the proximal aspect of the 4th rib. The caudal lobar arteries and veins are best assessed on the ventrodorsal/dorsoventral view. The caudal lobar arteries are peripherally located relative to the bronchi and veins. As such, the veins are centrally located and are said to be "central and ventral" within the triad of artery, bronchus, and vein on the radiographic views. The size of the caudal lobar pulmonary arteries and veins can be compared to the diameter of the 9th ribs as they cross on the ventrodorsal view; they should be similar in size to each other and to the 9th rib at the location of their crossing. If the pulmonary arteries and veins are normal in size, the summation of the vasculature crossing the rib will form a square.

Congestive Heart Failure

Right-sided congestive heart failure is the inability of the heart (specifically the right atrium) to accommodate blood volume returning from systemic circulation. Increased right atrial pressure causes those vascular structures draining into the right atrium from the systemic circulation (cranial vena cava, caudal vena cava,

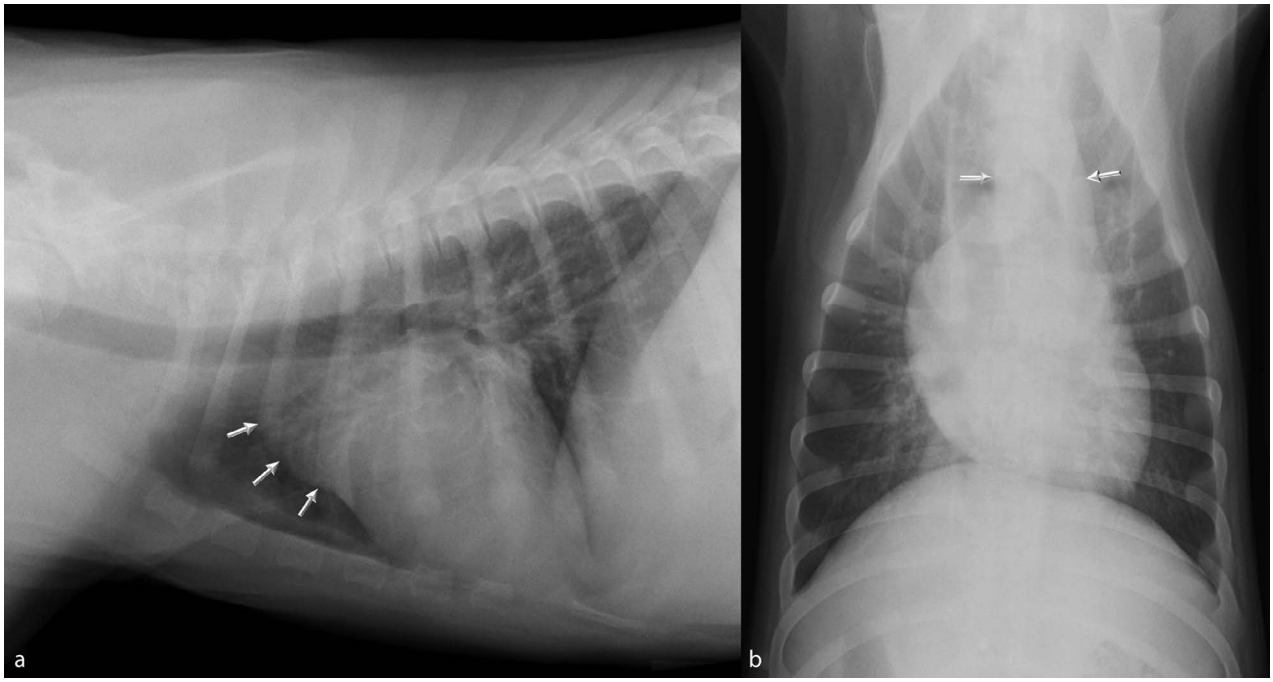


FIGURE 3.26 Lateral **(a)** and ventrodorsal **(b)** views in a dog having an enlarged aortic arch due to a poststenotic dilatation from subaortic stenosis. On the lateral view, a focal bulge is seen at the cranial cardiac base in the 8:00–11:00 position (a, white arrows). On the ventrodorsal view, an increase in soft tissue opacity is seen at the caudal aspect of the cranial mediastinum, also associated with the 11:00–1:00 position of the cardiac silhouette (b, white arrows).

lymphatics) to become congested and unable to transmit blood volume forward into the heart. The compensatory mechanisms of the heart are overwhelmed and result in congestive failure. Right-sided cardiomegaly does not automatically imply right heart failure; however, when right-sided cardiomegaly is diagnosed radiographically, evidence of failure should be intentionally sought. Radiographic signs indicating

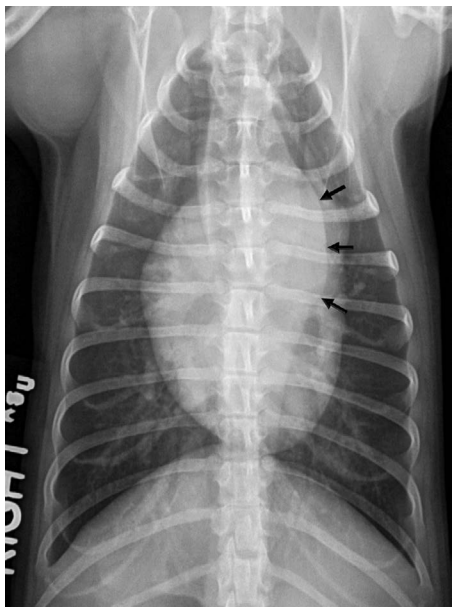


FIGURE 3.27 Ventrodorsal radiograph of a dog having enlargement of the proximal descending aorta secondary to a patent ductus arteriosus. The proximal aspect of the descending aorta has a focal convexity at the level of the proximal descending aorta (black arrows) that is distinct from aortic arch enlargement due to aortic stenosis.

TABLE 3.13 Differential diagnoses for abnormal pulmonary vascular size

Dilated pulmonary veins
- Elevated left atrial pressure
  - Mitral insufficiency, cardiomyopathy, etc.

Dilated pulmonary arteries
- Arteritis secondary to parasitic infection (e.g., heartworm infection)
- Pulmonary hypertension
- Pulmonary thromboembolism

Dilated pulmonary arteries and veins
- Left-to-right shunting of blood
  - PDA, VSD, ASD
- Volume overload
- Chronic or severe mitral valvular disease (pulmonary venous dilation expected prior to arterial dilation)

Small pulmonary arteries and veins
- Hypovolemia
- Shock
- Severe pulmonic stenosis
- Tricuspid dysplasia or severe tricuspid insufficiency
- Right to left shunts
  - Reverse PDA
  - VSD combined with pulmonic stenosis or pulmonary hypertension
  - Tetralogy of Fallot

Box 3.11 Radiographic findings of right heart failure include right-sided cardiomegaly or pericardial disease in combination with one or multiple of the following:

- Dilated caudal vena cava
- Generalized hepatomegaly
- Peritoneal effusion
- Pleural effusion*

* In dogs, effusion occurring in the pleural space due to right heart failure occurs only after effusion in the peritoneal space. Therefore, peritoneal effusion or bicavitary effusion has a differential diagnosis of right heart failure, but pleural effusion alone is not typically caused by right heart failure.

right-sided heart failure are shown in Box 3.11 and Figure 3.28.

Left-sided congestive heart failure is the inability of the heart (specifically the left atrium) to accommodate blood volume returning from pulmonary circulation. Increased left atrial pressure causes the pulmonary veins to become congested and unable to transmit blood volume into the chamber. The compensatory mechanisms of the heart are overwhelmed and result in congestive failure with excess blood volume in the pulmonary veins. Left-sided cardiomegaly does not imply left heart failure. The radiographic study must be specifically evaluated for indications of failure, which include dilated pulmonary veins and cardiogenic edema characterized by interstitial or alveolar pulmonary opacity typically having a perihilar/caudodorsal distribution. The edema is most often symmetrical but can be asymmetrical as well. An asymmetrical distribution tends to occur most often secondary to mitral valvular disease. Radiographic signs indicating left-sided heart failure are shown in Box 3.12 and Figure 3.29a–c. In cats, the distribution

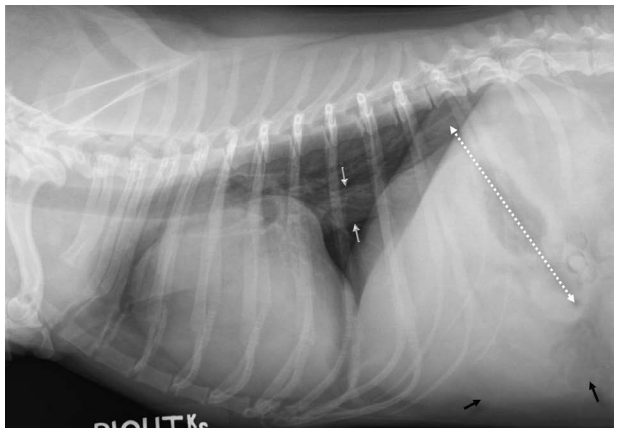


FIGURE 3.28 Lateral thoracic radiograph in a dog having right-sided cardiac failure due to pulmonic stenosis and tricuspid dysplasia. The caudal vena cava is dilated and fails to taper towards the diaphragm (between white arrows). The liver is enlarged, causing caudal displacement of the gastric axis (dotted white arrow). Peritoneal effusion is present, causing soft tissue opaque streaking and a decrease in detail of visible abdominal structures (black arrows). These findings combined with an enlarged, wide cardiac silhouette are indicative of right-sided heart failure.

Box 3.12 Radiographic findings of left heart failure include left-sided cardiomegaly in combination with one or multiple of the following:

- Dilated pulmonary veins
- Cardiogenic pulmonary edema
  - As pulmonary venous dilation and congestion progress, the increased pressure causes edema within the pulmonary interstitium. As edema worsens, the pulmonary pattern becomes alveolar
  - *Dogs:* Cardiogenic edema centered in perihilar/caudal lung lobe regions – symmetrical or asymmetrical
  - *Cats:* Cardiogenic edema has multifocal distribution and can be anywhere

of cardiogenic edema is often less predictable in regional distribution and can be diffuse or multifocal, as shown in Figure 3.30a, b. Additionally, although the mechanism is unclear, pleural effusion often accompanies cardiogenic edema in cases of left-sided failure in cats. This is not a feature seen in dogs, where only right-sided heart failure causes pleural effusion.

Pericardial Effusion

Pericardial effusion is most often idiopathic or neoplastic, such as right atrial hemangiosarcoma, heart base chemodectoma, or mesothelioma. Pericardial fluid increases pressure within the pericardium that can overwhelm the right atrial and ventricular pressure, resulting in cardiac tamponade and right-sided heart failure. Radiographic signs associated with pericardial effusion are summarized in Box 3.13 and Figure 3.31a, b. Effusion within the pericardial space creates a globoid cardiac silhouette, when severe, that precludes visibility of normal cardiac chambers. A key feature differentiating pericardial effusion from generalized cardiomegaly is the absence of visible left atrial dilation. Severe right-sided cardiomegaly and pericardial effusion can appear radiographically similar. Smaller volumes of effusion have potential for causing cardiac tamponade, with normal cardiac chambers still being visible radiographically, especially in acute cases. Secondary signs of right-sided heart failure are often seen at the time of diagnosis as part of the presenting complaint. Clinically significant pleural effusion that is severe enough to cause right heart failure is rare in cats. Small volumes of pericardial

Box 3.13 Radiographic appearance of pericardial effusion

- Globoid cardiac silhouette
  - Cardiomegaly without radiographic evidence of specific chamber enlargements
- Right-sided heart failure
  - Dilated caudal vena cava
  - Generalized hepatomegaly
  - Peritoneal effusion
  - Pleural effusion

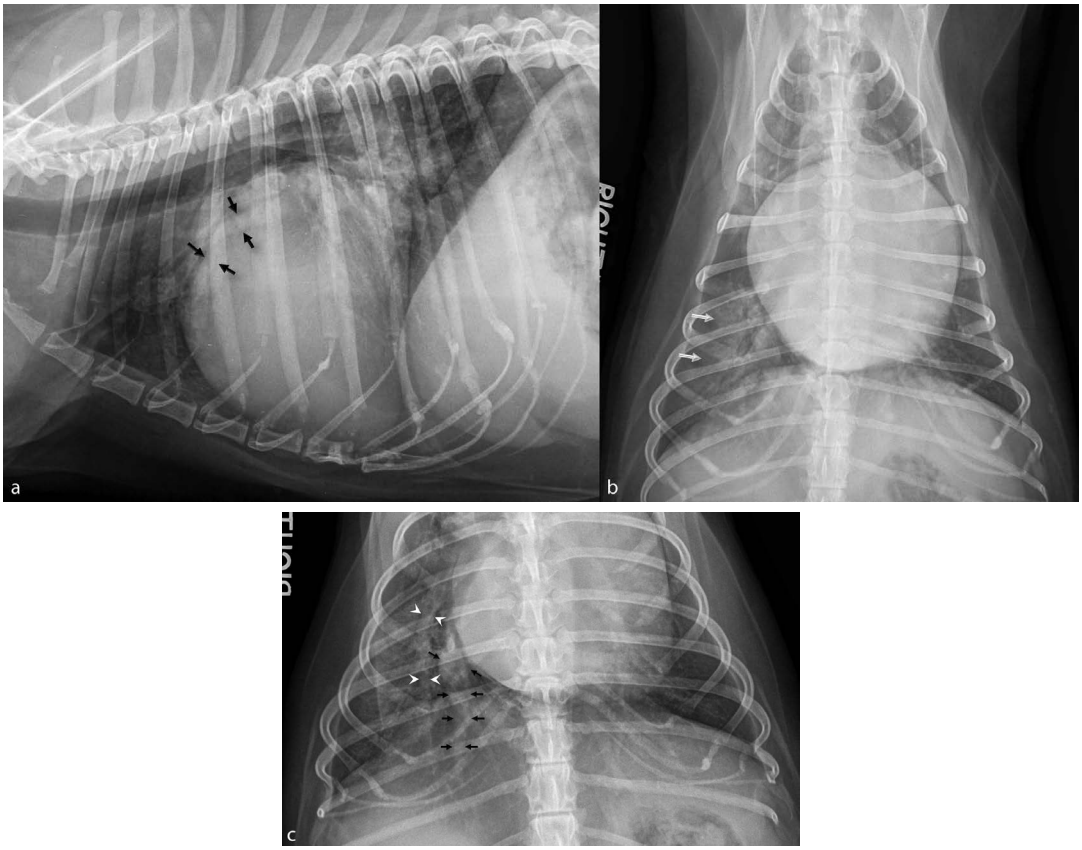


FIGURE 3.29 Lateral **(a)**, ventrodorsal **(b)**, and dorsoventral **(c)** thoracic radiographic views of a dog having left-sided cardiac failure due to mitral valvular insufficiency. The cranial lobar veins are increased in size (a, between black arrows). The caudal lobar vasculature is partially obscured by an increase in pulmonary opacity that is located in the perihilar and caudodorsal lungs, which is more severe on the right side (b, white arrows). On the dorsoventral view of the thorax, the dilated caudal lobar pulmonary veins (c, black arrows) are more clearly seen relative to the normal pulmonary arteries (c, white arrow heads). These findings combined with evidence of left-sided cardiomegaly (a tall cardiac silhouette and marked left atrial enlargement) indicate left-sided cardiac failure.

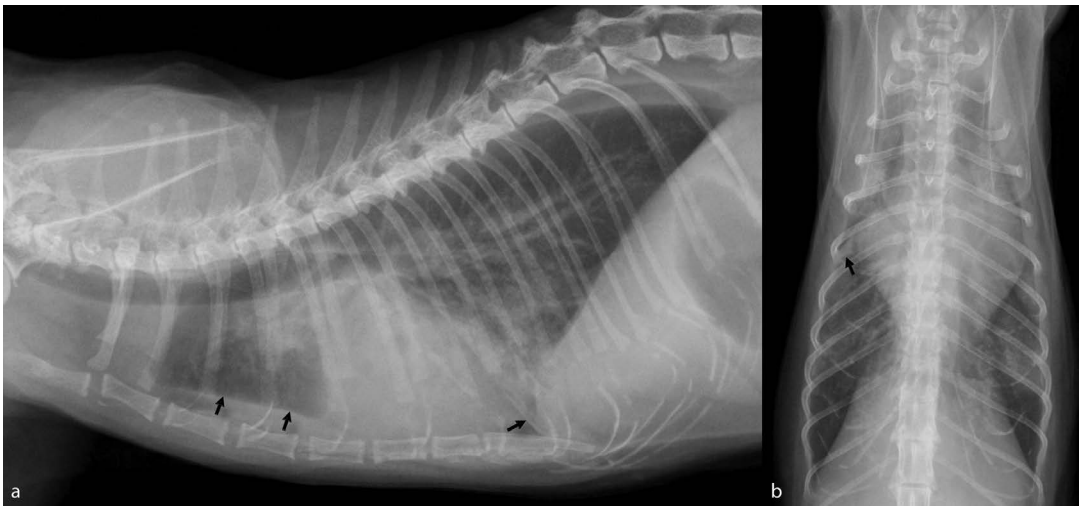


FIGURE 3.30 Lateral **(a)** and ventrodorsal **(b)** thorax radiographs in a cat with left-sided congestive heart failure due to feline cardiomyopathy. The regional distribution of cardiogenic edema is multifocal and predominantly ventral, causing partial border effacement of the cardiac silhouette. Cardiac enlargement can be assumed due to dorsal elevation of the trachea and the visibility of atrial enlargement on the ventrodorsal view. Additionally, evidence of mild pleural effusion is visible where lungs are retracted from the thoracic wall, and small pleural fissure lines are present (a and b, black arrows). A small volume of pleural fluid is a common finding in cats with left-sided cardiac failure.

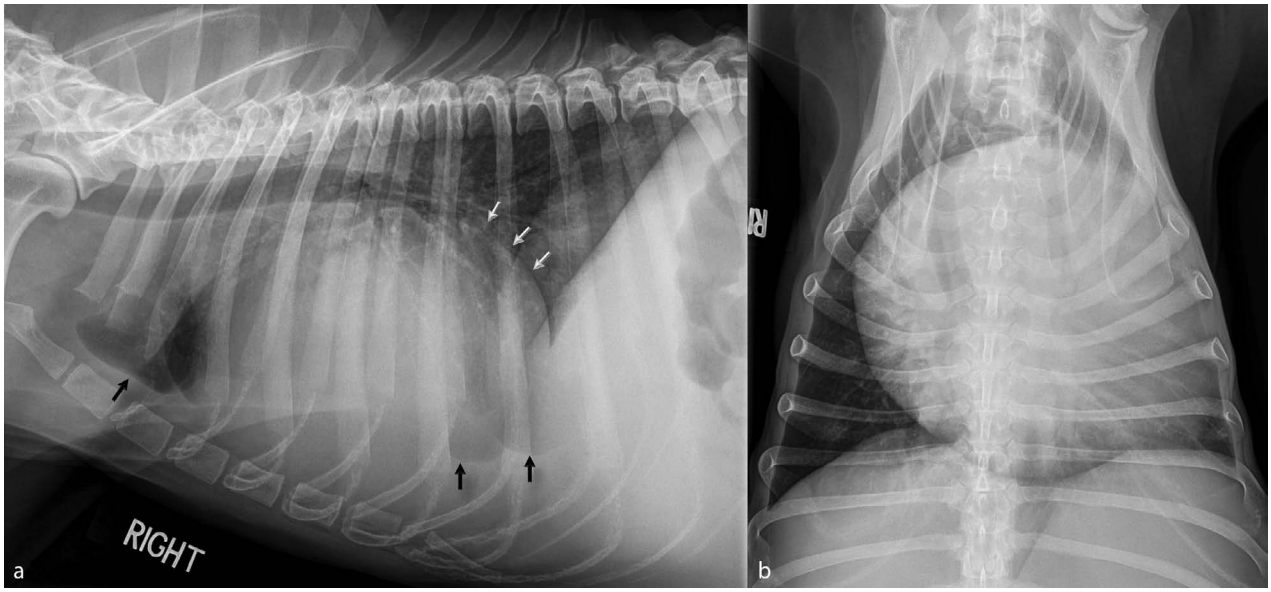


FIGURE 3.31 Lateral **(a)** and ventrodorsal **(b)** thoracic radiographs in a dog having marked pericardial effusion. The cardiac silhouette is globoid with no evidence of specific chambers that are enlarged. Notice the absence of visible left atrial enlargement (a, white arrows). Right heart failure is also present denoted by poor abdominal serosal detail and pleural effusion (retraction of lungs from the thoracic wall by fluid; b, black arrows).

effusion are often seen in cats presenting with heart failure secondary to feline cardiomyopathy.

Microcardia is a small heart due to decreased systemic venous return. Causes are similar to those for small pulmonary arteries and veins and include shock, dehydration/hypovolemia, hypoadrenocorticism, overinflated lungs, pneumothorax, and obstructed venous flow. Microcardia is often accompanied by a consistently small vena cava in addition to decreased pulmonary vascular diameter.

5. Lungs

Alveolar Pulmonary Pattern

Three descriptive hallmarks are seen with alveolar disease of any cause: Air bronchogram, lobar sign(s), and border effacement. Having any one of these three would classify the pulmonary pattern as alveolar. Often, not all hallmarks are present. An air bronchogram occurs when alveoli are not aerated, i.e., they contain fluid (edema, hemorrhage, pus) or are collapsed while the bronchi remain aerated. Its appearance is likened to a "tree in a snowstorm," where the branching lucent bronchus is evident against a white backdrop. A lobar sign occurs when alveolar disease is peripheral relative to lobar margins and inconsistent among lung lobes. This allows the margin of the lung lobe to be evident as a relatively distinct line between an affected lobe that is adjacent to a more aerated lobe. Border effacement is the most consistently present hallmark of alveolar disease. When objects are effaced, their margins can no longer be delineated. In order for this to occur, the objects have to be identical in opacity (usually both are soft tissue/fluid opaque), and they have to be in direct physical contact with each other. When alveolar disease is present, fluid within alveoli, which is identical in opacity to the heart, pulmonary vasculature, and bronchial walls, contacts any of these structures such that their margins are no longer distinguishable. The hallmarks of alveolar disease are depicted in Figure 3.32a–d.

The first descriptive discriminator in differentiating causes of alveolar disease is lung size. A decrease in lung size due to collapse of airways is called atelectasis. Atelectasis results in an increase in pulmonary opacity and decreased lung volume seen as a mediastinal shift towards the opaque lung (ipsilateral mediastinal shift) and ipsilateral cranial positioning of the diaphragm. Atelectasis can be due to obstructive or nonobstructive causes. Obstructive (or resorption) atelectasis occurs when the diameter of the airway is reduced or blocked, most commonly from mucus plugging, bronchial wall inflammation, or a neoplastic mass. The reduction in diameter may be luminal, mural, or extramural in origin. Regardless, trapped gas is resorbed and not replaced, resulting in decreased lung volume. This form of atelectasis is most commonly seen in cats with bronchial disease, resulting in mucus plugging and so-called right middle lung lobe syndrome or atelectasis of the right middle lung lobe. Nonobstructive atelectasis may be due to compression/relaxation, surfactant deficiency, or loss of pulmonary compliance due to cicatrization (e.g., fibrosis of pleura limiting lung expansion).

When not caused by atelectasis, alveolar disease is typically caused by fluid accumulation (edema, hemorrhage, or pus) or cells (granuloma or neoplasia) within alveoli. The regional distribution is the most effective means of distinguishing these, as shown in Table 3.14. Pulmonary edema can be caused by cardiogenic or noncardiogenic mechanisms. The causes of noncardiogenic pulmonary edema are listed in Box 3.14.

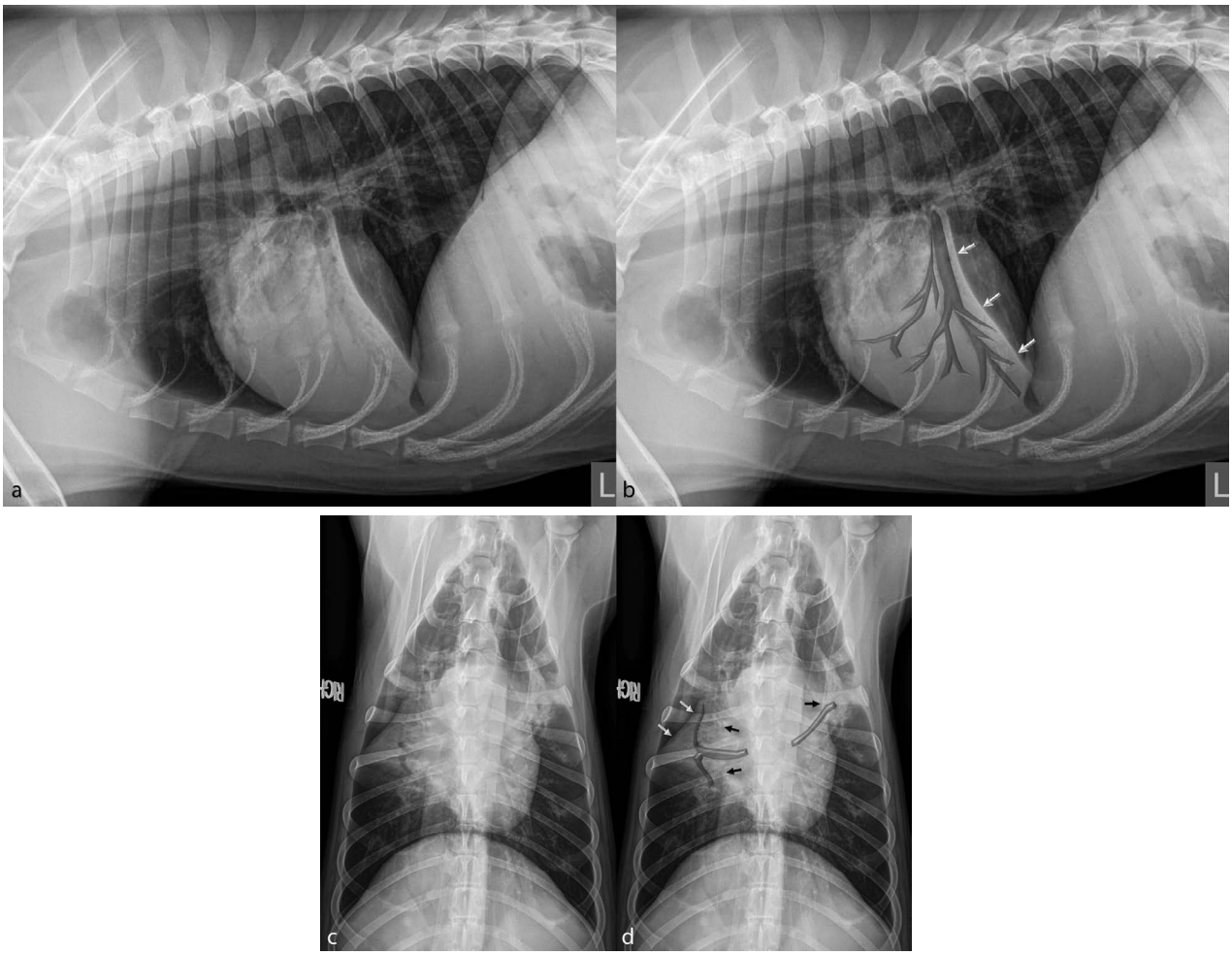


FIGURE 3.32 Lateral **(a)** projection with accompanying schematic **(b)** and ventrodorsal **(c)** projection with accompanying schematic **(d)** thoracic views of a dog having alveolar pulmonary disease within the right middle and left cranial lung lobes due to aspiration pneumonia. All hallmarks of alveolar disease are evident. Air bronchograms can be seen as gray branching structures (b and d, highlighted in gray) against a white backdrop and are visible on both projections, in this case. Lobar signs (b and d, white arrows) are visible between the right middle lung lobe and the more aerated adjacent lobes. Finally, border effacement prevents ability to see the right and left cranial cardiac margins (b and d, black arrows) and margins of vasculature/bronchi within the affected lobes.

Interstitial Pulmonary Pattern

The interstitial pulmonary pattern is subcategorized into structured and unstructured. The unstructured interstitial pulmonary pattern is notoriously difficult to diagnose, as the appearance of the interstitium is greatly influenced by technical factors and respiratory phase. Additionally, it may indicate active or past disease. An unstructured interstitial pulmonary pattern is described by an increase in pulmonary opacity that is less intense per unit area when compared to alveolar disease such that margins of vessels are less delineated but not totally effaced, as shown in Figure 3.33a–d. Any disease resulting in an alveolar pulmonary pattern can appear as an unstructured interstitial pulmonary pattern with a similar regional distribution. As the evolution of fluid changes from less to more severe or as resolution occurs with treatment, a shift can be seen from interstitial to alveolar and from alveolar to interstitial, respectively. Therefore, the distributions and differential diagnoses for interstitial disease can be described as that described previously for alveolar disease. Additionally, in cases of an unstructured pulmonary pattern that is distributed diffusely, fibrosis, neoplasia (lymphoma, hemangiosarcoma), or hematogenous pneumonitis (infectious/noninfectious inflammatory) should be considered.

The structured pulmonary pattern is reserved for any nodular or mass lesion(s) seen within the lung. This pattern can be relatively intense per unit area, depending on size of the nodule. The difference between a nodule and a mass is strictly size, where a mass is 3 cm or greater. Masses and nodules are best delineated from other lesions of high intensity per unit area (i.e., alveolar lung disease) by the rounded, sometimes well-defined margins seen with structured interstitial disease. The main differential diagnoses for this pulmonary pattern are summarized in Table 3.15. Granulomatous pneumonia tends to occur in younger animals, and the nodules

TABLE 3.14 Regional distribution of lung diseases resulting in an alveolar pulmonary pattern

Causes of alveolar pattern	Regional distribution
– Aspiration or bronchopneumonia	– Ventral to trachea
– Cardiogenic pulmonary edema	– Perihilar/ caudodorsal/diffuse – Multifocal in cats – Peribronchial in dogs with DCM
– Noncardiogenic pulmonary edema	– Caudodorsal
– Hemorrhage – Trauma – Coagulopathy	– Variable – Variable/ caudodorsal
– Interstitial pneumonia	– Caudodorsal/diffuse
– Pulmonary thromboembolism	– Variable
– Atelectasis	– Often ventral to trachea/variable
– Primary lung tumor	– Lobar/caudal lobes/ variable

DCM, dilated cardiomyopathy.

Box 3.14 Causes of noncardiogenic pulmonary edema

- Upper airway obstruction
- Head trauma
- Electrocution
- Uncontrolled seizures
- Hypoglycemia
- Thoracic trauma
- Smoke inhalation
- Near drowning
- Acute lung injury/acute respiratory distress syndrome
  - Acute interstitial pneumonia/pneumonitis
  - Systemic inflammatory response syndrome
  - Pancreatitis
  - Sepsis
  - Uremia

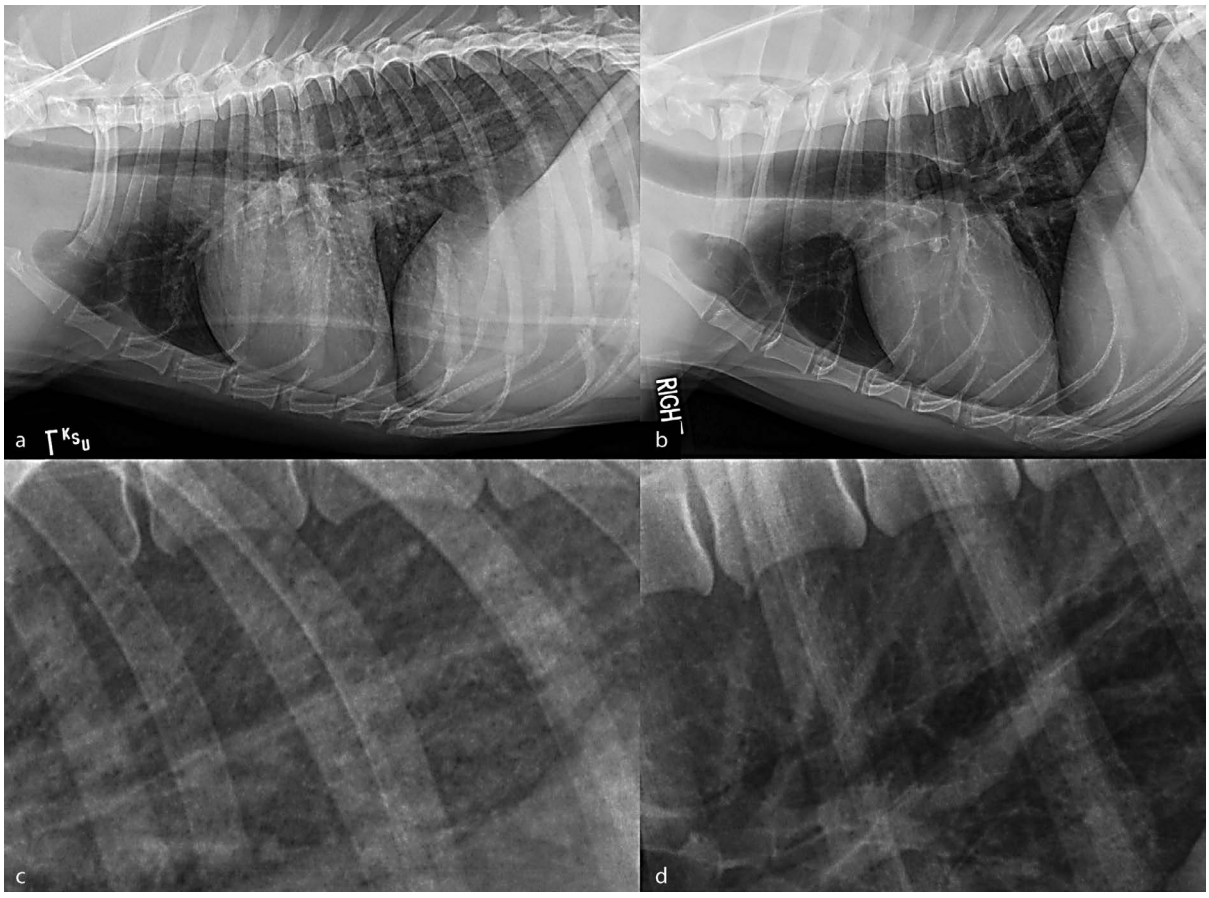


FIGURE 3.33 Unstructured interstitial pulmonary pattern. Lateral thoracic radiographic view **(a)** and closeup **(c)** of a dog with confirmed uremic pneumonitis creating an interstitial pulmonary pattern. A lateral thoracic radiograph **(b)** and closeup **(d)** of a normal dog not having clinical respiratory disease is shown for comparison. The caudodorsal distribution of pulmonary opacity makes noncardiogenic pulmonary edema more likely, which is a typical appearance for acute lung injury due to uremic pneumonitis.

TABLE 3.15 Differential diagnoses for a structured interstitial pulmonary pattern

Number and description	Differential diagnoses
Multiple soft tissue nodules	Metastasis, granulomatous pneumonia, septic emboli, parasitic (e.g., *Paragonimus kellicotti*), cysts, artifactual (end-on vasculature, superimposed superficial nipple or debris)
Solitary soft tissue nodule or mass	Primary tumor, single metastasis, granuloma (foreign body), abscess, fluid-filled cyst, artifactual (see mentioned in the text earlier)
Multiple or single cavitary nodule(s)/ mass(es)	*Thick-walled:* Neoplasia (primary or metastatic), abscess, granuloma, parasitic *Thin-walled:* Bulla, cyst, airway dilation (bronchus/bronchiectasis, alveoli/ emphysema)
Single or multiple mineral nodule(s)	Pulmonary osteomas, chronic fungal granulomas, rarely parasitic nodules, or neoplasia

tend to be of a similar size with indistinct margins. Sometimes, nodules can appear very small creating a miliary type of pulmonary pattern, as shown in Figure 3.34. Multiple nodules due to metastatic disease tend to occur in older animals. The nodules are more often variable in size with well-defined margins. Multiple mineralized pulmonary nodules, called pulmonary osteomas, pulmonary osteomata, or heterotopic bone, occur as a benign finding in dogs, especially Boxers and Shetland Sheepdogs. They are often in higher numbers ventrally and only a few millimeters in size. True soft tissue opaque nodules of this size would be poorly detected on radiographs, so when a nodule that is 3 mm or less is visible on radiographs, the interpreter must consider a mineralized nodule or end-on vessel. Additionally, these mineralized pulmonary osteomas are typically irregularly marginated when

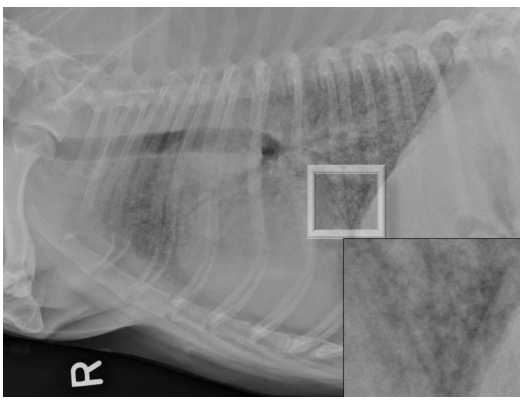


FIGURE 3.34 Lateral thoracic radiograph with magnified inset in a dog with a miliary structured interstitial pulmonary pattern due to Blastomycosis. The nodules are very small in size, resembling an accumulation of millet seeds, and have very indistinct margins, reflecting active inflammation. The diagnosis was achieved with lung aspiration.

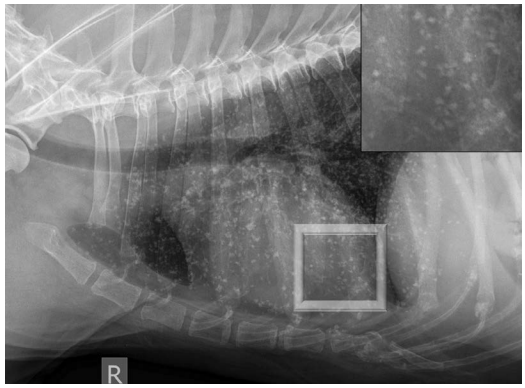


FIGURE 3.35 Lateral thoracic radiograph obtained of a Shetland Sheepdog for metastasis check. Numerous, well-defined mineralized nodules are present. Many of these nodules are less than 3 mm in size yet are highly visible, supporting suspicion of mineralized benign pulmonary osteomas. On close inspection of the magnified inset, the nodules are highly irregularly marginated rather than being round in shape.

inspected closely, also distinguishing them form many soft tissue opaque nodules. As mentioned, pulmonary osteomas are benign and can be quite numerous, as shown in Figure 3.35. Mineralized malignant nodules are extremely rare in veterinary medicine.

Regardless of whether or not the interstitial pulmonary pattern is structured or unstructured, a definitive diagnosis is most often determined via lung aspiration rather than airway sampling.

Bronchial Pulmonary Pattern

The bronchial pulmonary pattern implies disease that is airway related. Fluid or cells infiltrate bronchial walls and result in radiographically evident thickening. In most cases, the ailment affecting the bronchus extends into surrounding peribronchial interstitium. In some cases, the infiltration may be limited to peribronchial interstitium; however, airway-related disease remains the most common underlying cause. It is a common mistake to assign a bronchial pattern when normal bronchi are noticed, especially if clinical signs such as coughing are present. Seeing bronchi does not make the study abnormal. Disease can be assumed, however, when the bronchi are thickened, irregular, and/or indistinct in margination. Irregular and thickened bronchial walls create the so-called tram tracks and rings within the lungs, as shown in Figure 3.36a, b.

In addition to bronchial walls being thickened and irregular when radiographically visible disease is present, bronchi can fail to taper due to bronchiectasis (Figure 3.37). Bronchiectasis is important to recognize as an irreversible sequela of chronic airway-related disease and as a predisposing factor for future airway-related symptoms and bronchopneumonia.

Vascular Pulmonary Pattern

This pattern is reserved for cases where the pulmonary vasculature is too big or too small. Many do not

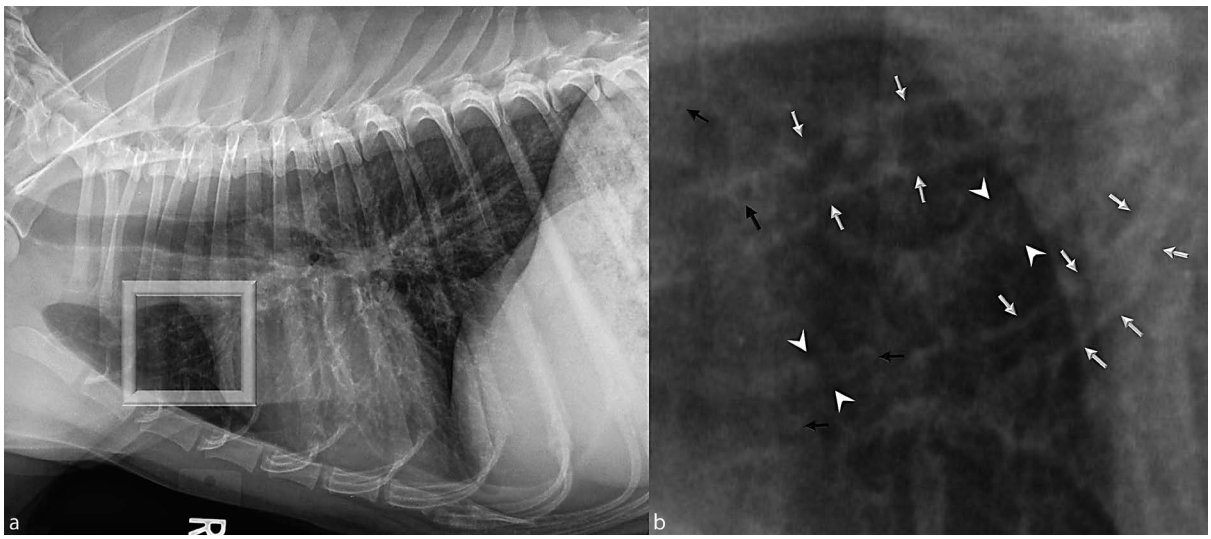


FIGURE 3.36 Lateral thoracic radiograph **(a)** and magnified inset **(b)** of a dog having chronic bronchial disease. The bronchial walls seen in longitudinal orientation (b, white arrows) and those seen end-on (b, black arrows) are thick and irregular, creating the tram-tracks and rings expected with bronchial disease. The walls are thinner and more irregular than adjacent pulmonary vasculature (between white arrowheads). A noninfectious, inflammatory airway inflammation was determined based on bronchoalveolar lavage.

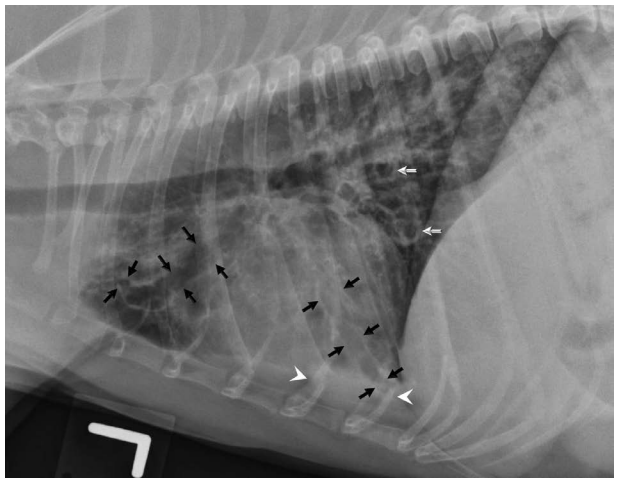


FIGURE 3.37 Left lateral thoracic radiograph in a dog having a chronic cough of 11 years' duration. Increased irregular, well-defined linear and ring markings are present in all lung lobes, consistent with a chronic bronchial pattern. Multiple bronchi fail to taper at the periphery of the lung (black arrows). The tubular shape of the bronchi is consistent with cylindrical bronchiectasis. Enlarged, dilated rings are also visible dorsally, consistent with bronchiectasis viewed end-on. Focal ventral alveolar disease is also present, consistent with bronchopneumonia (white arrowheads), a common predisposing factor and sequela seen in cases of bronchiectasis.

consider this a true pulmonary pattern. If arteries and/or veins are enlarged or small, causes of cardiopulmonary vascular disease should be pursued, as previously discussed. The most common causes of a vascular pulmonary pattern are left-to-right shunts (enlarged arteries and veins) and, in endemic regions, heartworm infection in dogs. The characteristic changes identified in heartworm infection are shown in Box 3.15.

Box 3.15 Radiographic appearance of heartworm infection

- Right ventricular enlargement
  - Concentric nature of hypertrophy makes radiographic detection insensitive until severe
  - *Lateral view:* Wide cardiac silhouette, increased sternal contact, elevated cardiac apex
  - *Ventrodorsal view:* Bulge in 5:00–9:00 position at the right cardiac margin
- Main pulmonary arterial enlargement
  - *Lateral view:* Bulge in the 8:00–11:00 position at the cranial cardiac base
  - *Ventrodorsal view:* Bulge in the 1:00–2:00 position at the left cranial cardiac margin
- Peripheral pulmonary arterial enlargement
- Pulmonary eosinophilic inflammation
  - Peribronchial interstitial to alveolar pulmonary opacity
  - Multifocal nodular pulmonary pattern, in some cases
- Right-sided heart failure
  - Dilated caudal vena cava
  - Generalized hepatomegaly
  - Peritoneal effusion
  - Pleural effusion

RECOMMENDED FURTHER READINGS

1. Suter PF. *Thoracic Radiography: A Text Atlas of Thoracic Diseases of the Dog and Cat*. Wettswil, Switzerland: P. F. Suter, 1984.
2. Thrall DE. *Textbook of Veterinary Diagnostic Radiology*. St. Louis, MO: Saunders, 2013.
3. Dennis R, Kirberger RM, Wrigley RH, Barr FJ. *Handbook of Small Animal Radiological Differential Diagnosis*. London: W. B. Saunders, 2001.
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CHAPTER 4

Approach to Abdominal Radiographs

L. Abbigail Granger

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BASICS OF ABDOMINAL RADIOGRAPHY

To properly interpret abdominal radiographs, lesion description using the six Roentgen signs (size, shape, margination, opacity, location, and number) must be used to translate the image to text so that differential diagnoses can be researched using imaging resources. An understanding of the differing appearance of the five radiographic opacities is crucial to avoiding misinterpretation of findings, such as falciform fat being mistaken for fluid. The five radiographic opacities in order from most lucent to most opaque are: Air, fat, soft tissue/fluid, bone/mineral, and metal. The ability to distinguish organs in the abdomen is primarily created by soft tissue opaque structures being surrounded by fat. Fat is less opaque than soft tissue/fluid, making borders visible. Along similar lines, soft tissue and fluid are of identical radiographic opacity; therefore, thickness of gastrointestinal (GI) walls and the urinary bladder wall cannot be determined on radiographs without the use of contrast. Also, organs can be poorly visible when the peritoneum contains large volumes of fluid because organ margins become effaced when fluid (which has identical opacity as soft tissue) is in direct contact with their borders.

Technique and Positioning

Positioning

An abdominal study should include the entire diaphragm as the cranial boundary and the coxofemoral joints as the caudal boundary. The right and left lateral views are named according to the recumbency of the animal. The ventrodorsal view is obtained with the animal in dorsal recumbency and is the primary orthogonal view obtained in abdominal imaging. A dorsoventral view with the animal positioned in sternal recumbency is rarely obtained. With each view, the hindlimbs should be extended caudally to limit crowding of abdominal organs.

Choosing the Abdominal Views

Like any radiographic study, at least two views must be obtained of the abdomen in order to properly evaluate the study and reconstruct a 3D description from a set of 2D images. Most commonly, right lateral and ventrodorsal views are obtained. In the right lateral view, the tail of the spleen is more commonly visible, and the kidneys are better distinguished as separate structures when compared with the left lateral view. Gravity, mobility of organs, and the changes in distribution of gas and fluid with recumbency can be used to optimize the diagnostic capability of radiographic studies in many common clinical scenarios. Because of this, many radiologists advocate the use of right and left lateral views in addition to an orthogonal view as standard practice for imaging the thorax and the abdomen.

The variation in abdominal organ appearance with recumbency is most notable in the GI tract. Luminal contents within the stomach and small intestine often contain some degree of fluid and gas. Because patients are positioned in recumbency (rather than standing), and views are obtained with a vertical beam (rather than horizontal beam), the classic appearance of a combination of contents in the GI tract is a summation of opacities created by both gas and fluid that change with positioning (Figure 4.1). The redistribution of gas within the GI tract (without administration of additional contrast agents) by obtaining a left lateral view has been used to diagnose pyloric outflow obstructions, locate obstructions within small intestines, highlight intussusceptions, distinguish colon from dilated small intestine, rule out gastric malpositioning, and definitively locate the pylorus, among other applications.

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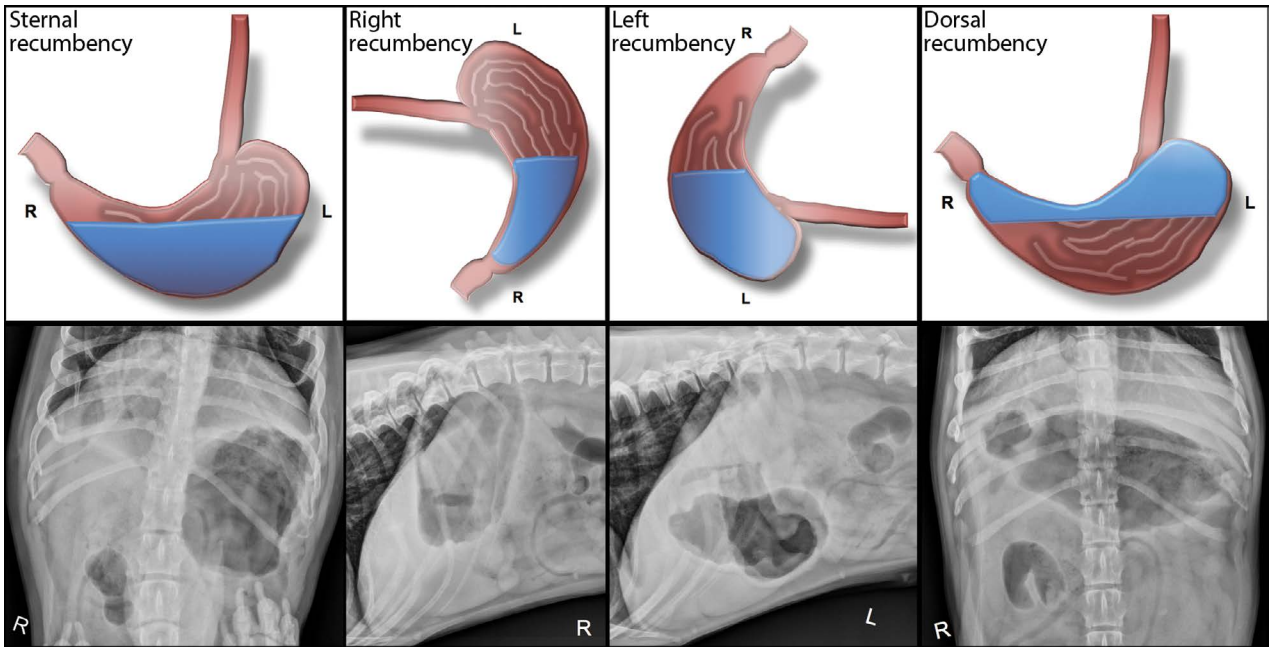


FIGURE 4.1 Diagram showing the distribution of gravity-dependent stomach contents with recumbency. Accompanying radiographic appearance is shown below each diagram. When the animal is positioned in sternal recumbency (dorsoventral view), gas rises to the most dorsal part of the stomach, the fundus, and fluid falls to the most ventral part, the gastric body. As a result, the gastric fundus is more apparent because luminal gas creates the most contrast with surrounding soft tissue opaque organs. In the right lateral view, mobile fluid falls to the most gravity-dependent part of the stomach, the pylorus, while gas rises to the fundus, the largest gastric compartment. As a result, the gas-containing gastric fundus is most visible on right lateral view. On the left lateral recumbent view, gas rises to the nongravity-dependent pylorus, while fluid falls to the fundus, making the region of the pylorus most radiographically evident. Finally, when animals are positioned in dorsal recumbency (ventrodorsal view), gas rises to the most ventral part of the stomach, the gastric body, while fluid falls to the gastric fundus and pylorus. This results in increased visibility of the gastric body.

Special Views

Depending on the clinical circumstances, an additional view outside the standard protocol may provide vital diagnostic information. For example, a flexed hindlimb view of the caudal abdomen can be obtained to evaluate the entire penile urethra for calculi in a male dog while avoiding superimposition of the femurs. Simple additional techniques include positional radiography (left lateral abdominal projection and horizontal beam radiography), compression radiography, and simple negative contrast radiography (pneumocolonogram and pneumogastrogram). These views will be addressed in appropriate sections throughout the chapter.

READING THE ABDOMINAL RADIOGRAPH

Systematic Approach

The interpretation of abdominal radiographs is best accomplished using a checklist-style systematic evaluation of each organ on each view (Box 4.1). Evaluating each organ on every study, regardless of clinical signs, increases the comfort level in recognizing normal from abnormal structures and prevents findings from going undetected. The familiarity gained from a systematic approach will prevent newly recognized organs or organs better seen in one patient versus another from being automatically or inappropriately deemed abnormal. Also, many structures within the abdomen are not seen in normal animals on radiographs. The location of these normally unseen structures should be considered, as disease has the potential to make them visible.

INTERPRETATION OF ABDOMINAL ABNORMALITIES

1. Extra-abdominal Structures

Review and consideration of extra-abdominal structures early in the interpretation process can prevent misplaced importance of those findings and allow limitations of the study to be considered. For example, wet hair can mimic peritoneal effusion, which is typically a significant finding, so early recognition can prevent misdiagnosis.

Abdominal Wall, Skeleton, and Visible Thorax

Initially, the ventral abdominal wall should be characterized as tucked, pendulous, or normal in contour. This will assist with differentiating potential causes of decreased detail, if it exists, and give an overall clue as to the body condition of the animal. An animal with a

Box 4.1 Systematic evaluation of the abdomen

- Extra-abdominal structures
  - Abdominal wall, including soft tissues and axial skeleton
  - Visible thorax
  - Visible pelvic limbs
- Peritoneal space
  - Peritoneum*
  - Mesentery, omentum, falciform fat
  - Mesenteric lymph nodes*
- Liver
  - Gallbladder and biliary tract*
- Spleen
- Retroperitoneal space
  - Retroperitoneal fat
  - Medial iliac and other sublumbar lymph nodes*
- Upper urinary tract
  - Kidneys
  - Ureters*
- Adrenal glands*
- Reproductive tract
  - Ovary/uterus*
  - Prostate†
- Lower urinary tract
  - Urinary bladder
  - Urethra*
- Gastrointestinal tract
  - Stomach
  - Small intestine
  - Colon
  - Pancreas*

* Organs not normally seen radiographically.
† Organ visibility in normal dogs, dependent on neuter status.

tucked abdominal contour may have decreased abdominal detail because of thin body condition, whereas an animal with a pendulous contour and decreased peritoneal detail may have peritoneal effusion or large volumes of peritoneal fat deposition causing increased scatter. Young animals also tend to have a pendulous contour and decreased detail.

Abnormalities within the visible thorax and skeleton may not be responsible for clinical signs but could be significant regardless or could assist with appropriate ranking of differential diagnoses if given consideration.

2. Peritoneal Space

Peritoneal Effusion

The influence of fluid within the peritoneal space can range from a mild decrease in detail to total border effacement of abdominal organs (Figure 4.2a, b). Smaller volumes of peritoneal effusion may cause soft tissue opaque streaking within the falciform and mesenteric fat, making serosal margins less distinct. In some cases, fluid is so severe that the only indication of organ position is the gas within small intestinal loops. An asymmetric distribution of small intestine may indicate mass effect or may simply be due to an absence of gas-filled intestine in a particular region. When differentiating various causes of abdominal effusion, a fluid composition approach is most inclusive. Fluid may be due to transudates, exudate, hemorrhage, urine, bile, or chyle. The causes of each fluid type can then be considered as potential differential diagnoses. Clinical history is also very useful in differentiating causes of effusion. In many instances, fluid sampling and subsequent analysis is the next step with or without abdominal ultrasound.

Decreased serosal detail (Box 4.2) can include the entire abdomen or can have a clear regional distribution indicating disease limited to local organs. Focal or global regions of decreased detail may also be due to

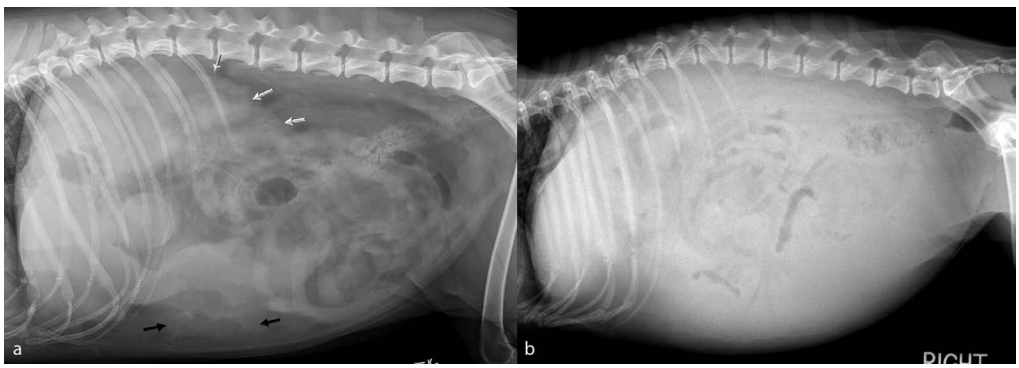


FIGURE 4.2 Lateral abdominal radiographs in a dog having a small volume of peritoneal effusion (a) and a dog having marked peritoneal effusion (b). In the dog having a smaller volume of peritoneal effusion, soft tissue opaque streaking can be seen within ventral abdominal fat (a, between black arrows). Margins of the liver spleen, intestines, and urinary bladder are somewhat visible but are less distinct than in a normal animal. The splenic tail, though less distinct, can be recognized as having a nodular appearance. In this case, the margins of the kidneys remain sharp because they are retroperitoneal in location, and effusion is not concurrently present in the retroperitoneal space. In the dog having a large volume of peritoneal effusion (b), serosal margins of peritoneal structures are completely obscured. The only indication of organ location is the distribution of intestines containing gas. Abdominal ultrasound and/or fluid analysis are the next logical steps in evaluating cases with this volume of effusion.

Box 4.2 Potential causes of reduced peritoneal detail

- Underexposure
- Wet air artifact
- Young animal (typically pendulous contour)
- Abdominal effusion (pendulous contour)
- Mass effect (pendulous contour)
- Obesity (pendulous contour)
- Emaciation or thin body condition (tucked contour)
- Peritonitis
- Carcinomatosis or neoplastic seeding (typically pendulous contour)

peritonitis, which appears similar to small volumes of effusion. In such cases, attempts to sample may be unrewarding, and ultrasound is recommended to determine the underlying cause.

Horizontal Beam Radiography

Abnormalities within the peritoneal space may manifest as excess lucency rather than increased opacity. Free gas within the abdomen can highlight serosal margins, making them apparent when otherwise invisible, e.g., gas dissecting between liver lobes, making their margins visible. Potential causes of free peritoneal gas are listed in Box 4.3. Additionally, most causes of free peritoneal gas also cause some degree of abdominal effusion, resulting in a mixed gray opacity that can be difficult to differentiate from GI contents if care is not taken to avoid misinterpretation. In such cases, horizontal beam radiography can be immensely helpful in confirming suspicion of free gas; however, suspicion of free gas must be present in order to consider use of horizontal beam radiographs.

Box 4.3 Causes of free peritoneal gas

- Perforated hollow viscus
  - Stomach
  - Small intestine
  - Colon
  - Uterus
  - Urinary bladder (gas rarely present)
- Penetrating or perforating injury
  - Bite wound
  - Gunshot
- Ruptured abscess (gas-producing bacteria)
- Recent abdominal surgery (within about 3 weeks)

Horizontal beam views of the abdomen can be obtained by placing the animal in left lateral or dorsal recumbency (Figure 4.3a–d). The basis of these views is to

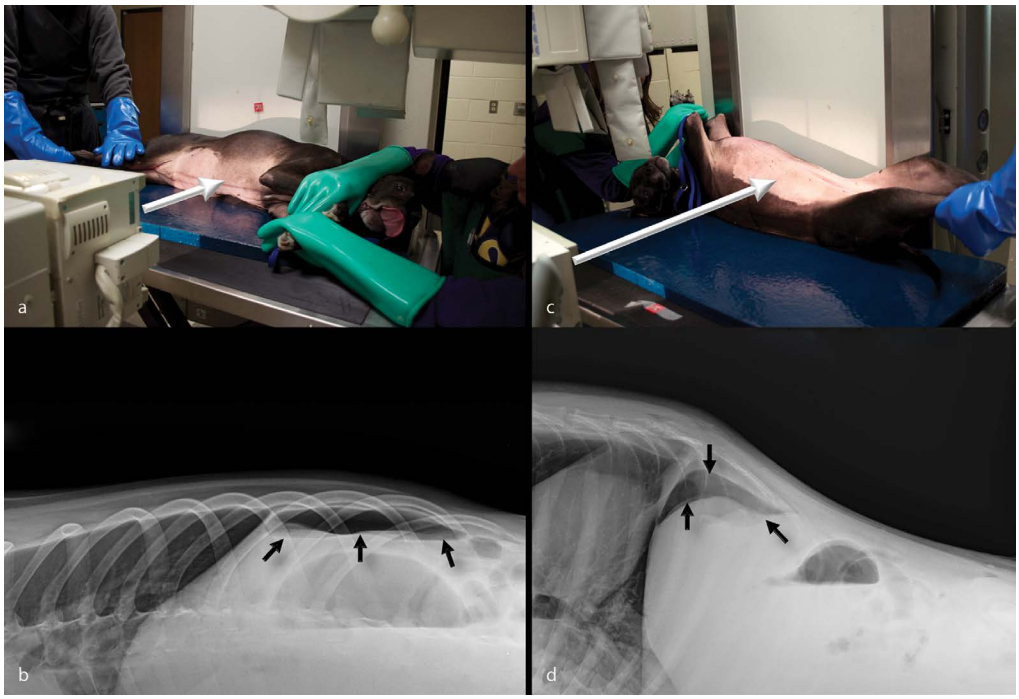


FIGURE 4.3 Horizontal beam radiography of the abdomen. Positioning **(a)** to obtain horizontal beam radiograph with the patient in left lateral recumbency; white arrow denotes direction of the x-ray beam. Resultant horizontal beam ventrodorsal view **(b)** showing free peritoneal gas accumulated caudal to the diaphragm on the right side (arrows). Positioning **(c)** to obtain horizontal beam radiograph with the patient in dorsal recumbency; white arrow denotes direction of the x-ray beam. Resultant horizontal beam lateral view **(d)** showing free peritoneal gas accumulated caudal to the diaphragm, ventrally (arrows).

force gas to accumulate in a predictable location (i.e., non-gravity dependent) and specifically image this location.

Pneumoperitoneum is most often caused by a penetrating/perforating wound or a perforated hollow viscus, usually the GI tract. Unless the cause of the pneumoperitoneum is iatrogenic (i.e., previous abdominal surgery within about 3 weeks), the diagnosis of pneumoperitoneum often indicates septic peritonitis, and surgical intervention is required.

Compression Radiography

The purpose of compression radiography is to isolate a specific region of interest or remove superimposition of peritoneal structures by use of a radiolucent compression device. The most typically used device is a radiolucent wooden spoon or spatula; however, any rigid radiolucent device with a handle can be used. The indications for this study include isolation of specific organs of interest that are otherwise obscured by superimposition or to better delineate margins of a normal or abnormal structure seen on survey radiographs. This technique has been used to better delineate palpable or radiographically visible abdominal masses, isolate the urinary bladder to prove presence or absence of calculi, remove superimposition of the GI tract on kidneys, separate small intestines from each other, and confirm the presence of uterine enlargement, among other potential applications.

Patient positioning depends on the region of interest to be evaluated. Often, standard abdominal views are used to assist in determining the region of interest and positioning for the compression study. Palpation may also dictate a specific region of interest. The specific location should be isolated with a hand, then the hand replaced by the wooden spoon or other compression device. The device should be similar in size to or 1.5 times larger than the specific organ or regions of interest being isolated. The act of compressing reduces the thickness in the region of interest; therefore, the radiographic technique should be reduced to avoid overexposure (decrease kilovoltage peak [kVp] by 10%). Collimating is advisable to avoid personnel exposure and optimize the image (**Figure 4.4a–c**).

Compression should be avoided in cases where rupture is a potential concern, such as a severely enlarged uterus or splenic mass, or in cases of diaphragmatic hernia where organs may be further displaced into the pleural space.

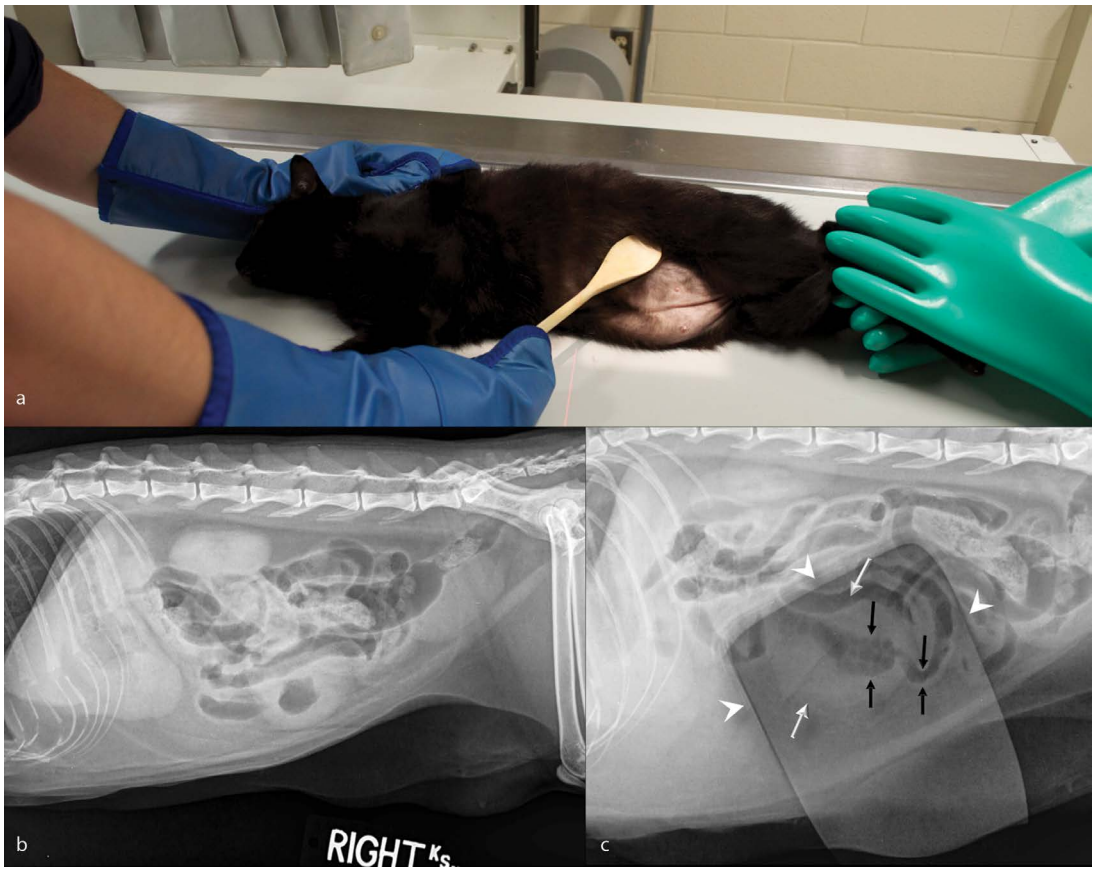


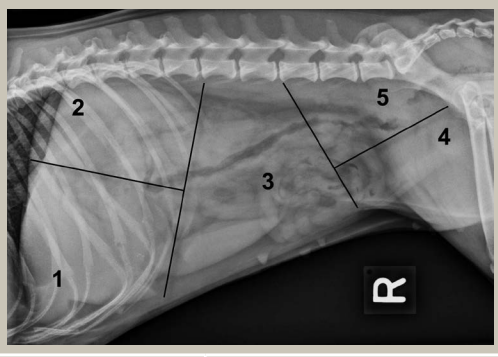
FIGURE 4.4 Technique for performing compression view **(a)** and lateral abdominal survey **(b)** and compression **(c)** radiographs in an 11-year-old female spayed Domestic Shorthair cat presenting with a yearlong history of intermittent vomiting. Typical positioning for a palpable abdominal mass is shown in (a). A ventrally located soft tissue opacity having an indistinct dorsal margin is seen on survey radiographs (b). A lateral radiograph was obtained after using a radiolucent wooden spatula to isolate the mass (c). The wooden spatula decreases thickness of tissues in the region of the mass, which results in an increase in overall apparent exposure in the location of the spatula (c, white arrowheads). The soft tissue opacity is better defined on the compression view (c, white arrows). Also, a gas-containing small intestinal loop leads into the mass, which has an irregular tubular gas center (black arrows), consistent with a small intestinal organ of origin for the mass.

Mass Effect

The visibility of serosal margins can be diminished when organ crowding occurs. Mass effect is the altered distribution of organs within the peritoneal space. A mass, which may or may not be discretely visible, is the object that causes the altered distribution of organs. The description of mass effect is the biggest clue as to the most likely organ of origin for an abdominal mass. For the sake of description of mass effect, the abdomen can be considered to have defined compartments on the lateral and ventrodorsal views. Potential organs of origin for visible masses correspond to the location of the mass effect related to these compartments, as shown in Table 4.1. Description of the organ displacement is the key to determining the most likely compartment for a mass effect and, therefore, the most likely organ of origin and the most likely differential diagnoses for the mass. Location of the mass effect needs to be considered on orthogonal views in order to assign the most likely organ of origin. Keep in mind that a mass effect can be identified without a well-defined mass

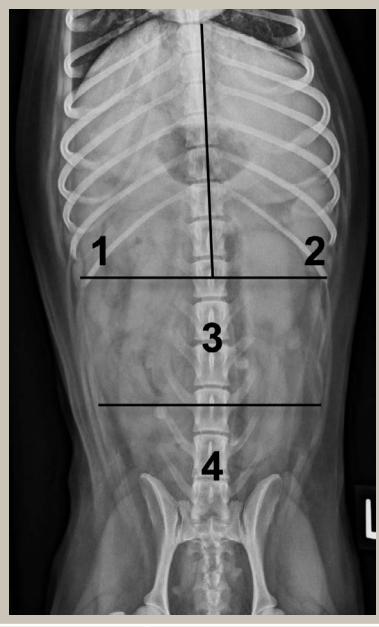
TABLE 4.1 Potential organs of origin for masses located in regions of the peritoneal space

Lateral view



Location of mass effect	Potential organ of origin
1. Cranioventral	– Liver – Spleen – Gastric body and pylorus – Right pancreatic limb – Gallbladder and biliary system – Hepatic and gastric lymph nodes
2. Craniodorsal	– Liver – Splenic head – Gastric fundus – Kidneys – Adrenal glands – Ovary – Left pancreatic limb – Splenic lymph nodes
3. Central	– Spleen – Mesenteric lymph nodes – Mesentery – Uterus – Intestine – Ovary – Retained testicle – Left kidney
4. Caudoventral	– Urinary bladder – Prostate – Uterus – Retained testicle
5. Caudodorsal	– Sublumbar lymph nodes – Distal descending colon – Ureters

Ventrodorsal view



Location of mass effect	Potential organ of origin
1. Right cranial	– Liver – Gallbladder and biliary system – Pancreas – Right kidney – Right adrenal – Pylorus and proximal duodenum – Gastric and hepatic lymph nodes
2. Left cranial	– Spleen – Liver – Gastric fundus – Left pancreatic limb – Left adrenal
3. Central	– Spleen – Mesenteric lymph nodes – Intestine – Left kidney – Uterus – Ovary – Retained testicle
4. Caudal	– Urinary bladder – Uterus – Prostate – Sublumbar lymph nodes – Distal descending colon

Note: Separate regions are delineated with black lines.

Box 4.4 Differential diagnoses for abdominal masses

- Cyst
- Hematoma
- Abscess
- Neoplasia
- Granuloma
- Nodular regeneration, hyperplasia, extramedullary hematopoiesis (liver and spleen)
- Physiologic enlargement (e.g., renal hypertrophy or splenomegaly due to tranquilization)
- Distension of a hollow viscus (gastrointestinal tract, urinary bladder, uterus)
- Organ torsion/congestion

being visible; however, displacement of organs such as the small intestines indicates the presence of an abnormality. Very few differential diagnoses exist for abdominal masses, and they are highlighted in Box 4.4 and are ranked according to the most likely organ of origin.

3. Liver

Hepatic size is a subjective determination based primarily on its shape and the position of the stomach. The axis of the stomach is a line drawn from the gastric fundus to the ventral aspect of the gastric body/pylorus. The gastric axis should be roughly parallel to the ribs or perpendicular to the spine. When the axis of the stomach is angled cranially, causes of microhepatia should be considered. When the axis is angled caudally, causes of hepatomegaly should be considered. The majority of the liver is within the confines of the costal arch; however, it can extend caudal to the arch in normal animals. Increased caudal extension of the caudoventral liver margin indicates hepatic enlargement. Additionally, in some cases of hepatic enlargement, the caudoventral liver margin will appear rounded rather than sharp and triangular.

Increased Liver Size

Hepatomegaly can be categorized as focal, generalized, or nodular. The distinction is important because differential diagnoses are based on the categorization (Table 4.2).

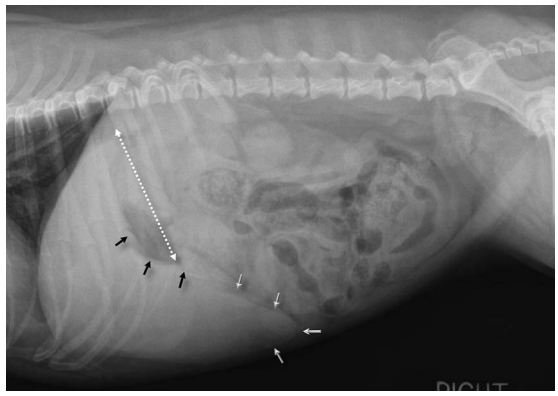


FIGURE 4.5 Lateral abdominal radiograph of a dog having generalized hepatomegaly due to vacuolar hepatopathy associated with hyperadrenocorticism. There is caudal extension of the caudoventral liver margin, which is rounded (white arrows). The gastric axis is caudally displaced (dotted white line) due to caudal and dorsal displacement of the gastric body and pylorus relative to the gastric fundus (black arrows).

Generalized hepatomegaly will most often appear as a rounded caudoventral margin with increased extension beyond the costal arch and caudal displacement of the gastric axis (Figure 4.5). The pylorus tends to be dorsally and caudally displaced, and the right kidney is often caudally displaced. With generalized hepatomegaly, often the right stomach (pylorus) is more caudally displaced than the left. Severe asymmetric displacement, however, often indicates focal hepatomegaly/hepatic mass.

Nodular hepatomegaly will appear as a generalized enlargement with irregular margins rather than the smooth margins maintained by generalized hepatomegaly. Differential diagnoses are ranked differently, with metastatic neoplasia, nodular regeneration, and hepatocutaneous syndrome being most likely.

Focal hepatomegaly is caused by a mass. Differential diagnoses for masses are listed in Box 4.4. However, once it is determined that the organ of origin is most likely to be liver, the ranking can be organized to include neoplasia, regenerative changes, cyst, and abscess at the top of the list. Focal hepatomegaly causes focal caudal displacement of the stomach to the right or left side, depending on its location. The margin of the liver at the location of the mass tends to be rounded rather than sharp. Most liver masses appear ventral in location, but dorsal masses can occur. Masses cranial to the stomach are typically hepatic in origin; however, in some cases, hepatic masses can extend caudal to the stomach (called

TABLE 4.2 Classification of hepatomegaly with respective differential diagnoses

Generalized hepatomegaly	Focal hepatomegaly	Nodular liver
– Vacuolar hepatopathy (e.g., steroid hepatopathy, hepatic lipidosis) – Passive congestion – Hepatitis (acute) – Infiltrative neoplasia (e.g., lymphoma, mast cell tumor) – Amyloid deposition	– Primary hepatic neoplasia (e.g., hepatocellular carcinoma in dogs, biliary cystadenoma in cats) – Regenerative changes – Cyst – Abscess – Hematoma – Granuloma – Liver lobe torsion	– Metastatic neoplasia (with hepatomegaly) – Nodular regeneration (with hepatomegaly) – Hepatocutaneous syndrome (with hepatomegaly) – Cirrhosis/fibrosis (with microhepatia)

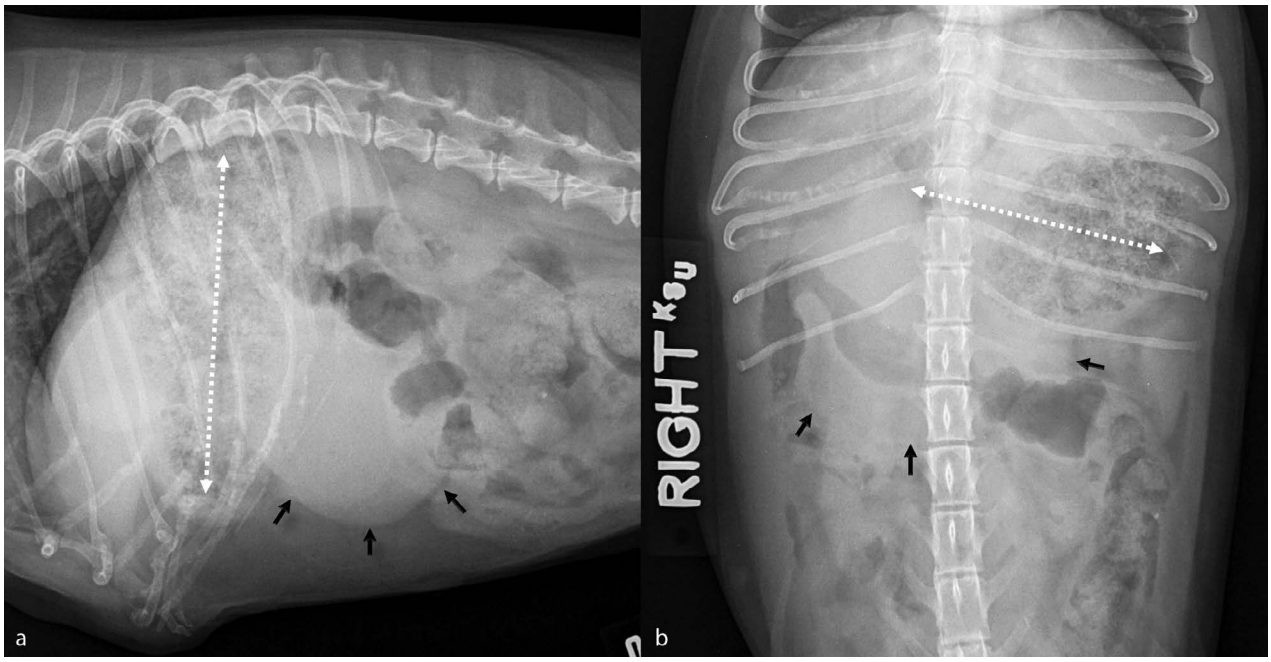


FIGURE 4.6 Lateral **(a)** and ventrodorsal **(b)** abdominal radiographs in a dog having a pedunculated liver mass. A soft tissue opaque mass having a well-defined rounded ventral and caudal margin (black arrows) is located caudal to the gastric axis (dotted white line). The mass located on the right side is causing the stomach to be displaced to the left. Right-sided small intestines are caudally displaced. A single pedunculated hepatic mass was found on ultrasound examination. A hepatocellular adenoma was subsequently diagnosed with aspirates.

a pedunculated liver mass), appearing in the location of the splenic tail on lateral views (Figure 4.6a, b). Liver masses in dogs and cats are most often neoplastic. The most common mass-like neoplasm in the canine liver is hepatocellular carcinoma; in cats, it is biliary cystadenoma.

Reduced Liver Size

Microhepatia is diagnosed when the liver size is small, as denoted by a cranially positioned gastric axis. The causes of microhepatia are shown in Box 4.5. Shape can sometimes be used to distinguish the causes of microhepatia. In cases of cirrhosis/fibrosis, the liver margin may be irregular in shape, giving it a nodular appearance. This abnormal shape is not always radiographically apparent, however. Additionally, ascites is uncommonly present in dogs with a congenital portosystemic shunt, so the presence of peritoneal effusion makes cirrhosis, fibrosis, or noncirrhotic portal hypertension more likely.

Box 4.5 Differential diagnoses for microhepatia

- Congenital portosystemic shunt
- Cirrhosis
- Fibrosis
- Microvascular dysplasia
- Noncirrhotic portal hypertension (portal vein hypoplasia)

Alterations in Hepatic Opacity

Radiographic abnormalities within the liver can sometimes appear as an alteration in opacity. Hepatic mineralization is most commonly due to mineralization within the intrahepatic biliary system rather than within the hepatic parenchyma itself. This causes linear branching mineral opacities that are most commonly accumulated in the right liver. This finding is often incidental; however, previous biliary disease or active disease cannot be ruled out. Mineralized calculi can also accumulate within the gallbladder. These choleliths can be incidental findings or can result in obstruction of the common bile duct. They appear as single, rounded mineral opacities or as an accumulation of mineral opacities within the right ventral liver in the region of the gallbladder. When multiple smaller calculi are present, the ventral margin of the accumulated choleliths tends to be rounded. Finally, the gallbladder wall itself can mineralize due to chronic cholecystitis or cystic mucinous hyperplasia, appearing as a well-defined, rounded, thin, mineral-rimmed structure in the right cranial liver in the region of the gallbladder.

Hepatic gas accumulations occasionally occur within the liver parenchyma or gallbladder. Parenchymal hepatic gas is most often associated with a mass due to abscessation. Hepatic abscesses are uncommon, typically exist as a single mass lesion, and most often do not contain gas. On occasions where gas is present, it will accumulate

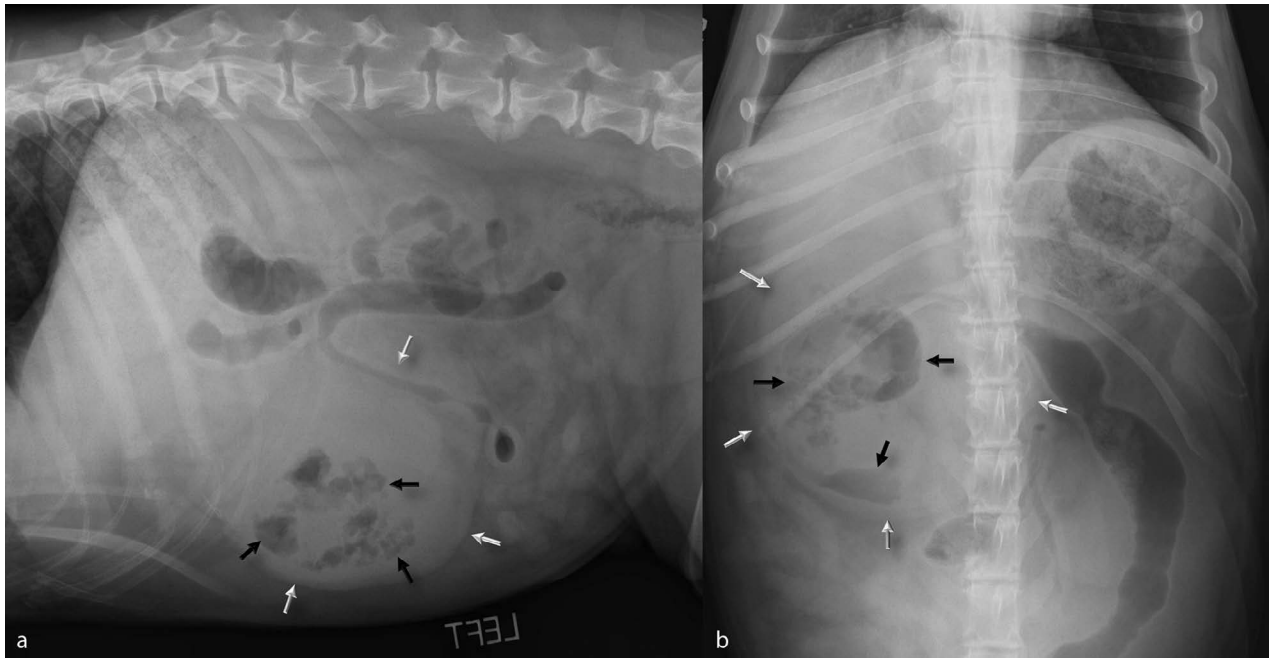


FIGURE 4.7 Lateral **(a)** and ventrodorsal **(b)** abdominal radiographs in a dog having a hepatic abscess. A large, well-defined, rounded soft tissue opacity is present in the right cranioventral abdomen (white arrows). The mass causes caudal and dorsal deviation of small intestines and leftward deviation of the stomach. Multiple, well-defined, variably sized and shaped gas opacities are located within the mass (black arrows).

within the margins of the mass (Figure 4.7a, b) and will not relocate with the use of horizontal beam radiography. Concurrent peritoneal effusion is commonly present. Most often, gas located within the abscess does not extend to the peritoneal space, but locations within both spaces can occur with rupture.

4. Spleen

Next, the spleen should be located and evaluated. The spleen can be divided into a cranial head, body, and caudal tail. It can be variable in position due to the mobility of the splenic tail. On the lateral view in dogs, the tail of the spleen, when visible, is typically in the cranioventral abdomen caudal to the margin of the liver and stomach. This is most reliably seen on the right lateral projection. In normal cats, the splenic tail is typically not visible on the lateral view of the abdomen. The head of the spleen is often visible, though, on the lateral view in the craniodorsal abdomen near the plane of the right kidney. The head of the spleen is in a more predictable, stable position due to the presence of the gastrosplenic ligament. On the ventrodorsal view, the head of the spleen is the portion that is most consistently visible, caudal to the gastric fundus and cranial to the left kidney, as a triangular soft tissue opacity that is formed where the spleen appears end-on near the junction of the splenic head and body. The overall apparent size of the spleen is smaller in cats than in dogs. Abnormalities within the spleen will typically manifest as an alteration in size, shape, location/orientation, and, rarely, opacity.

Splenomegaly

Splenic size is subjectively assessed. Generalized splenic enlargement will appear as an increase in thickness of the splenic tail or head. The margins of the spleen will be rounded and may or may not be irregular, indicating nodular changes. Mass effect associated with generalized splenic enlargement will typically cause rightward displacement of small intestines on the ventrodorsal view and dorsal displacement of intestines on the lateral view (Figure 4.8a, b). Generalized splenomegaly can cause cranial and ventral displacement of the gastric fundus. In cats, if the splenic tail is visible on the lateral view, it is considered enlarged. Focal splenomegaly occurs when mass lesions are present within the spleen. Given the focal nature of many splenic masses, unaffected sections of the spleen can appear radiographically normal. Masses associated with the splenic head will be located in the craniodorsal abdomen and on the left side. Masses associated with the splenic body or tail are typically more ventral in location and can be right- or left-sided. Masses are more commonly seen within the splenic tail and body; therefore, most splenic masses are located in the ventral cranial to midabdomen. As a general rule, masses within the splenic body or tail can appear identical to pedunculated liver masses (Figure 4.9a, b). Distinction between generalized and focal splenomegaly is important, as differential diagnoses differ (Table 4.3).

Alterations in Splenic Location

Splenic malpositioning due to torsion can occur as a single event (isolated splenic torsion) or, more commonly,

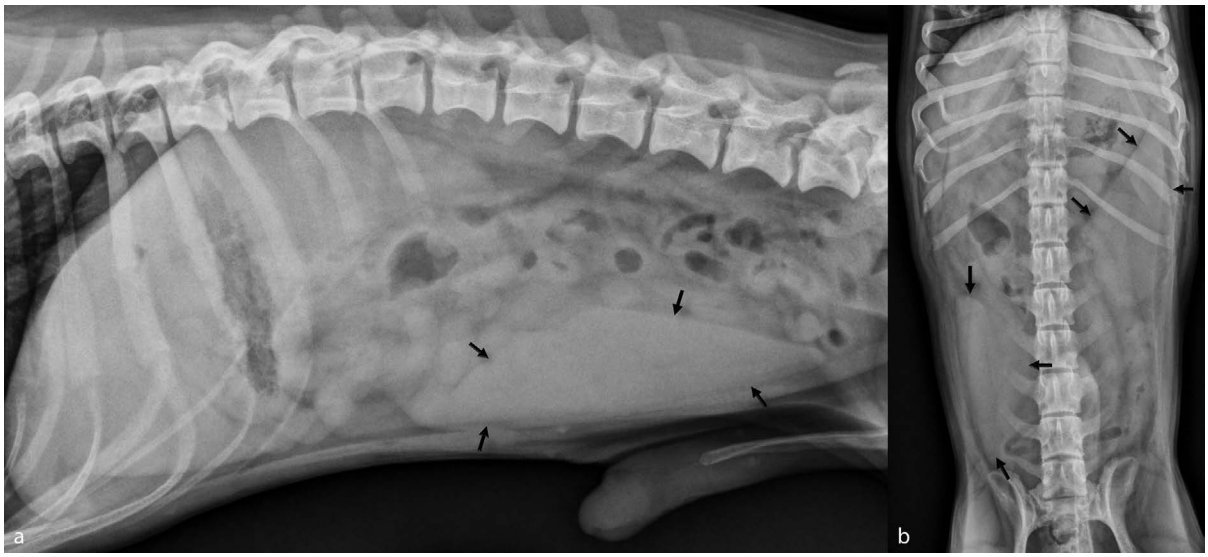


FIGURE 4.8 Lateral **(a)** and ventrodorsal **(b)** abdominal radiographs in an anemic dog having marked generalized splenomegaly due to benign extramedullary hematopoiesis. The margins of the spleen are rounded, and there is subjectively increased thickness of the spleen on both views (black arrows). The spleen extends excessively caudal, approaching the pelvic inlet. Additionally, the spleen extends to the caudal abdomen on the right side, seen on the ventrodorsal view.

in association with gastric dilatation and volvulus (GDV). Splenic torsion is often accompanied by peritoneal effusion, making the margins of the spleen somewhat indistinct. Indications of splenic torsion include a mass effect in the cranial to midventral abdomen, a loss of visibility of the normal splenic head and body in the left cranial abdomen on the ventrodorsal view, visibility of overt splenomegaly, or gas accumulations within the spleen or within the mass effect associated with the ventral abdomen. Finally, in cases where splenic margins are readily identified, the position of the spleen may appear as a reverse "C" shape in the ventral midabdomen on the lateral view.

Alterations in Splenic Opacity

Splenic mineralization occurs, most often, secondary to metabolic diseases such as hyperadrenocorticism; however, it is uncommonly detectable on radiographs. Gas opacity within the splenic parenchyma rarely occurs but

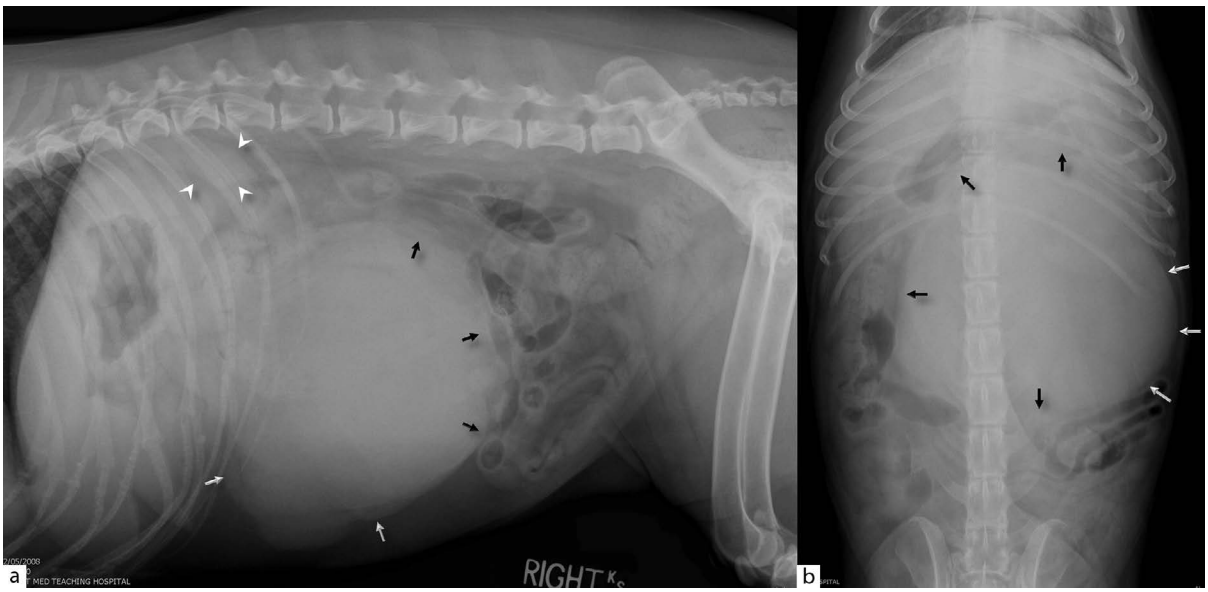


FIGURE 4.9 Lateral **(a)** and ventrodorsal **(b)** abdominal radiographs in a dog having a splenic mass. In the lateral view, a normal splenic head is seen in the craniodorsal abdomen (white arrowheads). A large, predominantly round, well-defined soft tissue opacity is present in the left cranial to midventral abdomen (white arrows). The mass causes marked caudal, dorsal, and rightward displacement of the small intestines and cranial displacement of the gastric fundus (black arrows). The main differential for organ of origin is a pedunculated liver mass.

TABLE 4.3 Classification of splenomegaly with respective differential diagnoses

Generalized splenomegaly	Focal splenomegaly (mass)
Inflammatory splenomegaly (splenitis) – Systemic or peritoneal bacterial infection – Chronic systemic infection **Hyperplastic splenomegaly** – Chronic infection – Hemolytic disorders **Extramedullary hematopoiesis** **Congestion** – Tranquilization – Right heart failure – Portal hypertension (rare) – Splenic torsion **Infiltrative neoplasia** – Lymphoma – Mast cell tumor – Multiple myeloma – Acute and chronic leukemia – Malignant histiocytosis **Amyloid deposition**	**Nonneoplastic** – Hematoma – Abscess – Nodular hyperplasia – Infarction – Cyst – Granuloma **Neoplastic** – Hemangiosarcoma – Hemangioma – Leiomyosarcoma – Leiomyoma – Myelolipoma – Lymphoma

can be a sequela to necrotizing splenitis or gas-producing bacteria within the spleen. This most commonly occurs secondary to splenic torsion and creates a classic mass (Figure 4.10a, b).

5. Retroperitoneal Space

The retroperitoneal space should be the next area evaluated. This space, being physically divided from the peritoneal space, can serve as a comparison for detail of organ visibility, where effusion causing reduced detail in the peritoneal space often spares the retroperitoneal space and vice versa. Causes of retroperitoneal effusion or mass effect must be considered, with knowledge of organs that exist in this space, such as the kidneys, adrenal glands, lymph nodes, and ureters, many being radiographically invisible under normal circumstances.

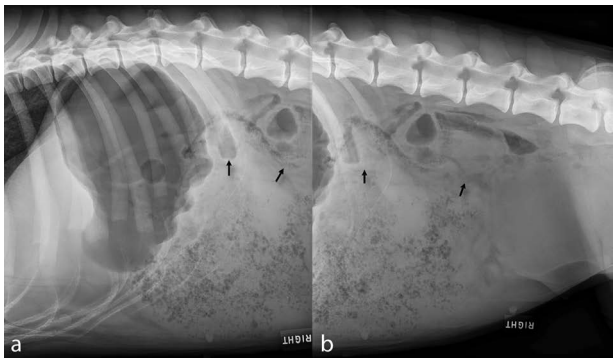


FIGURE 4.10 Lateral cranial (a) and caudal (b) abdominal radiographs in a dog having splenic torsion and secondary emphysematous splenitis. Peritoneal detail is reduced due to effusion. A large mass effect is present in the ventral abdomen that is causing dorsal displacement of small intestines (black arrows). A mass having indistinct margins is located in the ventral abdomen that is soft tissue opaque and contained numerous, well-defined gas bubbles. The location and opacity of the mass are classic for splenic torsion and splenitis.

Retroperitoneal Effusion and Mass Effect

Poor retroperitoneal detail is most often caused by effusion and/or mass. Retroperitoneal effusion causes a decrease in delineation of the renal margins. This may be unilateral or extend across the right and left peritoneal spaces. A large volume of fluid can cause a mass effect within the peritoneum where the colon and small intestines are pushed ventrally. When retroperitoneal detail is poor, the concurrent presence of a mass may not be readily visible. The masses themselves can cause similar border effacement of retroperitoneal structures. Causes of retroperitoneal effusion are shown in Box 4.6 and are best distinguished by considering fluid types. Causes of effusion must be considered together with history and clinical signs. For example, a history of trauma makes urine or hemorrhage the most likely cause of retroperitoneal hemorrhage, whereas a renal neoplasm is more likely if the animal has a history of hematuria.

Sublumbar Lymph Nodes

The medial iliac lymph nodes are located lateral to the aorta near the location of its trifurcation where the external iliac arteries branch from the abdominal aorta. Caudal to this, the internal iliac lymph nodes are located where the internal arteries branch. These lymph nodes combined are often called the sublumbar lymph nodes. They are radiographically invisible in normal cats and dogs. With severe enlargement, the sublumbar lymph nodes can cause a mass effect, displacing the distal descending colon ventrally near the pelvic inlet (Figure 4.11). When sublumbar lymphadenopathy is present, urogenital/perineal neoplasms or multicentric lymphoma should be considered first.

Box 4.6 Causes of retroperitoneal effusion

- Urine
  - Kidney rupture
  - Ureteral rupture
- Hemorrhage
  - Kidney rupture
  - Rodenticide/coagulopathy
  - Neoplasia
- Exudate
  - Renal abscessation
  - Retroperitoneal abscess
- Transudate/modified transudate
  - Urinary obstruction
  - Severe acute interstitial nephritis
- Neoplastic effusion

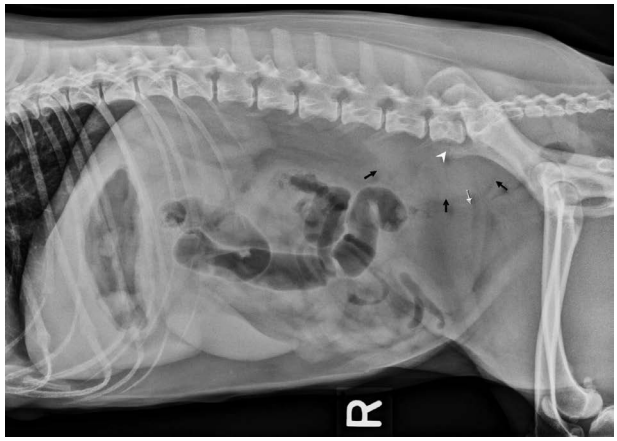


FIGURE 4.11 Lateral abdominal radiograph in a dog having transitional cell carcinoma of the urinary bladder. A moderately well-defined soft tissue opaque mass is present in the caudodorsal abdomen (black arrows). The mass causes ventral displacement of the distal descending colon (white arrow). Additionally, there is a very indistinct, irregular periosteal reaction associated with the ventral L7 vertebral body (white arrowhead) consistent with an aggressive bone lesion and metastatic disease.

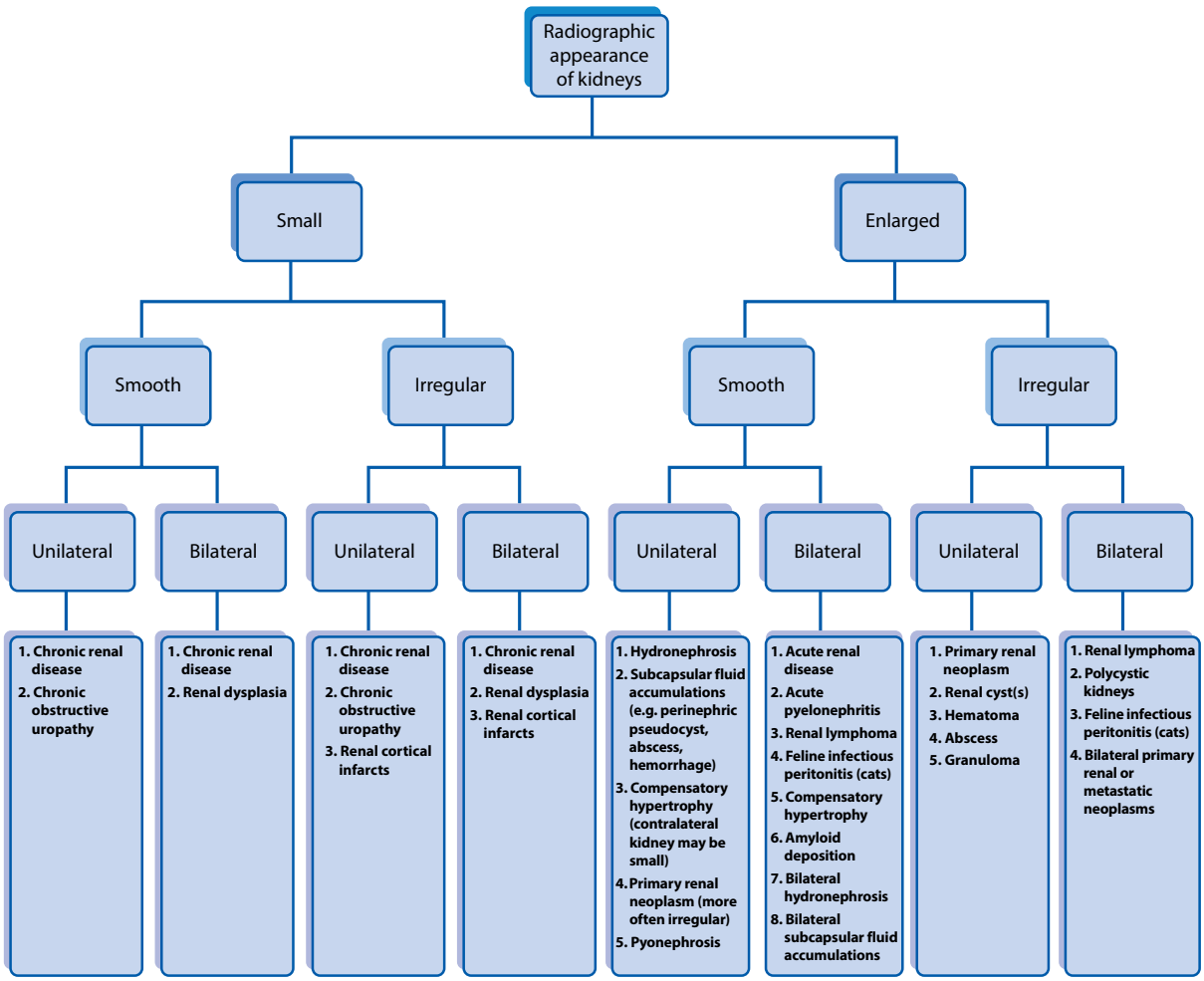
6. Upper Urinary Tract

Both kidneys and the ureters are retroperitoneal. The normal renal size in dogs is within 2.5–3.5 times the length of the L2 vertebral body as measured on the ventrodorsal view. In cats, the size of normal kidneys is within 2.0–3.0 times the length of the L2 vertebral body on the ventrodorsal view. Also, both kidneys should be similar in size and smooth. Normal ureters are never seen radiographically. Excretory urography is the only imaging modality that will allow assessment of the ureters.

Kidneys

Abnormalities associated with the kidneys will appear as an alteration in size, shape, opacity, and, rarely, number. Abnormal renal size must always be considered in combination with renal shape. Additionally, differential diagnoses are often ranked according to whether the radiographic abnormalities are unilateral or bilateral. An algorithmic approach can be used to determine differential diagnoses for the appearance of the kidneys, while taking clinical abnormalities into consideration (Box 4.7). Compression radiographs should be obtained

Box 4.7 Algorithmic approach to differentiating causes of abnormal kidneys



in cases where the kidneys are not easily seen due to a superimposed GI tract and when clinical evidence suggests renal disease.

Small Kidneys

Small, irregular kidneys (Figure 4.12a, b) are most often secondary to chronic renal disease or chronic obstructive uropathy. Renal dysplasia must also be considered in young animals having small, irregular kidneys, as the two causes can appear identical.

Renomegaly

Enlarged kidneys can cause a mass effect in the dorsal abdomen that can be right-sided, left-sided, or both, depending on the laterality of the diseased kidney(s). Ventral displacement of the intestines can be seen with renal masses or retroperitoneal effusion. Enlarged kidneys that are smoothly marginated or irregular have numerous causes that often require more advanced imaging, such as excretory urography or ultrasonography, to differentiate. Determination of the presence of unilateral or bilateral disease can assist with likely diagnoses, as some diseases such as acute kidney injury (AKI), pyelonephritis, lymphoma, feline infectious peritonitis, and amyloid deposition tend to be bilateral, while hydronephrosis and pyonephrosis tend to be unilateral. Renal carcinoma can be unilateral or bilateral and is often accompanied by retroperitoneal effusion due to hemorrhage. Peritoneal effusion is also occasionally seen because of invasion through the peritoneal lining. Subcapsular fluid accumulations due to perinephric pseudocyst occur in cats and dogs but are more commonly reported in cats having subcapsular edema accompanying AKI and urinary obstruction. Renomegaly can be severe and may be bilateral (Figure 4.13a, b) or unilateral. Polycystic kidneys are most commonly seen in Persian cats having an autosomal dominant mode of inheritance, but the condition has been reported in Bull Terriers, which also have an autosomal dominant mode of inheritance.

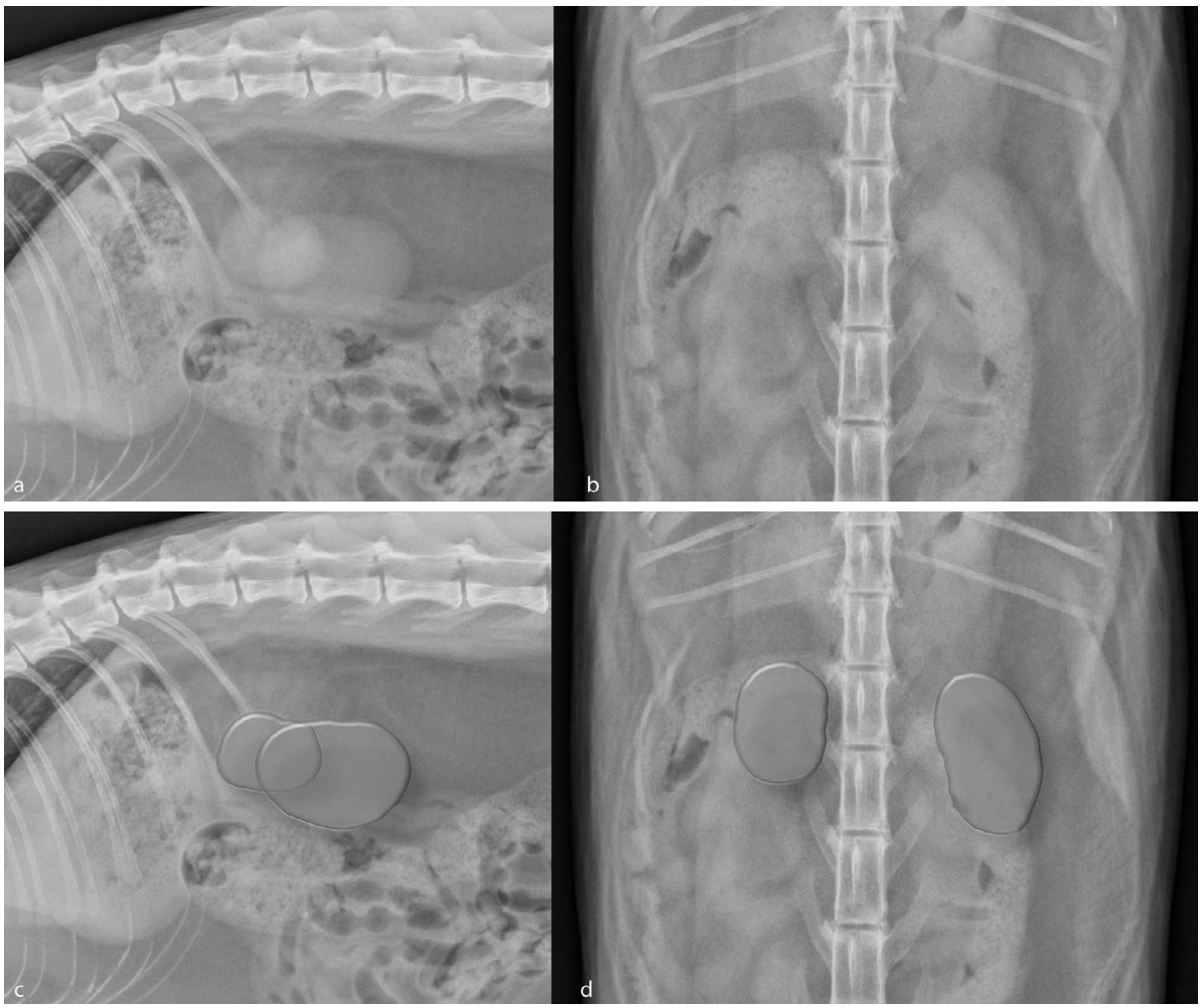


FIGURE 4.12 Lateral **(a)** and ventrodorsal **(b)** abdominal radiographs with accompanying schematic **(c** and **d)** showing small and irregular kidneys in a cat. Both kidneys are small in size and are markedly rounded and irregularly marginated (highlighted in schematic). In an older animal, this may be due to chronic kidney disease or chronic obstructive uropathy. In younger animals, renal dysplasia must also be considered.

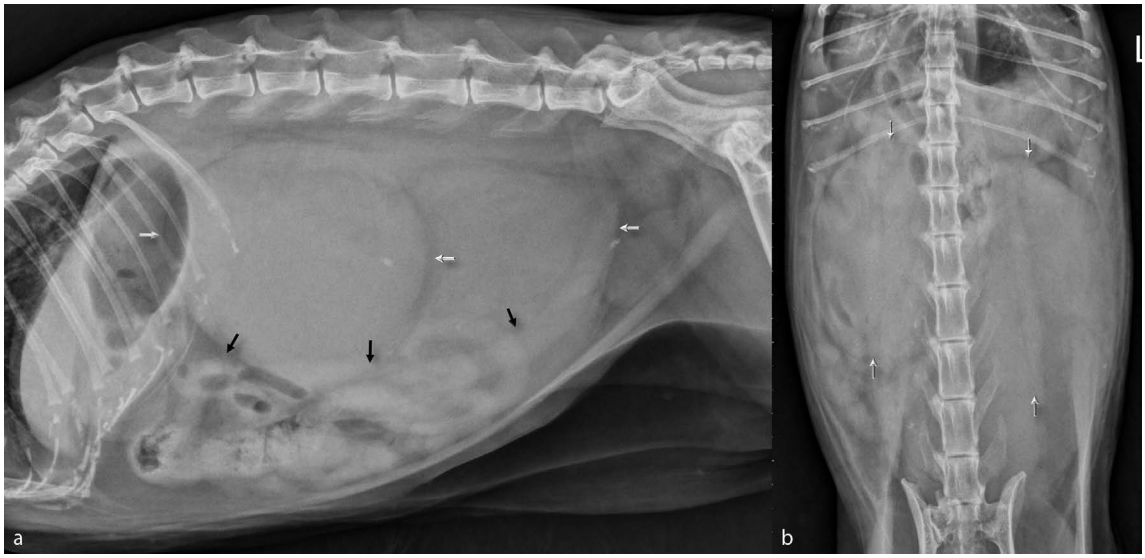


FIGURE 4.13 Lateral **(a)** and ventrodorsal **(b)** radiographs in a cat having a history of chronic renal disease and an increasingly distended abdomen. A marked mass effect is seen causing ventral displacement of the colon and small intestines, indicating a retroperitoneal organ of origin. The kidneys are markedly enlarged but remain smoothly marginated (white arrows).

Renal Mineral

Nephroliths associated with the kidneys are typically located in the region of the renal pelvises and can be variable in size. Nephroliths may persist indefinitely in the renal pelvis, or they may migrate into the ureter, increasing the risk of urinary obstruction. Nephrocalcinosis because of parenchymal mineralization may be dystrophic due to chronic disease or metastatic due to diseases resulting in altered calcium and phosphorus metabolism. Classic nephrocalcinosis appears as parallel linear mineralization located in the region of the renal diverticula. Parenchymal mineralization can accompany oxalate crystal deposition in ethylene glycol intoxication; however, this is generally not visible radiographically. When the presence of nephroliths or nephrocalcinosis is unclear because of superimposition, compression of the kidneys could be performed to confirm suspicion (Figure 4.14a, b).

Emphysematous Pyelonephritis

On rare occasions, gas can accumulate within the kidneys, most often within the renal pelvis, due to the presence of gas-forming bacteria or reflux of gas from the

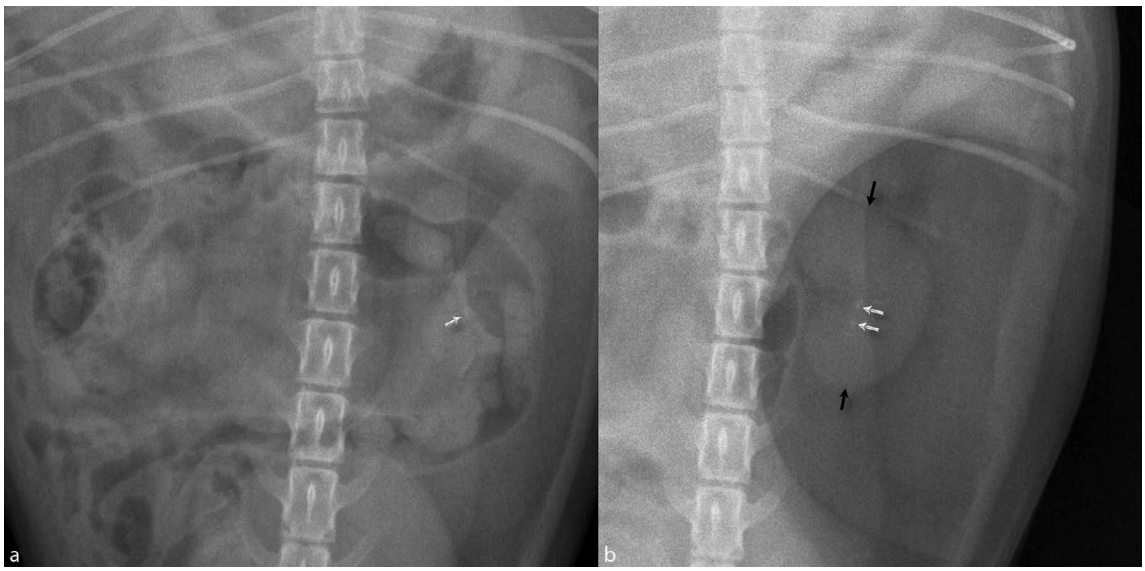


FIGURE 4.14 Ventrodorsal **(a)** and compression ventrodorsal **(b)** abdominal radiographs in a dog having small nephroliths. The kidneys were poorly seen on the survey study due to superimposed colon and small intestines. Superimposed over the left kidney, a small mineral opacity appeared to extend beyond the margins of the colon (a, white arrow). On the compression view, the margins of the left kidney are better identified (b, black arrows), and small calculi can be seen in the region of the renal pelvis (b, white arrows).

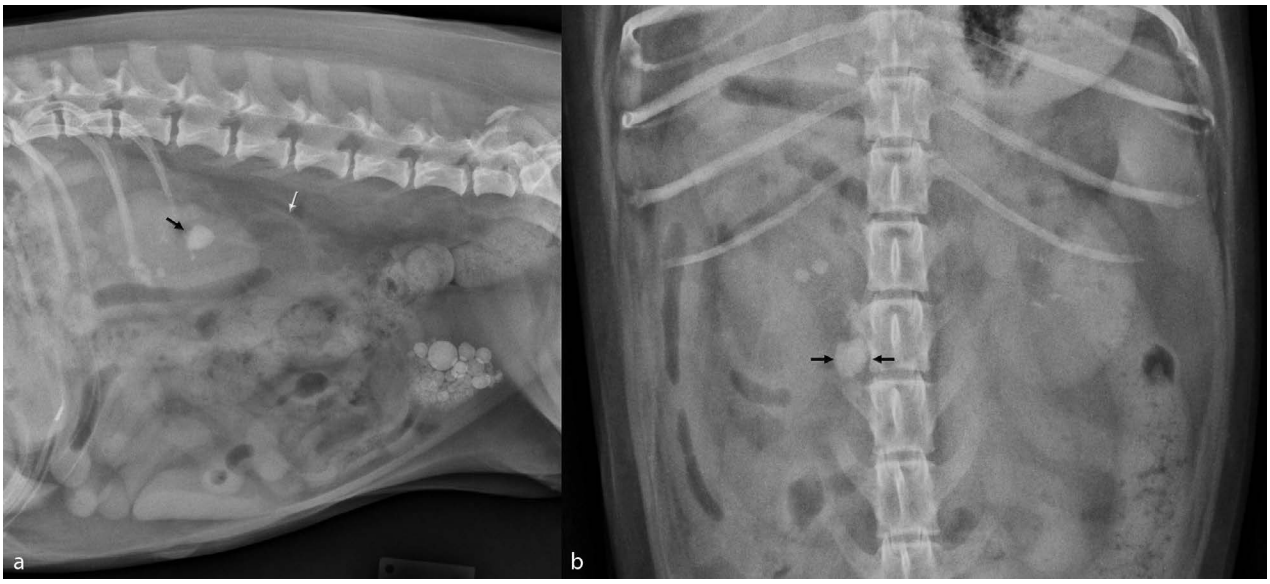


FIGURE 4.15 Lateral **(a)** and ventrodorsal **(b)** abdominal radiographs in a dog with azotemia and lethargy. Multiple mineral opaque calculi are superimposed over the kidneys. The largest calculus (black arrows), however, is superimposed medial to the margin of the right kidney in the expected location of a ureter. A small amount of soft tissue opaque streaking is present in the retroperitoneal space (white arrow). Urinary obstruction due to ureterolithiasis was confirmed on ultrasound examination. Numerous, round, well-defined calculi are also present within the urinary bladder.

urinary bladder. Emphysematous pyelonephritis most often occurs in combination with emphysematous cystitis in diabetic animals (see Lower Urinary Tract).

Ureters

As previously mentioned, ureters should never be seen radiographically without contrast in normal animals. The most common cause of ureteral visibility is due to ureterolithiasis. Ureteroliths appear as mineral opacities that are superimposed in the presumed location of a ureter (Figure 4.15a, b). In many instances, excretory urography or abdominal ultrasound is needed to confirm the presumed location of the calculus within the ureter.

7. Adrenal Glands

Both adrenal glands are retroperitoneal in location. They are paired and located medial to the cranial poles of each kidney. The aorta borders the left adrenal gland medially. The right adrenal gland is bordered by the caudal vena cava medially. Adrenal glands are not identified radiographically in normal animals. However, their position relative to the kidneys creates a unique appearance when they are enlarged, and a mass effect is created. When an adrenal gland creates a mass effect, it can cause lateral displacement of the cranial pole of its adjacent kidney. When severely enlarged, adrenal masses cause caudal displacement of the adjacent kidney, and, often, the cranial pole of the kidney is dorsally displaced (Figure 4.16a, b). Masses associated with the adrenal glands are most commonly neoplastic. Animals with adenomas or adenomatous hyperplasia due to pituitary-dependent Cushing's disease do not usually have radiographically visible adrenal glands. Bilateral adrenal mineralization can occur as a normal aging process in cats.

8. Reproductive Tract

Female Reproductive Tract

The uterine body is a tube located between the urinary bladder and the descending colon; its horns extend to each ovary. The uterus is typically not radiographically visible in normal animals. Visibility of the uterus is considered abnormal and indicates enlargement. The uterus is not expected to be larger in diameter than the small intestines in the normal animal.

Uterine enlargement results in a mass effect that causes dorsal, cranial, and medial displacement of small intestines. Various degrees of uterine enlargement can be seen ranging from mild to severe (Figure 4.17a, b). Differential diagnoses for generalized uterine enlargement include pregnancy, pyometra, mucometra, and hydrometra. Incorporation of clinical signs and history are needed to distinguish these causes. Mass lesions due to neoplasia, abscess, granuloma, hematoma, or cyst can also occur and create a mass effect with similar displacement of organs. Concurrent peritoneal effusion is often present with pyometra, stump pyometra, or inflammatory uterine diseases.

Uterine enlargement is readily detectable in pregnant cats and dogs prior to fetal mineralization. In dogs, the uterus is visible at 30 days post luteinizing hormone (LH) surge. In cats, uterine swelling can be seen at 17–21 days. Mineralization of the fetal skeleton initiates in the axial skeleton, beginning at 45 days after the LH surge in dogs and at 36–45 days after breeding in cats. Mineralization of the skeleton can be used

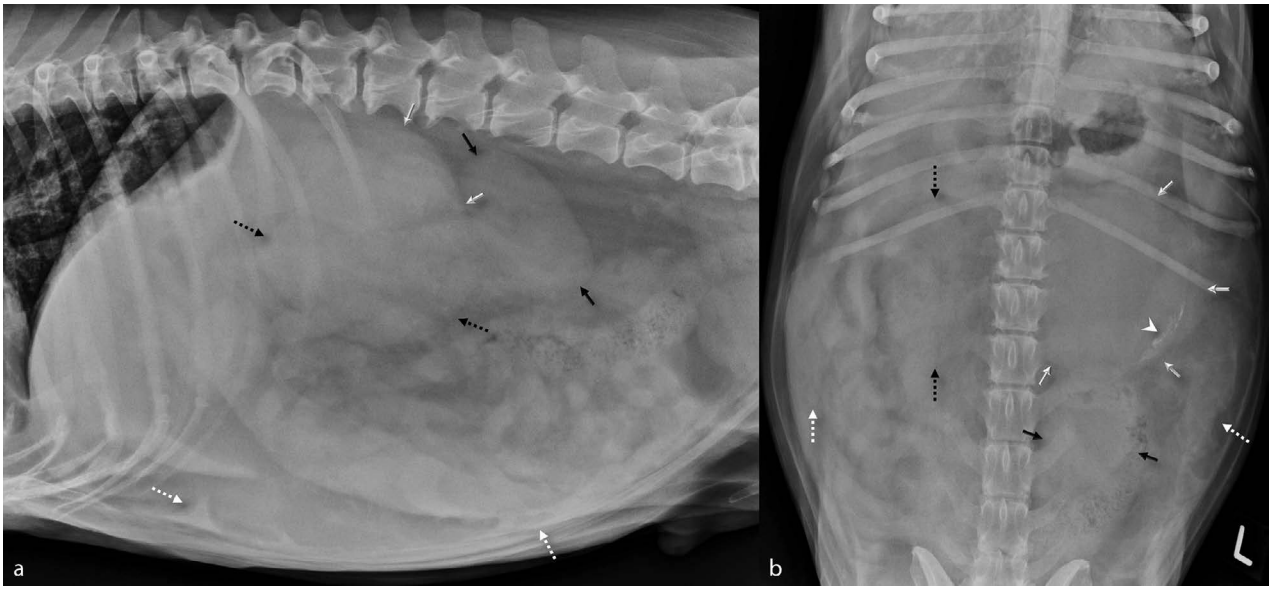


FIGURE 4.16 Lateral **(a)** and ventrodorsal **(b)** abdominal radiographs in a dog presenting for acute vomiting and a suspected foreign body. A retroperitoneal mass effect is present causing ventral and rightward displacement of cranial abdominal small intestines. Normally shaped right (dotted black arrows) and left (black arrows) kidneys are visible. An additional, large, round, soft tissue opacity having a well-defined dorsal and lateral margin is visible in the left craniodorsal abdomen. This structure causes marked caudal displacement and altered orientation of the left kidney, causing its cranial pole to be dorsally displaced. A rim of mineral is present at the lateral caudal periphery of the mass (white arrowhead). A mild amount of soft tissue opaque streaking is present in the peritoneal space (dotted white arrows) that is causing mild decreased detail. The location of this mass is compatible with left adrenomegaly.

to roughly estimate the stage of pregnancy and the likelihood of imminent parturition. In dogs and cats, the final skeletal structures to mineralize are the distal limbs (metatarsi, metacarpi, and phalanges) and the teeth. Once these are radiographically mineralized and visible, parturition can be expected within 0–5 days in dogs and 0–6 days in cats.

Radiography is insensitive to detecting fetal distress compared with ultrasound. If fetuses have been dead for >24 hours, signs of death may be visible as emphysematous changes within the uterus or fetus (Figure 4.18a, b) or collapse of the axial skeleton. Additionally, some causes of fetal dystocia are radiographically visible, such as fetal malposition, extreme maternofetal disproportion, or narrowed pelvic canal due to previous trauma.

Male Reproductive Tract

The prostate gland encircles the proximal urethra. The prostate gland in cats is invisible. To the author's knowledge, abnormalities causing a radiographically visible prostate in cats have never been reported. In neutered dogs, the prostate gland is typically not identified but is occasionally seen when the colon is empty or when compression radiography is used. When an enlarged prostate is present, the most reliable indicator of a prostatic organ of origin is the fat opaque triangle located between the urinary bladder and the prostate gland.

In intact males, the prostate gland most often becomes radiographically visible because of benign hypertrophy, which is the most common cause of prostatic enlargement (Figure 4.19). The prostate usually encompasses <50% of the diameter of the pelvic inlet from the sacrum to the pubis on the lateral view. The prostate will be intrapelvic in young dogs and will become intra-abdominal as the prostate enlarges in older intact males. Scottish Terrier dogs are reported to have increased severity of prostatomegaly due to benign hypertrophy. Prostatitis can cause radiographically visible enlargement and is more commonly diagnosed in intact dogs. Occasionally, regional peritoneal effusion and peritonitis are present when prostatitis is severe. Regardless, prostatic disease should be considered in male dogs having a ventral caudal abdominal mass effect.

The incidence of prostatic neoplasia is similar in intact and neutered males; however, prostatic neoplasia is highly likely in neutered males having a radiographically visible prostate and signs associated with prostatic disease. Mineralization is a common feature of prostatic neoplasia, but it is also less commonly found in benign prostatic enlargements. Generally, mineralization that occurs with benign prostatic diseases is not radiographically visible but can be more readily identified on ultrasound examination. Prostatic neoplasms commonly metastasize to the sublumbar lymph nodes, caudal lumbar spine, and pelvis. In male dogs with visible sublumbar lymphadenopathy or aggressive bone lesions of the caudal lumbar spine or pelvis, prostatic neoplasia should be ruled out as an underlying cause regardless of whether prostatic enlargement or mineralization is radiographically visible or not (Figure 4.20).

Prostatic mass effects due to abscessation, cyst, or paraprostatic cyst occur less commonly. Prostatic

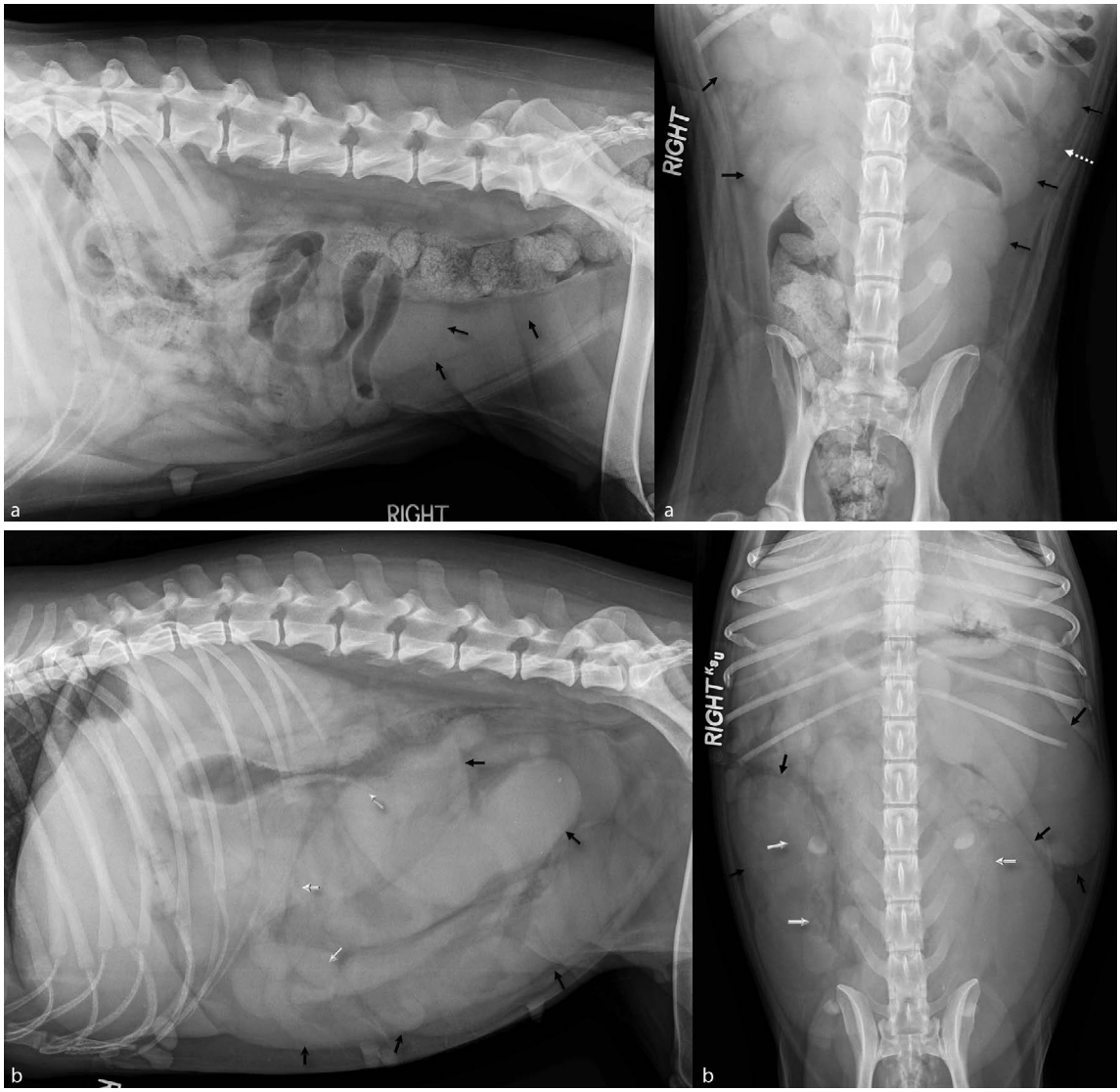


FIGURE 4.17 Lateral and ventrodorsal abdominal radiographs in two dogs having different degrees of uterine enlargement due to pyometra. In part **(a)**, there is moderate uterine enlargement with a soft tissue opaque tube visible bordering the dorsal aspect of the urinary bladder and located at the periphery of the right and left abdomen (a, black arrows). A small amount of soft tissue opaque streaking is present within abdominal fat near the left body wall (dotted white arrow) denoting a small volume of regional effusion. Marked uterine enlargement is shown in part **(b)**. Tubular-shaped soft tissue opacities are located in the caudal ventral to midabdomen (b, black arrows). The typical mass effect for uterine enlargement is cranial and dorsal displacement of intestines that are often pushed medially (b, white arrows). Mild soft tissue opaque streaking is visible at the periphery of the abdomen (white arrowheads).

abscesses and intraprostatic cysts will have a similar radiographic appearance to benign hypertrophy or prostatitis. However, inflammatory prostatic lesions due to abscessation are more likely to have regional peritoneal effusion. Paraprostatic cysts occur peripheral to the prostate and have a radiographic appearance that is distinct from prostatomegaly alone. In most cases, the paraprostatic cyst is located to the right or the left of the urinary bladder, thus overlapping the urinary bladder on the lateral view rather than being located caudal to the urinary bladder. Therefore, the typical fat opaque triangle associated with prostatic enlargement may not be a feature of paraprostatic cyst unless concurrent radiographically visible prostatomegaly is present. The appearance of paraprostatic cysts mimics that of a supernumerary urinary bladder.

9. Lower Urinary Tract

The Urinary Bladder

The urinary bladder is almost always visible on the lateral view in cats and dogs regardless of its size. It must be moderately distended before becoming visible on the ventrodorsal view. Bladder size can be variable; therefore, its position is inconsistent. Abnormalities associated with the urinary bladder are typically seen as an alteration in opacity or an abnormally large size

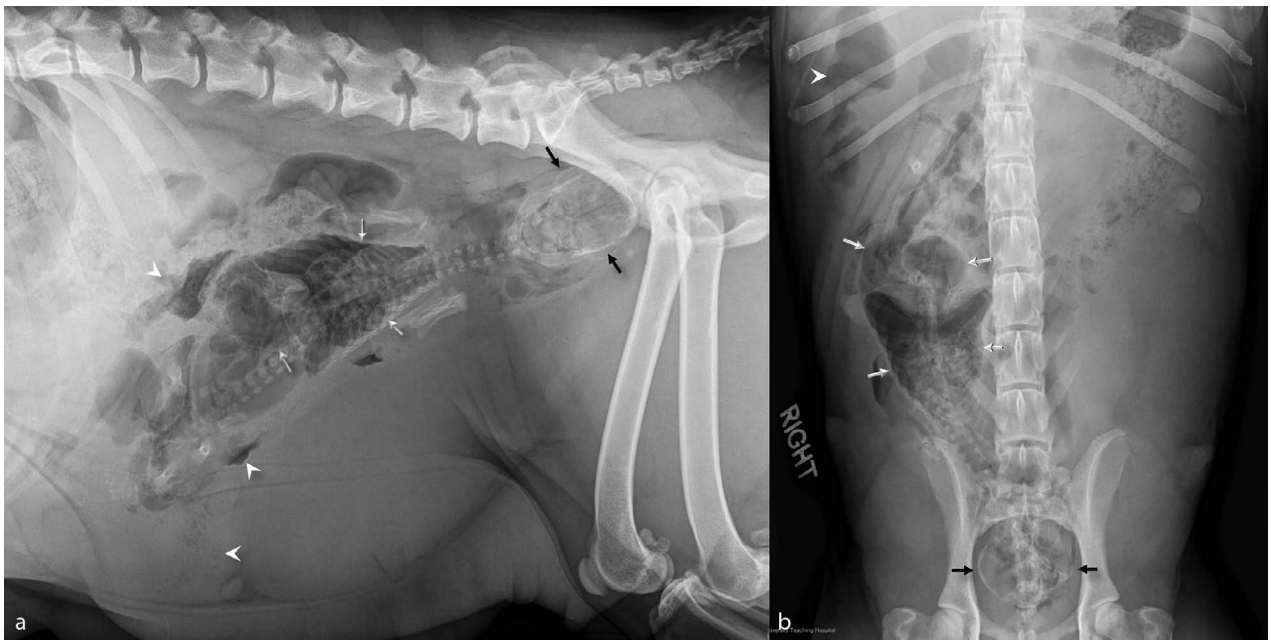


FIGURE 4.18 Lateral **(a)** and ventrodorsal **(b)** abdominal radiographs in a dog having dystocia of unknown duration. A single full-term fetus is present. Dystocia likely occurred due to maternofetal disproportion where the skull (black arrows) was unable to pass through the pelvic canal. Emphysematous metritis is present (white arrowheads) so that gas accumulates within the uterus and surrounding the fetus. Gas is also present within the fetal thorax and abdomen (white arrows).

in an animal showing clinical signs associated with urinary obstruction. Urinary bladder position can also be abnormal, but this is less commonly encountered.

Mineral opacity associated with the urinary bladder is most commonly due to radiopaque urocystic calculi. Calculi are radiopaque because of the presence of calcium in their composition. This includes mainly calcium phosphate and calcium oxalate stones or combinations of stone that are mixed (e.g., magnesium ammonium phosphate, also called struvite, which often contains calcium phosphate). Urate and cystine urocalculi are often radiolucent but may contain some degree of calcification, making them faintly visible. In general, the determination of urocystic calculus composition cannot be definitively made radiographically. Urinary calculi can

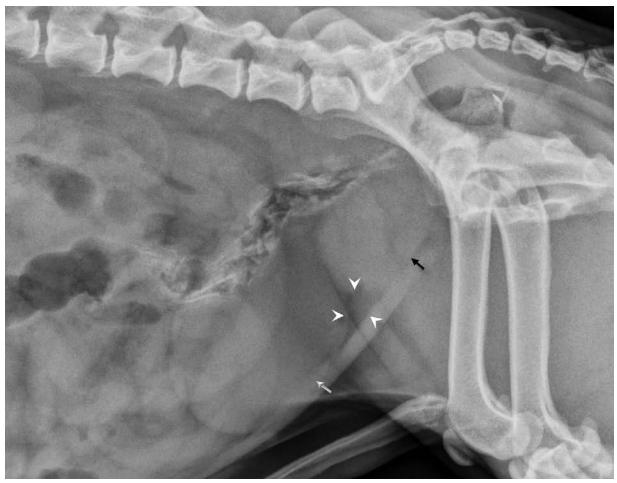


FIGURE 4.19 Lateral abdominal radiograph in a dog having prostatomegaly due to benign hypertrophy. The fat triangle (between white arrowheads) located between the prostate and the urinary bladder indicates a prostatic organ of origin for the rounded soft tissue opacity at the pelvic inlet. The prostate is enlarged (black arrow) but encompasses less than 50% of the dorsoventral diameter of the pelvic inlet. The urinary bladder is cranially positioned (white arrow) likely due to prostatomegaly.

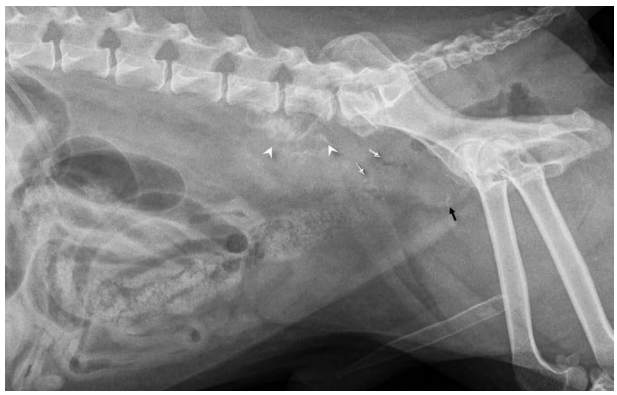


FIGURE 4.20 Lateral abdominal radiograph in a dog having prostatic neoplasia. The prostate is radiographically visible (black arrow) and contains a small amount of pinpoint mineral near its ventral margin. There is mass effect in the caudodorsal abdomen that is causing mild ventral displacement of the distal descending colon (white arrows) consistent with sublumbar lymphadenopathy. Indistinct mineral is superimposed ventral to the caudal lumbar spine (white arrowheads). The ventral margin of these vertebrae is indistinct, indicating an aggressive bone lesion. This is due to metastatic disease from prostatic neoplasia.

be variable in size and shape. Urocystic calculi should be mobile; therefore, they will most often be superimposed over the body of the urinary bladder centrally on orthogonal views. Mineral that is superimposed in a noncentral location over the urinary bladder indicates a lack of mobility and may be due to adherent luminal calculi or sediment, mineralization of the urinary bladder wall, or mineralized neoplasia.

Gas opacity is occasionally identified within the urinary bladder associated with the lumen or the urinary bladder wall. Most commonly, gas is found in the lumen and is iatrogenic due to catheterization or cystocentesis. In these cases, the gas bubble is mobile and will locate in the most nongravity-dependent part of the urinary bladder as the animal is positioned in lateral or ventrodorsal recumbency. As a result, the bubble will be located at the level of the urinary bladder body on both views. Rarely, gas can be located within the urinary bladder due to gas-forming bacteria, most commonly in diabetic animals with glucose-fermenting infections. Emphysematous cystitis can result in luminal gas or mural gas within the urinary bladder wall. When gas is located within the urinary bladder wall, it will remain superimposed over the same portion of the urinary bladder regardless of the view or the position of the animal and is curvilinear in shape, following the margin of the urinary bladder wall (Figure 4.21a, b). Reflux of gas through the ureters or presence of concurrent emphysematous pyelonephritis will cause gas to be located within the region of the renal pelvis.

The Urethra

In male dogs, the urethra can be divided into the prostatic urethra, the membranous urethra, and the penile urethra. As its name implies, the prostatic urethra is located in the prostate. The membranous urethra is located caudal to the prostate. The landmark for the junction between the membranous urethra and the penile urethra is the ischial arch. The penile urethra distal to the ischial arch is the longest portion in dogs. The male feline urethra is divided into pelvic and penile parts, where the ischial arch is the landmark for the junction between the two sections. The pelvic part is the longest portion of the urethra in the male cat and includes preprostatic, prostatic, and postprostatic parts. The female urethra in cats and dogs has a pelvic and postpelvic part. When the urinary bladder is distended, the pelvic urethra is more cranially positioned and can be radiographically visible within the abdomen, especially in cats. Otherwise, the urethra is not identified as a separate structure radiographically.

When assessing male dogs for suspected urinary calculi, especially if evidence of urinary obstruction is present or the urinary bladder is distended, a flexed hip lateral view centered at the pelvis and including the perineal region should be incorporated into the protocol so that the entire urethra is visible without superimposition by the femurs (Figure 4.22a, b). Evaluation of the urethra on both lateral and flexed lateral views will also prevent mistaking the fabellae for penile urethral calculi, as the fabellae will move with the femur with each view. Keep in mind that in male dogs urethral calculi tend to obstruct at the level of the os penis (Figure 4.22a, b). The flexed hip view is not necessary in cats or in female dogs; however, the views should include the entire perineal region. The pelvic urethra is another location common for obstruction, especially in female dogs. The portion of the urethra within the pelvis must be closely evaluated on both views to ensure that a calculus is not overlooked as a normal part of

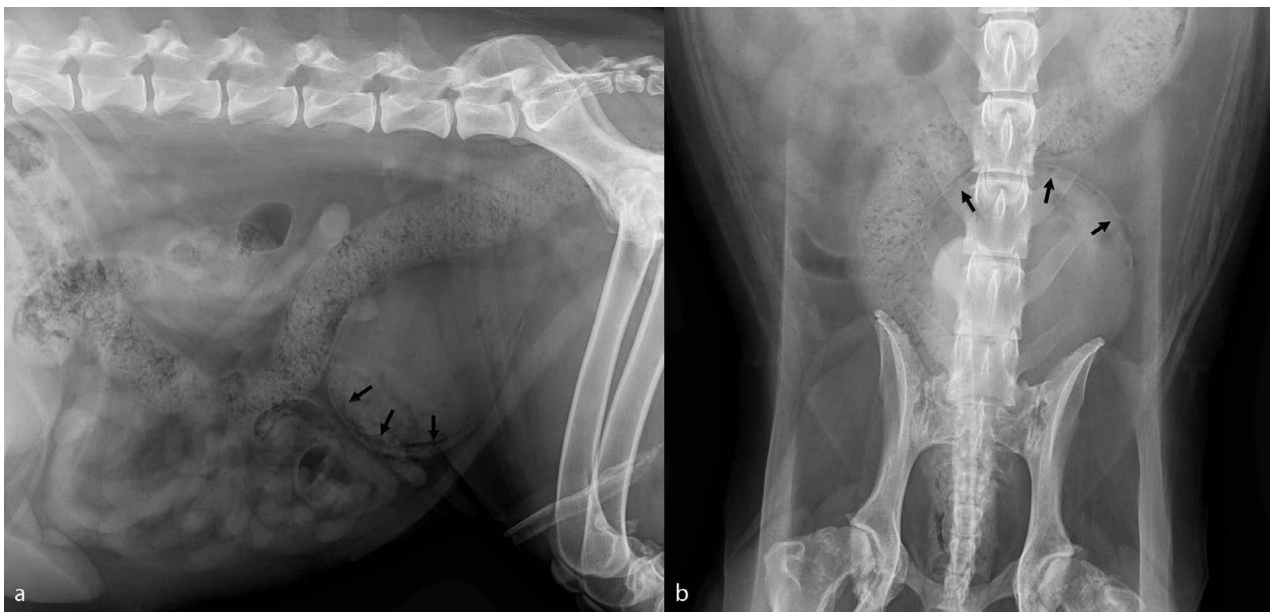


FIGURE 4.21 Lateral (a) and ventrodorsal (b) abdominal radiographs in a dog having emphysematous cystitis. Rather than gas being superimposed over the body of the urinary bladder, as would be expected with mobile luminal gas, a curvilinear rim of gas is present at the bladder apex consistent with its presence within the urinary bladder wall. Bilateral coxofemoral osteoarthritis is also evident.

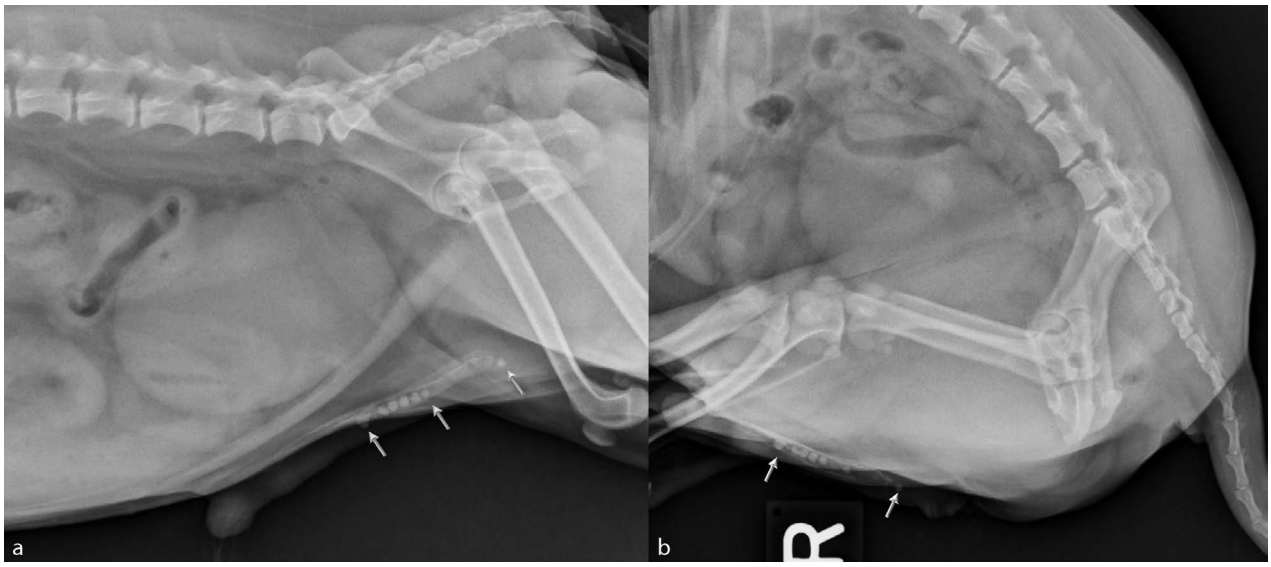


FIGURE 4.22 Standard lateral **(a)** and flexed hindlimb lateral **(b)** abdominal radiographs in a male dog having clinical signs consistent with urinary obstruction. Multiple, round, well-defined calculi are present within the penile urethra (white arrows). To confirm the correct number of calculi, a flexed hindlimb view (b) is needed to view the entire urethra and remove superimposition of the femurs over the urethra.

the bony pelvis (Figure 4.23a, b). The size of a urinary calculus that can pass through the entire urethra is not reliably predictable.

10. Gastrointestinal Tract

The stomach is typically readily identifiable unless void of any content, including gas. When evaluating the intestines, the colon should be identified first because it is in a more predictable location and is easier to recognize. Next, any remaining intestine that is distended or has abnormal contents is probably within small intestine, making it more likely to be of clinical significance. It is common for beginner interpreters to only recognize portions of the GI tract containing gas and ignore portions that are empty or contain only fluid opacity. Attempts must be made to evaluate portions that are soft tissue/fluid opaque, as they may be abnormal and the gas-filled loops more normal. Also, many beginner interpreters assume a decrease in peritoneal detail when evaluating the abdomen of an animal having little to no luminal gas within the intestines. Evaluation of serosal

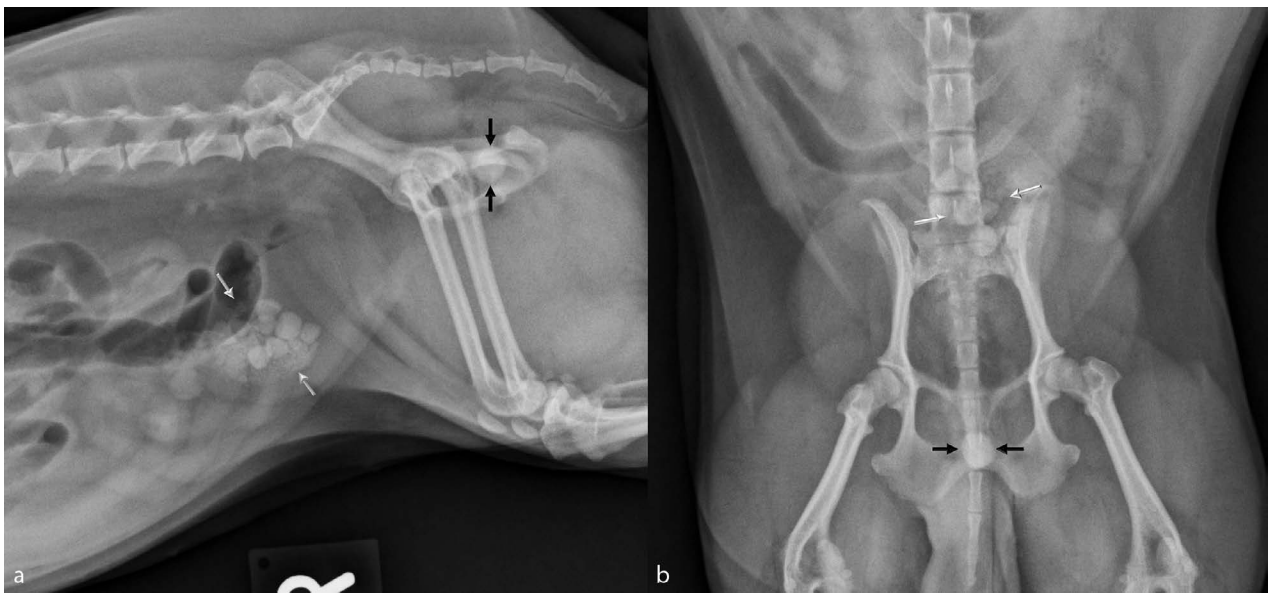


FIGURE 4.23 Lateral **(a)** and ventrodorsal **(b)** abdominal radiographs in a female dog having clinical signs associated with urinary obstruction. Numerous calculi are readily visible within the urinary bladder (white arrows). A single, large calculus is present within the pelvic urethra that is superimposed over the bony pelvis on both views (between black arrows). This calculus was not initially identified prior to removal of the bladder calculi and was removed on a subsequent cystotomy.

margins to determine their visibility will confirm or reject the presence of decreased serosal detail.

Stomach

A normal size measurement for the stomach does not exist; therefore, distension is a subjective determination. An empty stomach is typically intercostal in location. With increasing distension, the stomach extends caudally and ventrally, as commonly seen in cats and especially dogs that have recently eaten large volumes. The fundus is always the largest portion of the stomach regardless of the degree of distension (this is useful when evaluating the stomach for malpositioning, often occurring with distension). The fundus should be located on the left side of the abdomen and is dorsal. In dogs, the gastric body crosses from left to right and is the most ventral portion of the stomach. The pyloric antrum and pylorus are slightly more dorsal in location than the gastric body and are located on the right side. In cats, the stomach is "J" shaped and is primarily located on the left side, with the pylorus being close to midline. Alterations in stomach size, position, and opacity can occur.

Gastric Distension

A distended stomach causes caudal displacement of small intestines and the head and tail of the spleen. Gastric dilatation can be caused by mechanical or functional ileus. Several considerations should be made when evaluating a distended stomach. The clinical signs, history, and description of the luminal content alter the ranking of differential diagnoses associated with a distended stomach. In the case of recent ingestion, the luminal content of the stomach is usually an inhomogeneous mixture of gas, soft tissue, and sometimes granular or faint mineral opaque material. The content of the stomach can rarely be definitively distinguished as food or foreign material. Foreign materials, such as tough, expansile glues containing diphenylmethane diisocyanate, and indigestible materials, such as fabric or grass, can have an inhomogeneous appearance similar to that of recently ingested food. When it is unclear whether or not the stomach is filled with food or foreign material, repeat radiographs should be obtained 6–8 hours after fasting to see if gastric emptying is occurring. If the stomach is identical after this period of time, foreign or indigestible material (Figure 4.24a, b) should be considered.

In an animal with a functional ileus or a pyloric outflow obstruction, the stomach may or may not be distended, depending on the effectiveness of vomiting. Gastric contents in an animal that is concurrently anorexic often appear as a homogeneous shade of gray consistent with a combination of gas and fluid (Figure 4.25a, b) rather than the inhomogeneous opacity seen with recent ingestion of food or a stomach filled with non-digestible material (Figure 4.24a, b). Pyloric outflow obstructions can occur due to luminal foreign material that is nonmobile and lodged within the pylorus/proximal duodenum or can be due to mural thickening or a mass at the same level. The most common causes of a functional gastric ileus are acute gastritis or pancreatitis.

When a stomach containing homogeneous gas and fluid is encountered, the next step is to obtain a left lateral view. The left lateral view allows luminal fluid to fall to the gravity-dependent gastric fundus on the left side, while gas rises to the nongravity-dependent pyloric antrum on the right side. This recumbency allows gas to highlight materials that may be obstructing the pylorus and are not mobile, given that these materials are often soft tissue opaque (Figure 4.26a, b). Mobile soft tissue opaque materials (food or foreign) will follow luminal fluid with recumbency, being similarly gravity dependent, and may remain effaced by any fluid present, depending on the volume of gas versus fluid present in the stomach. Therefore, mobile foreign objects are not readily identified unless they are mineral or metal opaque or are surrounded, at least in part, by gas,

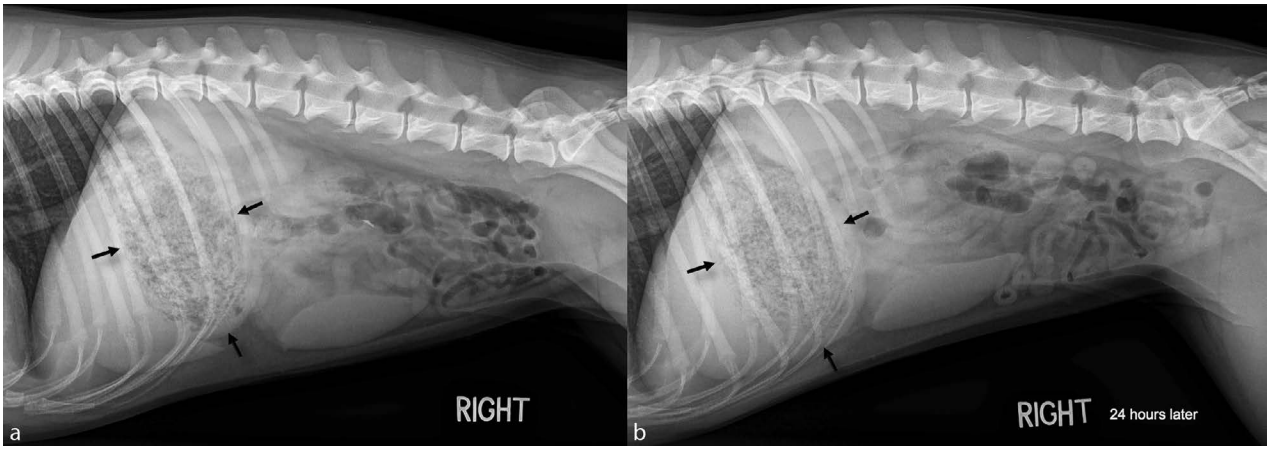


FIGURE 4.24 Lateral abdominal radiographs in an anorexic dog that vomited once prior to presentation. The stomach is moderately distended with inhomogeneous gas and soft tissue opaque material (**a**, black arrows). This could be due to recent ingestion of food or due to indigestible foreign material. The dog was fasted for 24 hours, and the study repeated **(b)**. The stomach is almost identical in appearance consistent with a lack of movement of content from the stomach and the presence of indigestible material. A large volume of hay was removed endoscopically.

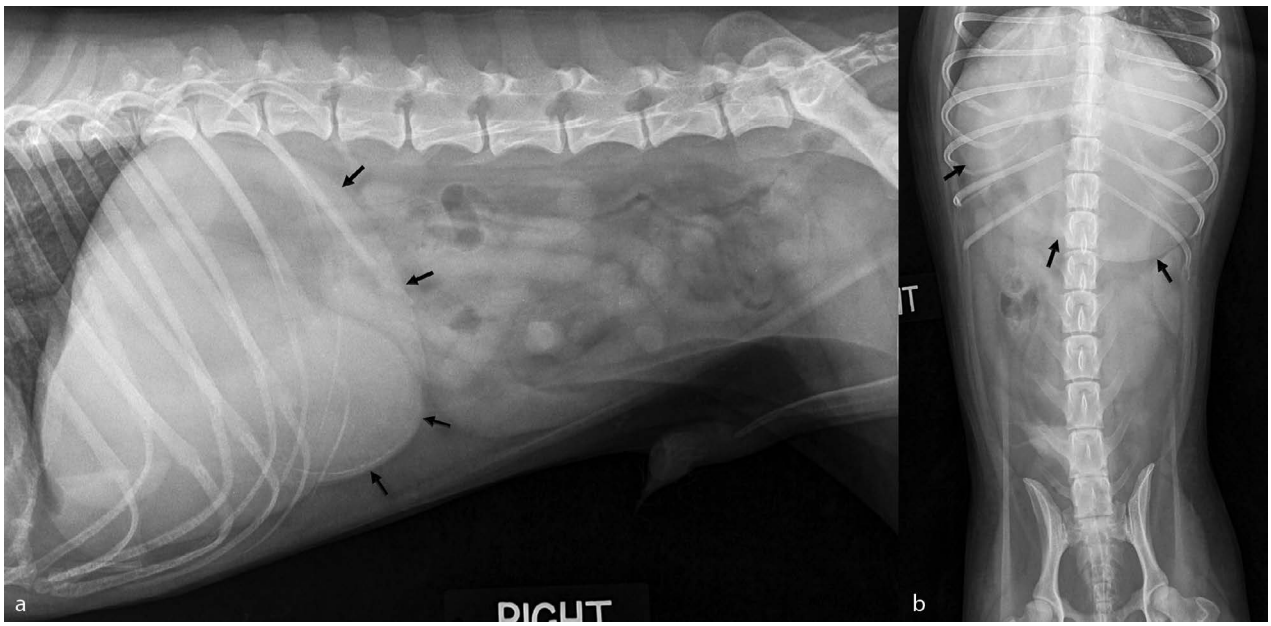


FIGURE 4.25 Lateral **(a)** and ventrodorsal **(b)** abdominal radiographs in a dog presenting for vomiting. The stomach is distended (black arrows) causing caudal displacement of the small intestines and the spleen. The stomach is a homogenous shade of gray created by a combination of luminal gas and fluid. This appearance is not typical for an animal that has recently eaten. It is more typical for a functional ileus or a pyloric outflow obstruction.

allowing their structure to be revealed. Effort should be made to determine the degree to which foreign material extends into the small intestinal tract, as lengthy or linear foreign bodies must be removed surgically rather than endoscopically. The left lateral projection can be used to highlight some mural gastric wall or pyloric

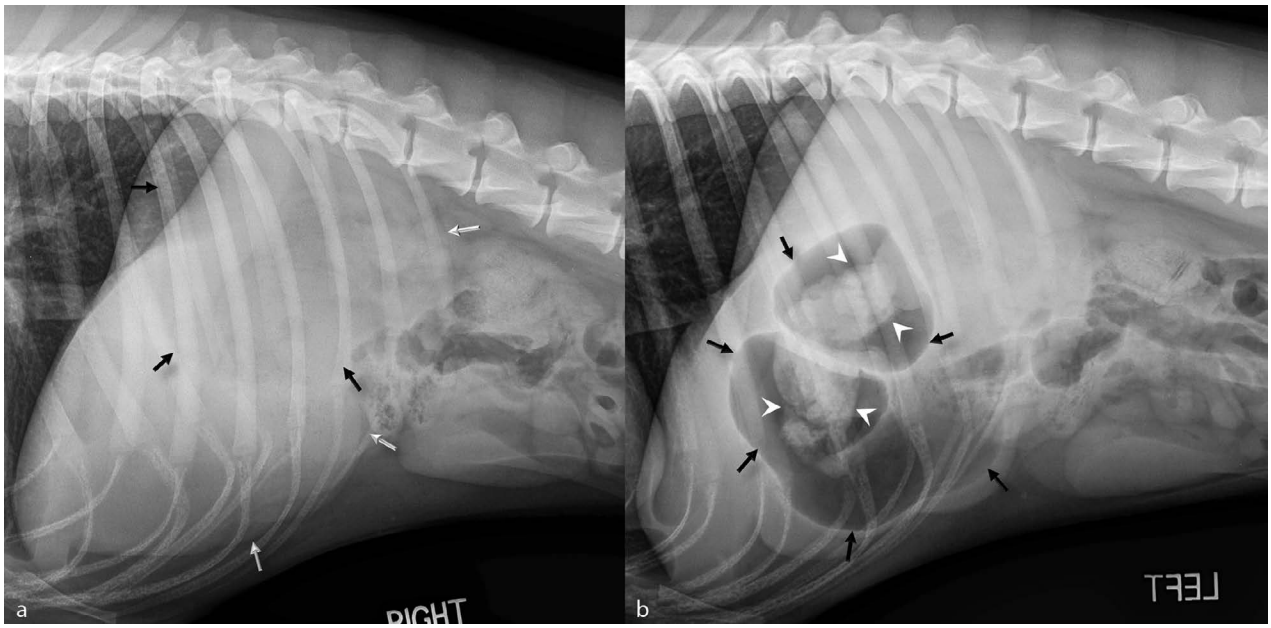


FIGURE 4.26 Right **(a)** and left **(b)** lateral radiographs in a dog presenting for acute and frequent vomiting. On the right lateral view, a distended stomach is seen (a, white arrows) which contained a shade of gray consistent with gas and fluid content. Due to recumbency in the right lateral view, faint gas is located in the gastric fundus (a, black arrows), and fluid is located at the level of the pylorus. Due to the clinical signs and appearance of the stomach, a left lateral projection was obtained. On this view, gas fills the nongravity-dependent pyloric antrum (b, black arrows) while fluid falls to the gastric fundus. Gas within the pylorus highlights a well-defined, tubular, soft tissue opacity (b, white arrowheads). This opacity is pyloric in location and must be nonmobile because it did not fall with luminal fluid to the gravity-dependent gastric fundus on the left lateral view, indicating positive evidence for obstruction. A sock was removed surgically.

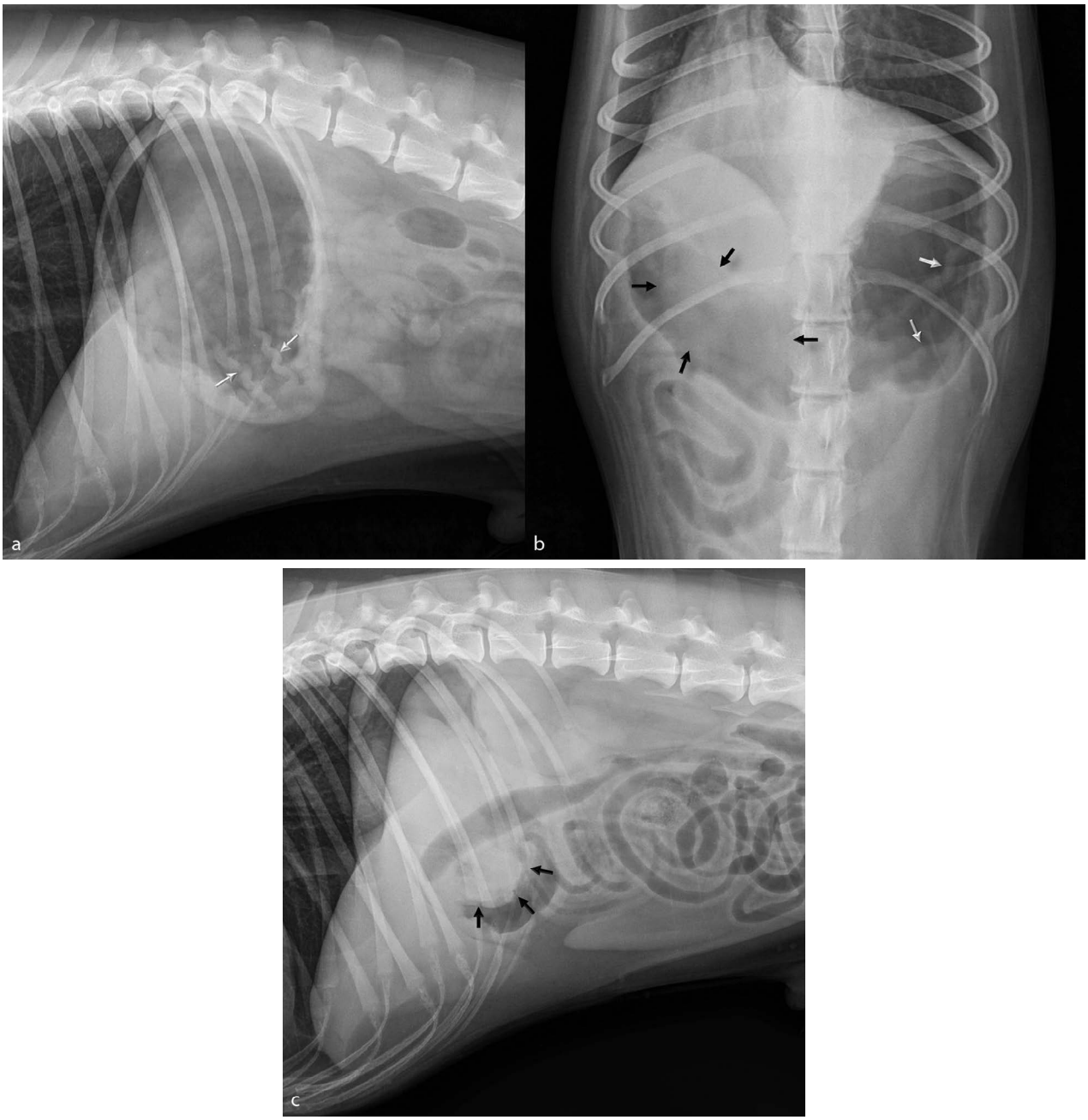


FIGURE 4.27 Right lateral **(a)**, ventrodorsal **(b)**, and left lateral **(c)** abdominal radiographs in a dog presenting for increasing episodes of vomiting over several weeks. The stomach is moderately distended and contains a large amount of gas causing a darker gray opacity; however, some fluid is also present that makes the gravity-dependent part of the stomach difficult to evaluate. In the right lateral projection, gas is present in the fundus, while luminal fluid falls to the gravity-dependent part of the stomach, the pylorus. Rugal folds located within the gastric body and fundus are highlighted by gas on the right lateral and ventrodorsal views (a and b, white arrows). Additionally, an indistinct soft tissue opacity is seen at the right gastric body and pyloric antrum on the ventrodorsal view (b, black arrows). This may be mobile luminal fluid or ingested content. On the left lateral view (c), gas has risen to the nongravity-dependent pyloric antrum and highlights a soft tissue mass that is partially surrounded by gas having an irregular luminal margin (c, black arrows), providing a more convincing view of a mural abnormality. Gastric adenocarcinoma was diagnosed via endoscopic samples.

abnormalities if they are large enough to extend into the lumen or create an irregular gas pattern in the pyloric antrum (Figure 4.27a–c).

In cases where the left lateral view does not reveal a luminal foreign object, a mural abnormality or luminal obstruction not highlighted by gas cannot totally be ruled out; however, causes of functional ileus such as gastritis and pancreatitis are considered higher on the differential diagnosis list, especially if acute vomiting is the predominant clinical sign. The left lateral projection

can also be used to prove that a cranioventral mass is a distended stomach rather than a liver or splenic mass.

Gastric wall masses are not usually diagnosed on radiographs alone because it can be difficult to differentiate a mass typically effaced by surrounding organs and luminal content unless a luminal abnormality can be highlighted by gas. A stomach wall mass can cause a similar mass effect to that seen with luminal gastric distension (i.e., caudal displacement of small intestines and the spleen). In many cases, a positive (barium sulfate, most commonly) or negative (room air, most commonly) contrast upper GI study or an abdominal ultrasound is ultimately required to determine the presence of a gastric wall mass.

Gastric Malpositioning

Alterations in stomach positioning can occur due to mass effect from surrounding organs or to volvulus. If the diaphragm is ruptured, the stomach can be cranially displaced within the pleural space or in the location of the liver and may be difficult to locate unless distended or contrast is administered. A small liver can cause a cranially positioned stomach. Conversely, hepatomegaly can cause caudal displacement of the stomach.

Volvulus occurs when the stomach axis rotates, typically clockwise when viewing the animal from caudal to cranial, altering the relative positions of the gastric fundus and pylorus. The pylorus rotates cranially, dorsally, and to the left while the fundus rotates to the right and ventrally. Often, the stomach is massively dilated concurrent with volvulus, hence the term GDV. In most cases, the stomach contains a large volume of gas; however, fluid or inhomogeneous ingesta may be the most notable luminal contents. The motion of gas and fluid within the normal stomach must be understood in order to appreciate the radiographic abnormalities that occur with GDV. The right lateral recumbent view is often the only view needed to evaluate for the presence of gastric malpositioning; however, additional views can be performed, if necessary. Due to gastric malpositioning with GDV, instead of fluid falling to the pylorus in the right lateral view, gas will rise to the pylorus, which is abnormally located on the left side. Therefore, having gas present in the pylorus on the right lateral view is a positive indication of gastric malpositioning (Figure 4.28). The volvulus combined with the severe distension creates a compartmentalized appearance to the stomach, which appears to be divided by a soft tissue band. This descriptive configuration of gastric malpositioning occurs with a 180-degree torsion, which is the most common torsion. In the case of a 360-degree torsion, gas and fluid will behave as expected in a normal animal, except that massive gastric distension will be seen, making this degree of volvulus more easily overlooked.

An alteration in stomach opacity occurs most commonly due to radiopaque luminal material that may be mineral or metal opaque and can be obstructive, or benign.

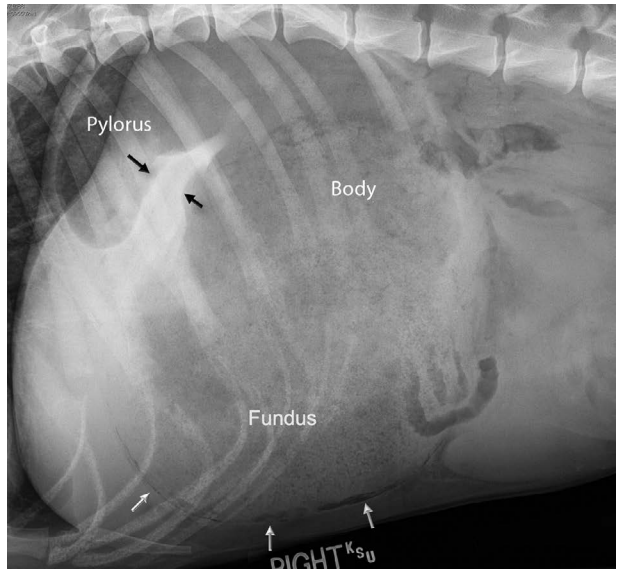


FIGURE 4.28 Right lateral abdominal radiograph in a dog having gastric dilatation and volvulus. Each portion of the stomach is labeled. On the right lateral view, the pylorus should contain fluid. In this case, the pylorus (identified as being the smallest gastric compartment) contains gas and is located dorsally and cranially. The fact that the pylorus contains gas in the right lateral recumbency indicates that it is located on the left side of the dog. A thick, soft tissue opaque band (between black arrows) is present between the gastric body and pylorus, typical for compartmentalization seen with massive distension and volvulus. Additionally, an irregular line of gas borders the ventral aspect of the gastric fundus, indicating intramural gas (gastric pneumatosis) and wall necrosis (white arrows).

Alterations in Gastric Wall Opacity

An alteration in stomach opacity occurs most commonly due to radiopaque luminal material that maybe mineral or metal opaque and can be obstructive, or benign. True alterations in stomach opacity can occur due to mural gas (gastric pneumatosis or emphysematous gastritis) or mucosal mineralization, as reported with uremic gastritis. In cats, fat within the submucosal layer of the stomach is sometimes radiographically visible as a lucent line paralleling the gastric wall and is a normal finding. This fat layer is not present in dogs, and its identification in cats must not be mistaken for pneumatosis. Mineralization associated with uremic gastritis occurs in the mucosal layer and can result in a faint mineral line that follows the rugal folds, likely due to metastatic mineralization and formation of whitlockite crystals. Mural gastric mineral can be identified in some dogs having schistosomiasis due to infection with *Heterobilharzia americana*. The mineral in this case is associated with heavy concentrations of mineralized parasitic eggs in the submucosa of the gastrointestinal tract.

Small Intestines

Inexperienced interpreters often rely solely on small intestinal diameter as an indication of abnormality.

Box 4.8 Descriptors for evaluation of small intestines

- Location
- Luminal content
- Serosal margin shape and margination
- Path of small intestinal loops
- Apparent number of small intestinal loop
- Diameter

Several other descriptors exist that should be evaluated when interpreting small intestine and are summarized in Box 4.8. With regard to small intestinal diameter, multiple measurements have been published for normal small intestine diameter. In dogs, the normal small intestinal diameter should be less than two rib widths. Also, an increase in diameter of a small intestinal segment >50% of the diameter of the remaining small intestinal loops is considered abnormal. Small intestinal dilation >1.6 times the dorsoventral diameter of the narrowest point of the L5 vertebral body is significantly associated with mechanical obstruction. Small intestines in cats should measure <12 mm in diameter. Small intestine must be distinguished from colon. The diameter of the colon can vary greatly, being quite large and often containing inhomogeneous fecal material in normal animals. Finding similar luminal material within small intestines to that normally seen within the colon is often of significance.

The luminal content in small intestines should be homogeneous in appearance. The small intestines normally contain gas or fluid, or are empty, producing a shade of gray depending on the volume of gas located within the segment. Additionally, normal luminal gas forms well-defined tubes or ovals without causing distension. Dogs tend to have more luminal gas than cats; however, great variation exists depending on the degree of aerophagia. Because they tend to be more evident, loops containing gas are often evaluated more closely by beginner interpreters than uniformly soft tissue opaque loops. Attempts must be made to evaluate loops that are empty or have homogeneous soft tissue opaque content. In homogeneous small intestinal content, having either definable structure or more descriptively matching luminal feces located within the large intestine, should raise suspicion of foreign material, especially when associated clinical signs are present. Obtaining right and left lateral recumbent views redistributes luminal gas and fluid within the small intestines and can make the presence of an abnormality more visible.

The serosal margin of small intestinal loops should be linear, smooth, and well defined. A roughened serosal margin most commonly occurs with fine plication due to the typically thin thread-like material, which causes linear foreign bodies in cats. Mural small intestinal masses can also cause an irregular serosal surface to small intestinal loops.

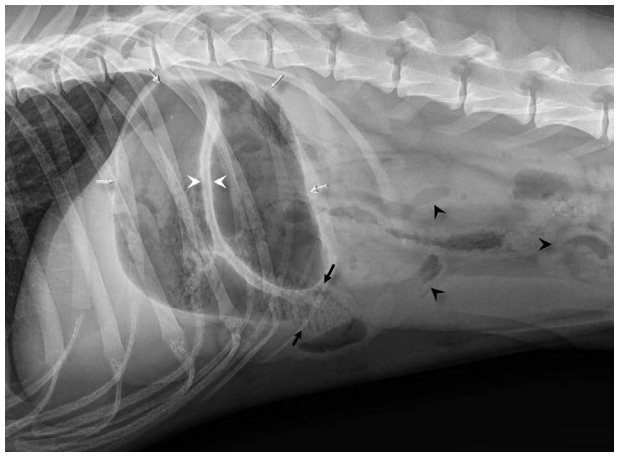


FIGURE 4.29 Lateral abdominal radiograph in a dog presenting for acute, frequent vomiting. A massively distended loop of small intestine containing mostly gas is present in the cranial abdomen (between white arrows). Due to the extreme distension, the loop of intestine is stacked upon itself and takes a hairpin turn, creating a squared-off end in the dorsal abdomen. The stacked intestinal walls create an apparent soft tissue opaque band (between white arrowheads) separating the luminal gas within each segment. Ventrally, a structured inhomogeneous opacity composed of gas and soft tissue is present that is partially surrounded by gas (between black arrows). Multiple small intestinal loops are normal in diameter (black arrowheads). Mechanical obstruction due to a corncob foreign body was diagnosed.

Normal intestinal loops have a path comprised of multiple broad turns. The presence of a tortuous path consisting of tight turns should raise suspicion for plication due to linear foreign material. Plication also tends to create a reduction in the apparent number of small intestinal loops. With severe small intestinal dilation, the small intestinal path can have extremely tight turns (so-called hairpin turns) giving the loops a stacked appearance with squared-off ends, indicating small intestinal crowding due to increased luminal volume (Figure 4.29).

The diameter of the small intestines should be uniform across all segments and should be within measurements previously discussed. When considering causes of dilated small intestines, segmental distribution of dilation is probably the most useful descriptor in determining the presence of obstruction. Uniform dilation is more often associated with a functional ileus, and the presence of dilated small intestinal loops in combination with loops that are normal in diameter is more characteristic of mechanical obstruction.

Small Intestinal Mechanical Obstruction

Small intestinal mechanical obstruction falls into two main categories, focal discrete obstruction and linear obstruction, and these have important differences in radiographic appearance. The typical radiographic appearance for a discrete obstruction is small intestinal

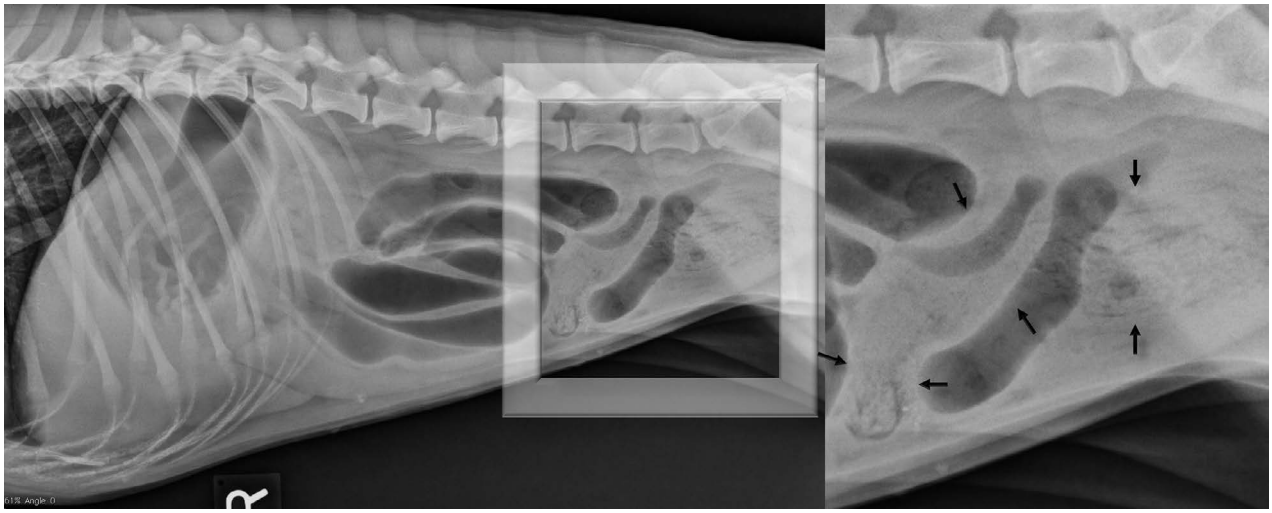


FIGURE 4.30 Lateral abdominal radiograph in a dog presenting with acute, frequent vomiting. Multiple gas-filled small intestinal loops are dilated. Too many visible dilated loops are present to be due to colon alone. In the caudoventral abdomen, a loop containing inhomogeneous luminal material having linear gas and soft tissue opaque striations is present (in boxed inset and between black arrows) that is typical for textile material. A hand towel was surgically removed.

dilation that is segmental in nature. In other words, some distended loops are identified, and, importantly, some loops that are normal in diameter are also identified. With more distal obstructions, an increase in the number of dilated small intestinal loops relative to normal ones is often identified because distension occurs orad to the obstruction. Potential causes for a discrete obstruction include luminal foreign material, a mural mass, or an intussusception. Close evaluation of small intestinal content may reveal the presence of focal structured or inhomogeneous material, further raising suspicion of mechanical obstruction due to foreign material. Sometimes, the discrete obstruction can have a characteristic appearance, such as a corncob having a lucent grid at regular intervals (Figure 4.29) or a textile having linear gas and soft tissue opaque striations (Figure 4.30). Additionally, luminal intestinal gas can highlight a foreign object, creating a gas–soft tissue interface that is inconsistent with a normal luminal gas bubble (Figure 4.31). Redistribution of gas using both lateral recumbencies can assist with foreign body diagnosis by potentially highlighting such interfaces. The lack of identification of the obstructing material should not preclude a diagnosis of obstruction when remaining descriptors indicate mechanical ileus.

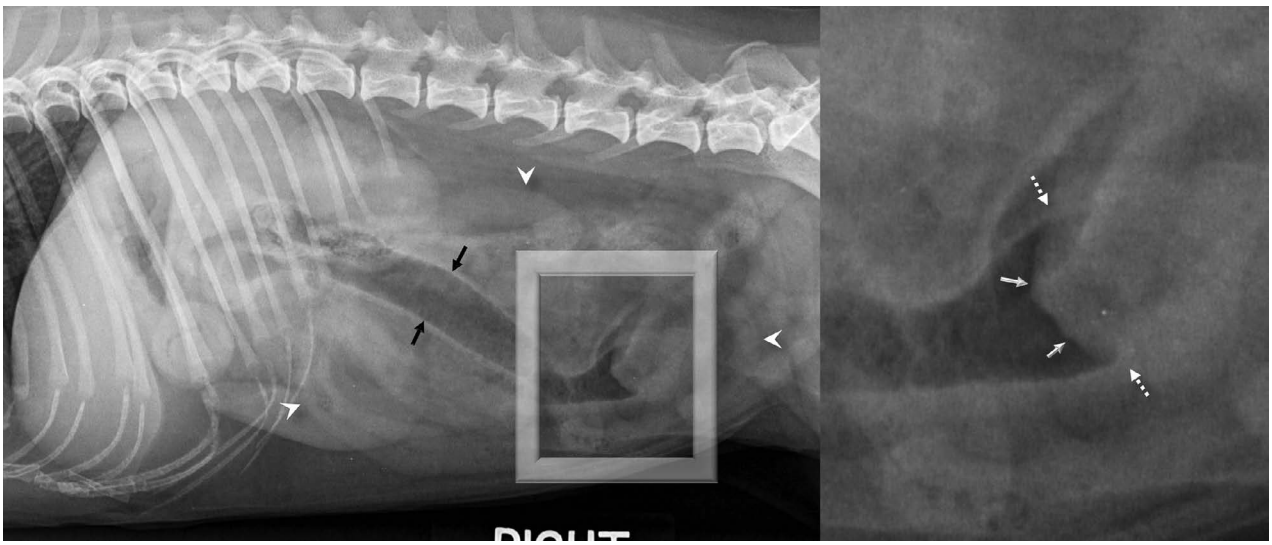


FIGURE 4.31 Lateral abdominal radiograph in a dog that was vomiting for one week. A gas-distended small intestinal loop is present (between black arrows). Several normal diameter loops are also present (white arrowheads). At the caudal aspect of the gas-distended loop, an irregularly marginated interface between the gas and a soft tissue opacity is seen (boxed inset, white arrows). The small intestinal loop visibly dilates at the level of this soft tissue opacity (dotted white arrows). A plastic toy nose was removed surgically.

Small intestinal masses can cause a focal, discrete obstruction. Small intestinal masses are most commonly neoplastic due to adenocarcinoma, lymphoma, or leiomyosarcoma. Focal masses can be circumferential surrounding the entire lumen (more typical of adenocarcinoma) or eccentric involving one side of the intestine (more typical of leiomyosarcoma). Diffuse or multifocal neoplasms such as lymphoma also occur. Focal, discrete, circumferential masses are most likely to cause mechanical obstruction. An accumulation of granular mineral material at a location within the intestinal tract (called a gravel sign) indicates a partial chronic obstruction, most likely due to a focal mural small intestinal mass where mineral opaque or desiccated material accumulates at the site of obstruction. The absence of small intestinal dilation does not rule a mechanical obstruction out. Especially with proximal small intestinal mechanical obstructions, frequent and effective vomiting can limit visible distension. In general, the small intestinal dilation seen with focal, discrete mechanical obstruction is often greater than the dilation seen with a paralytic or functional ileus.

Linear foreign material can span variable portions of the GI tract, causing small intestinal plication but not necessarily dilation. A tortuous path of small intestine or the presence of visible plication creating an irregular serosal margin is the most reliable evidence of a linear foreign body. Plication occurs because the material is anchored while the free end travels distally through the GI tract, where continual peristalsis causes the intestine to gather around the material like pleats in a drape. Two main features distinguish linear foreign bodies in cats from those in dogs. First, in cats, linear foreign material is usually very thin, such as thread or floss. Because of this, the plication that occurs with linear foreign material tends to be fine, appearing as an irregular serosal margin with little to no measurable small intestinal distension (Figure 4.32a, b). The small intestines can appear decreased in number and aggregated in a focal location (usually the right abdomen); however, these are often the least useful features for identification of linear foreign bodies and can be confused with the intestinal appearance in normal animals, especially obese cats. Some small intestinal loops may have small, irregular gas bubbles that are piriform in shape as gas becomes trapped in the pleats. Also, in cats, the material often becomes anchored at the base of the tongue, so examination of the mouth may confirm suspicion of linear foreign material. Linear foreign material in dogs tends to be thick textile material, such as socks, rope toys, and towels. This material tends to anchor at the level of the pylorus, causing an outflow obstruction. Because of the size of the linear material, small intestinal dilation is commonly seen with linear foreign body obstructions in dogs (Figure 4.33a, b). Also, due to the location of the obstruction at the pylorus, a left lateral view of a stomach containing adequate gas often reveals the origin of the linear object. Due to the thick nature of the textile causing most obstructions, the plication seen in a dog is characterized by frequent changes in direction of the small intestinal loop rather than the fine pleating that occurs with linear foreign material in cats, with an increase in likelihood for accompanying small intestinal dilation than is seen with linear foreign bodies in cats.

Functional Ileus

Functional ileus results in visible dilation of small intestines that is often diffuse but on some occasions can be focal, especially in association with pancreatitis. Focal narrowing of small intestine due to segmental peristaltic contractions is not seen radiographically when paralytic ileus is the cause of small intestinal dilation. Peritonitis, pancreatitis, enteritis, and infiltrative bowel neoplasms (e.g., lymphoma and mast cell tumor) are the most common causes of functional ileus. The distension that occurs with functional ileus is not usually as great as

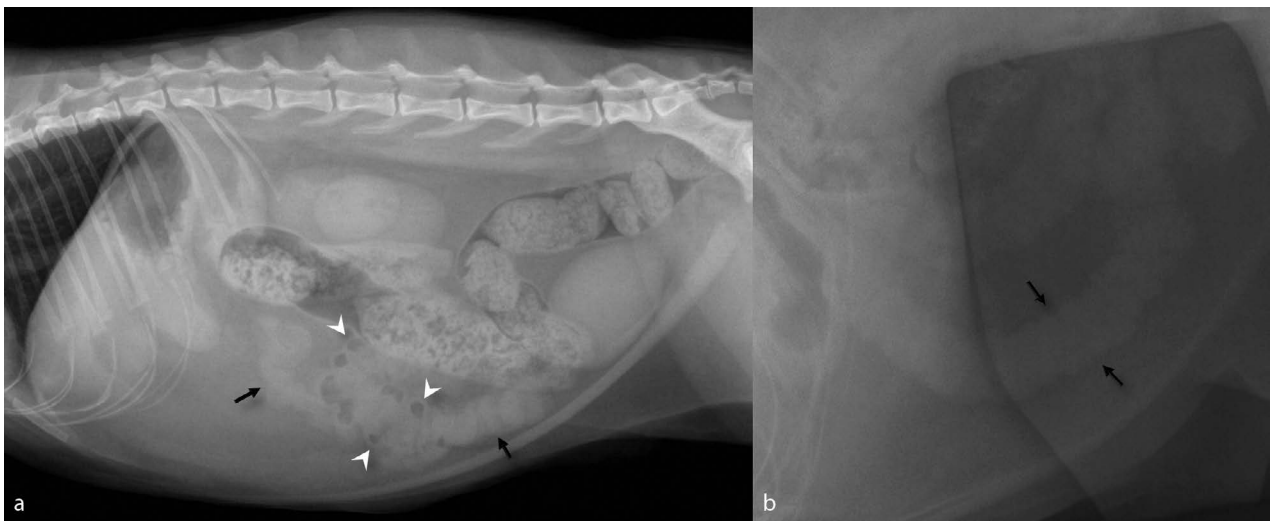


FIGURE 4.32 Lateral abdominal radiograph **(a)** and magnified compression view **(b)** in a cat presenting for acute vomiting. The apparent number of small intestines is subjectively decreased. The serosal margins of the loops are irregular with a tortuous path (a and b, black arrows). Several small gas bubbles are trapped within the pleats of the plicated intestinal loops (white arrowheads).

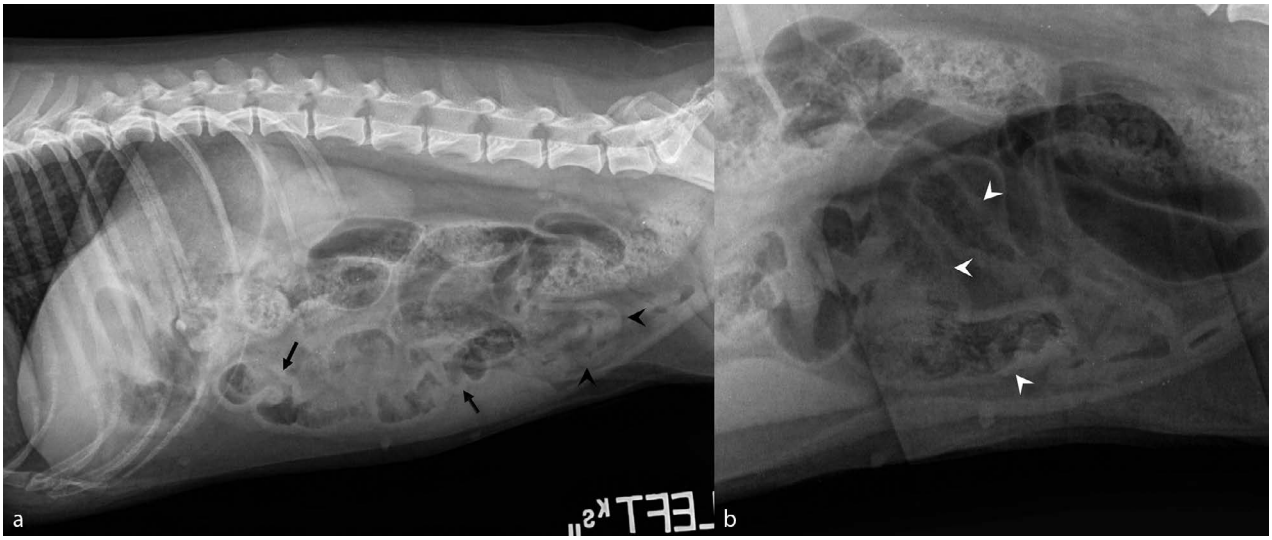


FIGURE 4.33 Lateral abdominal radiograph **(a)** and magnified compression view **(b)** in a dog presenting with acute, frequent vomiting. Multiple ventrally located small intestinal loops have a tortuous path (a, black arrows). The loops are also increased in diameter when compared to more normal loops (a, black arrowheads). The luminal content within the tortuous loops is inhomogeneous (b, white arrowheads), indicating foreign material.

that seen with mechanical obstruction. Regardless, functional ileus cannot always be distinguished from a distal mechanical obstruction without ultrasound examination or a positive contrast GI study. Less common causes of functional ileus, such as bowel ischemia and thrombosis or dysautonomia, can cause a profound small intestinal dilation that may be segmental rather than diffuse.

Colon

The colon is in a relatively predictable location and often contains luminal gas or feces, making it readily identifiable in most cases --Locating the colon should be the first step in evaluating the intestinal tract. The cecum is rarely identified in cats. The normal colon is typically larger in diameter than the small intestines and, as previously mentioned, is the only intestinal segment whose contents should be inhomogeneous, appearing as a mixture of gas, soft tissue, and granular mineral in locations where fecal material is present. Material of this characterization located in small intestines would be considered abnormal. Normal large intestinal diameter is difficult to characterize because it is so variable; however, the colon diameter should not exceed the length of the L7 vertebral body.

Alterations in colon location, size, and opacity can occur in diseased animals. Colon displacement occurs most commonly due to the abdominal mass effects previously discussed. Mass effects causing concurrent colon displacement and compression with subsequent extramural obstruction occur near the pelvic inlet, usually due to sublumbar lymph node or prostatic enlargement. Abnormal luminal distension is either due to functional or mechanical obstruction. Functional causes of colon enlargement due to nutritional, metabolic, neurologic, or chronic obstructive causes will result in a generalized enlargement of the colon (called megacolon). Mechanical causes of colon dilation result in enlargement orad to the obstruction and can be due to extramural, mural, or luminal causes. The most common location for a mechanical colon obstruction is at the level of the pelvic inlet; therefore, generalized megacolon tends to occur with functional or mechanical causes. Alterations in opacity of the colon most typically occur due to changes in luminal content. In animals having diarrhea, the colon will be characterized by a homogeneous gas or fluid opaque lumen rather than the inhomogeneous mixture typically seen with formed feces, making its contents similar in appearance to small intestinal content. Of course, an empty colon will appear soft tissue opaque and will be small in diameter. Colon masses or intussusceptions appear homogeneously soft tissue opaque. In many cases, an interface occurs where the homogeneously opaque obstructive mass or intussusceptum contacts inhomogeneous feces in a dilated colon (**Figure 4.34**). In most cases, when foreign material is positively located within the colon, surgical intervention is not required. Therefore, the interpreter must ascertain the origin of any radiopaque foreign objects or structured-appearing materials prior to deciding on a treatment plan. In some cases, contrast procedures are needed to confirm the exact location of suspicious material or a distended loop of intestine (pneumocolonography using room air is very useful to delineate the true location of the colon).

Pancreas

The right pancreatic limb borders the duodenum, the pancreatic body is located near the cranial duodenal

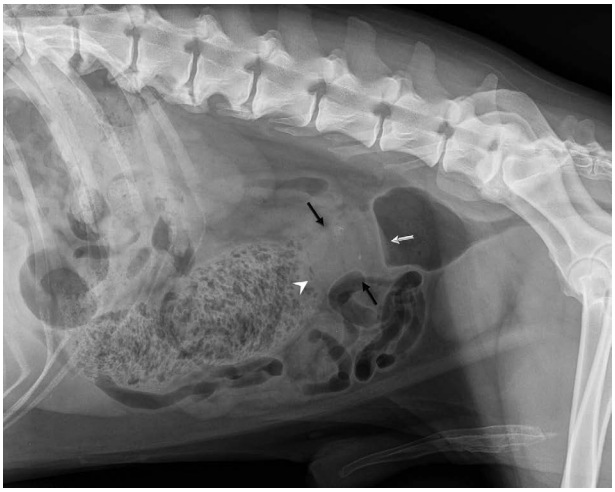


FIGURE 4.34 Lateral abdominal radiograph in a dog straining to defecate. The descending colon is markedly distended causing it to be ventrally located in the abdomen. A portion of the colon is homogenously soft tissue opaque (between black arrows). Homogenous soft tissue opacity is unexpected in a colon that is distended with fecal material. The cranial aspect of the soft tissue opacity interfaces with more typical inhomogeneous soft tissue and gas opaque fecal content (white arrowhead). The caudal aspect of the soft tissue opacity has a well-defined, flat interface with gas (white arrow). This configuration indicates gas highlighting a luminal structure. A circumferential colon wall mass was found on abdominal ultrasound. Colonic adenocarcinoma was diagnosed on aspiration.

flexure, and the left pancreatic limb borders the greater curvature of the stomach. The pancreas is never identified radiographically in the normal dog. Occasionally, in fat cats, the pancreas can be seen as an indistinct soft tissue opacity located between the gastric fundus, left kidney, and the spleen. Pancreatic diseases most often produce clinical GI signs. Rarely, radiographically visible changes are seen with pancreatic disease; however, radiographs are still recommended to assist with ruling out other potential causes of clinical signs. On occasions where radiographic changes of pancreatic disease are present, it will typically manifest as a loss in peritoneal detail (focal or diffuse), a right cranial abdominal mass effect, separation of the stomach from the transverse colon, and/or dilation of the stomach and the duodenum due to functional ileus (**Figure 4.35a, b**). The right cranial abdominal mass effect classically causes leftward displacement of the gastric body with rightward displacement of the duodenum toward the body wall. Additionally, the intestines are pushed caudally. Acute pancreatitis is the most common cause of a mass effect associated with the pancreas; however, pancreatic abscesses, pseudocysts, and neoplasms can have a similar appearance. Additionally, other organs of origin for a right cranial abdominal mass include liver, gallbladder, and duodenum.

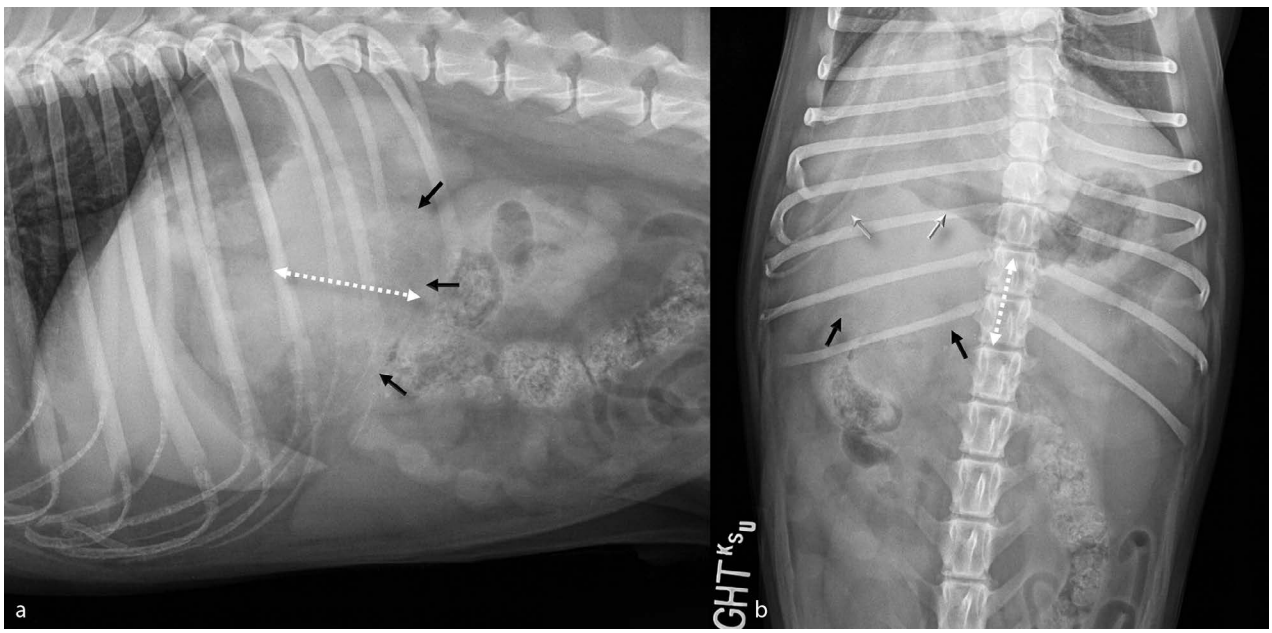


FIGURE 4.35 Lateral **(a)** and ventrodorsal **(b)** abdominal radiographs in a dog with acute pancreatitis. A focal loss of detail is present in the cranial abdomen with an indistinct increase in soft tissue opacity in the right cranial abdomen (black arrows). The gastric body and the pyloric antrum are cranially displaced and compressed with increased left-sided positioning of the stomach (white arrows). There is increased distance between the stomach and the transverse colon (dotted white line).

SUMMARY

When beginning a review of each study, the focus should be on systematic evaluation of each organ, keeping in mind those organs not normally seen radiographically. Also, an attempt should be made to increase the diagnostic usefulness of abdominal radiography with compression and positional views, and contrast procedures as warranted. When radiographs fail to diagnose or definitively rule out disease in a clinical patient, referral for abdominal ultrasound or computed tomography may be warranted.

RECOMMENDED FURTHER READINGS

1. Thrall DE. *Textbook of Veterinary Diagnostic Radiology*. St. Louis, MO: Saunders, 2018.
2. Dennis R, Kirberger RM, Wrigley RH, Barr FJ. *Handbook of Small Animal Radiological Differential Diagnosis*. London: W. B. Saunders, 2001.
3. Kealy JK, McAllister H, Graham JP. *Diagnostic Radiology and Ultrasonography of the Dog and Cat*. St. Louis, MO: Saunders, 2011.
4. O'Brien TR. *Radiographic Diagnosis of Abdominal Disorders in the Dog and Cat: Radiographic Interpretation, Clinical Signs, Pathophysiology*. Philadelphia, PA: Saunders, 1978.

SECTION

III

DISEASES OF SPECIFIC ORGAN SYSTEMS



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CHAPTER

5

Diseases of the Oral Cavity and Teeth

Erin P. Ribka and Brook A. Niemiec

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INTRODUCTION

Veterinary dentistry and oral surgery is a quickly expanding field. Veterinarians and pet owners alike are learning the importance of good oral health for companion animals. Thanks to this and other medical and nutritional improvements, pets are living longer, healthier lives. Dental disease is more common in our small breed and aging pet populations, and without proper care throughout their lives, extensive treatment is increasingly necessary. Recent research supports the connection between oral and systemic health, including negative effects on diabetes, systemic inflammatory markers, cardiac, hepatic, renal, and pulmonary diseases, and an increased incidence of certain neoplasias (particularly oral). In this chapter, we aim to provide a basic overview of normal oral anatomy and physiology as well as some of the most common issues encountered in small animal clinical practice. The entire breadth of oral diseases cannot be covered completely in a single chapter; therefore, resources for more detailed information are provided at the end of this chapter.

ANATOMY

A firm understanding of oral anatomy and terminology is essential. The accepted dental formulas for the dog and cat are shown in Table 5.1.

Several tooth numbering systems exist for efficient written or verbal communication regarding the oral cavity. The most commonly used system is the modified Triadan system. Each quadrant of the mouth is given a number, as is each tooth. The right maxillary quadrant is the 100 arch (500 for deciduous teeth), left maxillary is 200 (600), left mandibular 300 (700), and right mandibular is 400 (800). Teeth are numbered beginning with the first incisor and moving distally (or caudally) as 01–10 in the canine maxilla and 01–11 in the canine mandible. Therefore, the permanent right maxillary canine tooth would be termed 104. The maxillary fourth premolars are 108 (right) and 208 (left), and the mandibular first molars are 309 (left) and 409 (right). These teeth are typically referred to as the carnassial teeth (Figure 5.1a, b).

TABLE 5.1 Dog and cat accepted dental formulas

Canine deciduous (Total = 28) – Maxilla (2×) – 3 incisors, 1 canine, 3 premolars – Mandible (2×) – 3 incisors, 1 canine, 3 premolars
Canine permanent (Total = 42) – Maxilla (2×) – 3 incisors, 1 canine, 4 premolars, 2 molars – Mandible (2×) – 3 incisors, 1 canine, 4 premolars, 3 molars
Feline deciduous (Total = 26) – Maxilla (2×) – 3 incisors, 1 canine, 3 premolars – Mandible (2×) – 3 incisors, 1 canine, 2 premolars
Feline permanent (Total = 30) – Maxilla (2×) – 3 incisors, 1 canine, 3 premolars, 1 molar – Mandible (2×) – 3 incisors, 1 canine, 2 premolars, 1 molar

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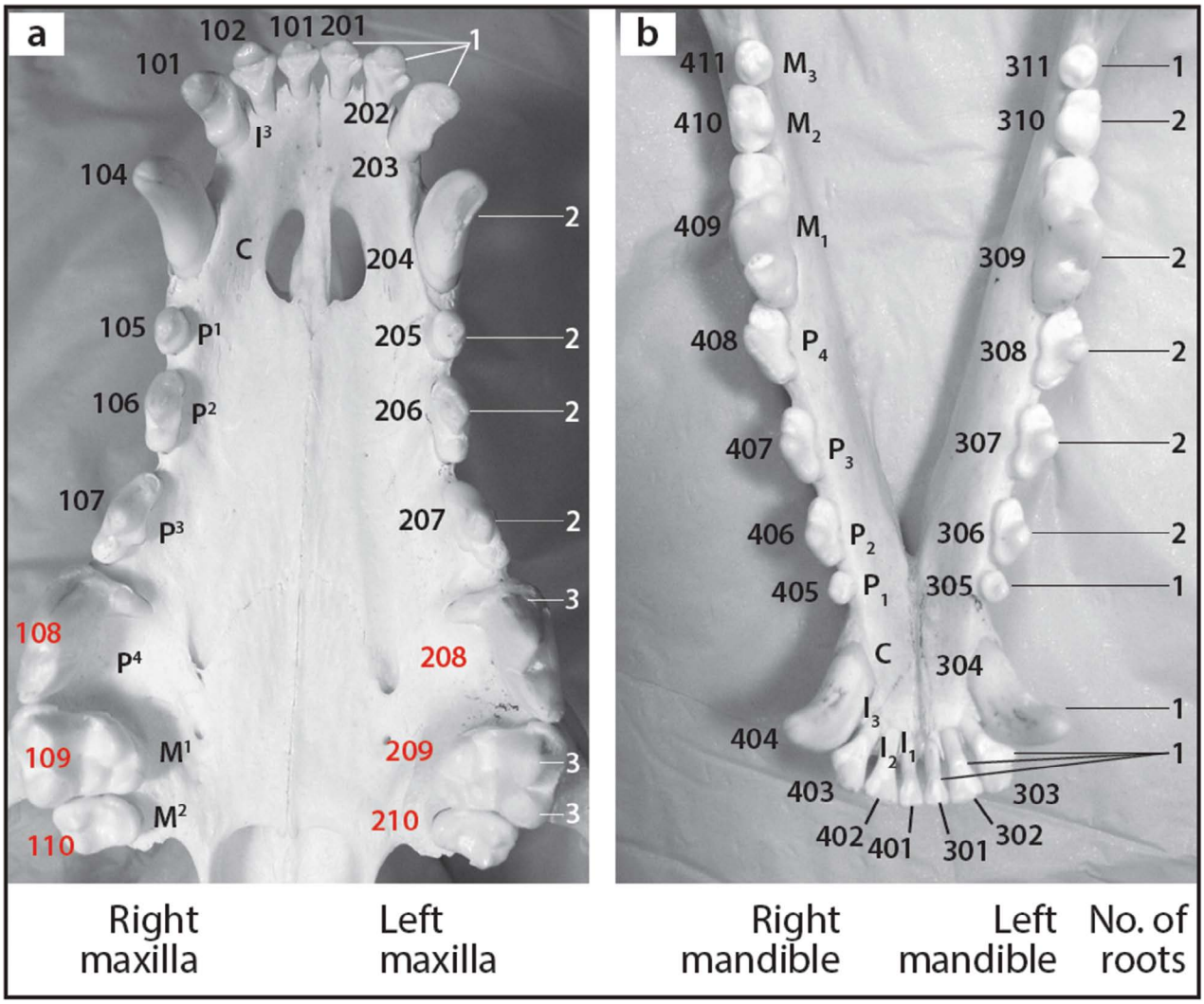


FIGURE 5.1 Modified Triadan numbering system in the dog. **(a)** Maxilla (3-rooted teeth numbered in red); **(b)** mandible. (*From Niemiec BA (2011).* Small Animal Dental, Oral and Maxillofacial Disease: A Color Handbook. *CRC Press, London, with permission.*)

Cats do not have a full complement of premolars and molars and so are "missing" several teeth, which are skipped in this system (Figure 5.2a, b).

The eruption times of deciduous and permanent teeth in the dog and cat are shown in Table 5.2.

Directionally, surfaces of teeth are referred to as (Figure 5.3a, b):

- *Mesial:* Nearer the rostral midline
- *Distal:* Away from the rostral midline
- Buccal surfaces face the inside of the cheeks
- Labial surfaces face the lips
- Lingual surfaces are next to the tongue
- Palatal surfaces face the palate

It is also important to understand tooth structure and development. The crowns of teeth are covered in enamel, which is the hardest substance in the body. Enamel cannot be regrown once it is lost and is much thinner in dogs and cats (<1 mm) than in humans. Beneath the enamel is dentin, which has a mineral content similar to bone. It is comprised of numerous microscopic dentinal tubules. Each dentinal tubule contains an odontoblastic process, which is essentially an extension of the root canal system. Dentin is produced throughout life, and this accounts for the decreasing width of the pulp canal evident on dental radiographs as patients age. Dentin is porous, and irritation or injury may incite its component cells to protect the tooth by forming reparative or tertiary dentin. Vessels and nerves enter and exit the teeth through the tip of the root or the apex. The entire root structure (in normal teeth) is surrounded and supported by the periodontal ligament, which holds teeth in place in the surrounding alveolar bone. The periodontium consists of the gingiva, periodontal ligament, cementum, and alveolar bone. The gingiva is part of the specialized

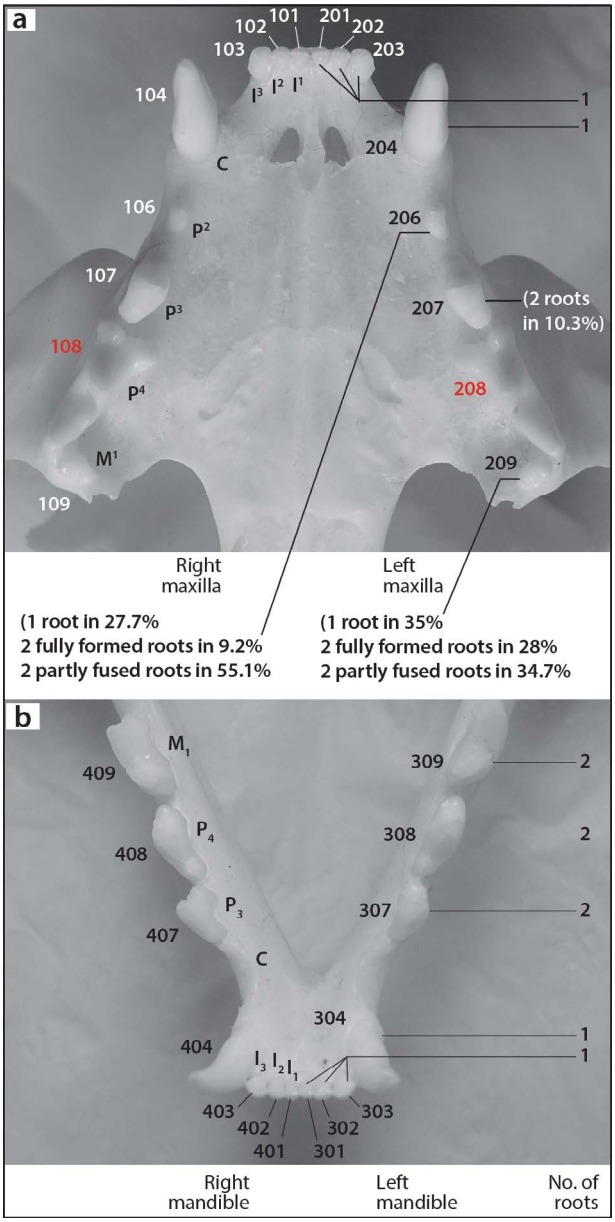


FIGURE 5.2 Modified Triadan numbering system in the cat. **(a)** Maxilla (3-rooted teeth numbered in red); **(b)** mandible. (*From Niemiec BA (2011).* Small Animal Dental, Oral and Maxillofacial Disease: A Color Handbook. *CRC Press, London, with permission.*)

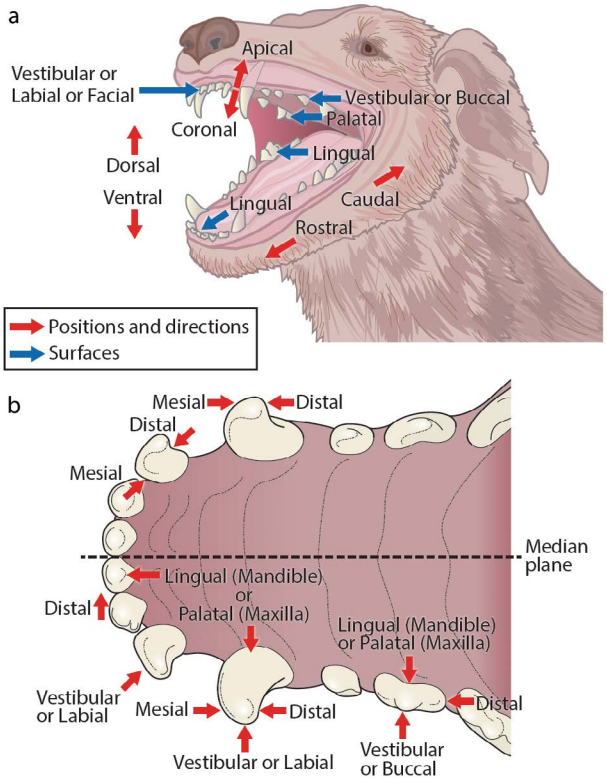


FIGURE 5.3 Dental anatomic terminology. **(a)** Extraoral view; **(b)** intraoral view. (*From Niemiec BA (2011).* Small Animal Dental, Oral and Maxillofacial Disease: A Color Handbook. *CRC Press, London, with permission.*)

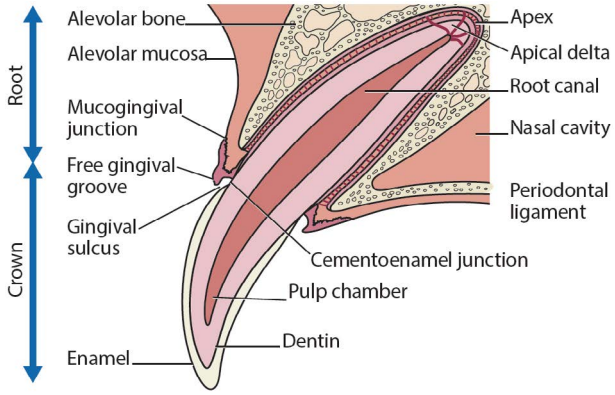


FIGURE 5.4 An adult maxillary tooth and its periodontium. (*From Niemiec BA (2011).* Small Animal Dental, Oral and Maxillofacial Disease: A Color Handbook. *CRC Press, London, with permission.*)

mucosa that protects the tooth and supporting structures from infection and detachment. Cementum covers the root much as enamel covers the crown of the tooth, increasing with age (Figure 5.4).

TABLE 5.2 Eruption times of deciduous and permanent teeth in the dog and cat

	Dogs				Cats			
	Incisors	**Canines**	**Premolars**	**Molars**	**Incisors**	**Canines**	**Premolars**	**Molars**
Deciduous (weeks)	3–4	3	4–12	–	2–3	3–4	3–4	–
Permanent (months)	3–5	4–6	4–6	5–7	3–4	4–5	4–6	4–5

ORAL EXAMINATION

Conscious visual examination may be limited or fairly detailed, depending on the patient's temperament and the skill of the examiner. It may be possible to diagnose persistent deciduous teeth, fractured teeth, caries, tooth resorptions, masses, and malocclusions/orthodontic problems and develop a preliminary sense of the level of periodontal disease. (Note: The conscious evaluation is not a replacement for an anesthetized examination.) There are many factors that make a complete examination impossible in an awake animal, not least of which are pain and aggression. An anesthetized examination should include a complete visual assessment of the entire oral cavity, including all soft and hard tissues, periodontal probing and exploring of all aspects of individual teeth and gingival sulci, and intraoral radiography of any abnormalities (Figures 5.5–5.7). Further, many veterinary dentists recommend full mouth radiographs be obtained for all dental patients. A specific radiographic area of interest is shown in Figure 5.8.



FIGURE 5.5 Impacted right maxillary first molar (109) in a 7-month-old Golden Retriever presented for routine orchiectomy.



FIGURE 5.6 Complicated crown fracture with exposed pulp of the left mandibular second molar (310). This injury was noted by the technician monitoring anesthesia during a routine, elective ovariectomy in a 7-month-old mixed breed dog.

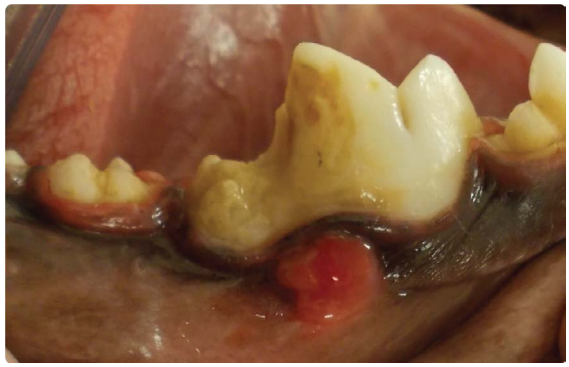


FIGURE 5.7 Evidence of developmental enamel abnormality and tooth root abscess were noted in the area of the tooth adjacent to the fractured molar.

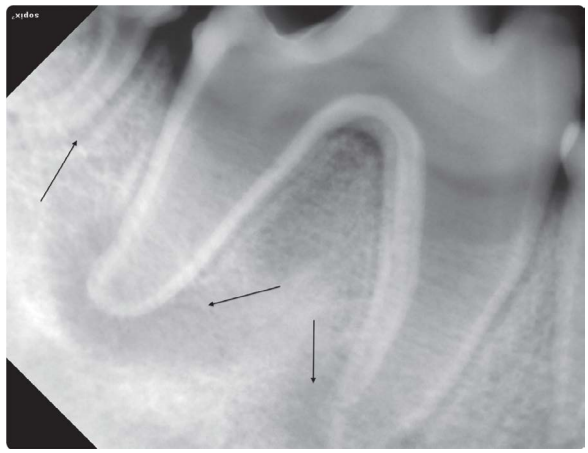


FIGURE 5.8 Dental radiographs were exposed, and the first molar was found to be nonvital. The teeth were deemed unsalvageable and surgically extracted during the same anesthetic episode. Note the periodontal lucency around tooth roots in the radiograph (black arrows). This is the same dog as in Figure 5.6.

PERIODONTAL DISEASE

Definition/Overview

Periodontal disease is the most common medical condition affecting small animal patients. It has long been established that 70% of cats and 80% of dogs exhibit some level of periodontal disease by 3 years of age. However, current research suggests that 90% or more of dogs have some degree of periodontal disease by just 1 year of age (Figure 5.9).

Periodontal disease encompasses gingivitis and periodontitis, which each represent a stage in the progression of the disease complex. Gingivitis is the earlier, reversible stage of inflammation confined to the gingival tissues. Once the inflammation reaches the deeper tissues of the periodontium (periodontal ligament and alveolar bone), it becomes periodontitis. Periodontal inflammation may result in osteoclastic resorption of the alveolar bone (Figures 5.9–5.11). This bone loss is considered irreversible without advanced periodontal surgeries and guided tissue regeneration. Therefore,



FIGURE 5.9 Canine periodontal disease. Note the red, swollen gingiva. The significant calculus build up does not equate to severity of periodontal disease.



FIGURE 5.10 Canine periodontitis. The probe is inserted to a depth of 11 mm. This is a deep periodontal pocket requiring radiographs to rule out periodontal–endodontic disease and open curettage or extraction.



FIGURE 5.11 Feline periodontal disease. The probe reaches to a depth of 4–5 mm, necessitating radiographs, closed root planing, and perioceutic administration at a minimum.

prevention is critical. There are numerous significant local/regional consequences of advanced periodontal disease, including ocular disease or damage, pathologic mandibular fractures, osteomyelitis, oral cancers, and periodontal–endodontic infections/abscesses.

In addition, recent research has linked periodontal disease to many deleterious systemic effects such as hepatic inflammation and disease, glomerulonephritis and renal insufficiency, valvular endocarditis and heart disease, cerebral infarction (strokes), diabetes mellitus, and early mortality.

Etiology

Plaque is the cause of periodontal disease. Plaque is a biofilm of oral bacteria. A biofilm is a unique compilation of organisms (bacteria), minerals, and proteins that develops into a complex structure, significantly more resistant to antibiotics and antiseptics than any of the individual bacteria themselves.

Pathophysiology

The development of periodontal disease begins with the adherence of plaque to oral structures, particularly teeth. The first step in the adherence of plaque to teeth is pellicle formation, followed by an initial adhesion and attachment and, finally, colonization and plaque maturation. There are a variety of conditions that result in roughened tooth surfaces and may increase plaque retention, including enamel hypoplasia, enamel defects, crown fractures, crowding, tooth resorptions, and malocclusions.

The rate and degree of progression of periodontal disease are determined by a combination of bacterial infection and host (patient) response. Systemic diseases (such as diabetes mellitus, endogenous or exogenous hypercortisolemia) that increase host susceptibility to infection and/or decrease wound healing also contribute to periodontal disease. It is more common in small and toy breed dogs, probably because of tooth crowding, extended life spans, and other genetic factors.

Clinical Presentation

The vast majority of patients with periodontal disease show no outward signs of disease. Patients with advanced disease may present with halitosis, ptyalism, pain, pawing at the mouth, tooth exfoliation, or even pathologic jaw fractures. Periodontal disease may be noted on routine conscious oral examination but is best diagnosed during anesthetized oral examination with probing and intraoral dental radiographs.

Differential Diagnosis

Neoplasia, immune-mediated disease, resorptive lesions, foreign bodies, candidiasis (thrush).

Diagnosis

Gingival inflammation (redness and swelling) is the first outward sign of periodontal disease. However, bleeding on probing or brushing is actually the first sign of periodontal disease; therefore, diagnosis is often delayed. These signs – redness, swelling, and bleeding – are enough to warrant a diagnosis of gingivitis. It is critical to note that while dental calculus (tartar) is typically associated with periodontal disease, it is not the source of the disease. Therefore, it should not be relied on to determine a

need for professional therapy. Orastrip (PDx Biotech) can be used quickly and easily in the conscious patient to test for the presence of thiol compounds, which are metabolic products of the subgingival bacteria which are the cause of periodontal disease. This will provide a diagnosis earlier in the disease process as well as an objective measure as to the level of periodontal disease. This knowledge may improve client compliance and allow earlier intervention.

Gingivitis may be diagnosed in the conscious patient by the gross appearance of red or swollen gums or in the owner's reporting of bleeding on brushing. Periodontitis generally requires anesthetized examination with probing and dental radiographs for diagnosis, unless there is marked gingival recession.

Periodontal probing of the circumference of each tooth during the anesthetized examination may reveal pocket depths greater than the normal gingival sulcular depth (generally 0–3 mm in dogs, 0–0.5 mm in cats). A normal probing depth does not necessarily indicate a disease-free state, as teeth affected by gingivitis can have normal sulcular depth or gingival recession. A simple color-coded probe (Niemiec periodontal probe, Dentalaire Products) has been developed to allow easy diagnosis of pathologic periodontal pockets. Periodontal disease may also be identified on dental radiography.

Management

Thorough anesthetized professional periodontal therapy and consistent home care are vital to the management of periodontal disease. Gingivitis can be reversed with such treatment. Pathologic pockets less than 6 mm are best treated with closed root planing and perioceutic treatment (Doxirobe, Zoetis; Clindoral, Trilogic Pharma). Deeper pockets or teeth with class II or III furcation defects must be treated with periodontal flap surgery and open curettage (+/– guided tissue regeneration) or extracted. Following these additional therapies, regular professional periodontal therapy and diligent home care are required. Teeth often become unsalvageable and require extraction. Examples include significantly mobile teeth or periodontal–endodontic lesions. Small teeth may also be sacrificially extracted to better access and treat more strategic teeth.

Prognosis

Outcomes depend much on severity of disease, quality of treatment, and client commitment to homecare and regular professional cleanings. Prognosis, therefore, ranges from good to guarded to poor.

MALOCCLUSION

Definition/Overview

A malocclusion is a deviation of one or more teeth and/or jaws from normal alignment. Malocclusions may be cosmetic only or result in slight to significant oral trauma. Malocclusions are categorized by class (Table 5.3 and Figures 5.12–5.14).

TABLE 5.3 Malocclusion classifications

- **Class 0:** Normal (orthoclusion). The mandibular canines are equidistant between the maxillary 3rd incisor and canine. The mandibular incisors sit just caudal to the maxillary incisors, and the premolars of the maxillary and mandibular arches interdigitate in a manner reminiscent of pinking shears, hence the term scissors bite.
- **Class I:** Normal jaw lengths (scissors bite) where one or more teeth are out of proper alignment (occlusion). These have been considered nonhereditary. However, the high incidence of certain syndromes in specific breeds does indicate a genetic predisposition. Class I malocclusions include linguoversed mandibular canines (base narrow) and mesioversed maxillary canines (lance effect). The former typically results in significant palatal trauma.
- **Class II:** Mandibular brachygnathism; the mandible is shorter than the maxilla. Also called overshot. This almost invariably causes significant palatal or tooth trauma.
- **Class III:** This is a jaw length discrepancy in which the mandible is longer than the maxilla and is also referred to as undershot. This class of malocclusion does not typically create significant trauma, but maxillary incisors may impinge on opposing soft and hard tissues and should be carefully examined.
- **Class IV** ("Wry bite"): This is a jaw length discrepancy in which one mandible or maxilla is shorter than the other. This results in a shift of the mandibular midline. A true class IV malocclusion occurs when one mandible is longer than the maxilla, and the other mandible is shorter than the maxilla.



FIGURE 5.12 Normoclusion. Scissors bite.



FIGURE 5.13 Class II malocclusion. Also termed overbite or overshot, the mandible is shorter than the maxilla. This malocclusion often requires interceptive orthodontia to relieve trauma and allow the mandible to develop to its full potential.



FIGURE 5.14 Class III malocclusion in an adult dog. Also termed under bite or undershot, the mandible is longer than the maxilla, and the mandibular incisors are rostral to the maxillary incisors.

Etiology

Most malocclusions are considered hereditary in nature, in particular the jaw length malocclusions (class II, III, IV). They may result from inbreeding to produce desirable head size or shape or from mating of parents with dissimilar jaw lengths. Mesioccluded or "lance" canines are also considered genetic (seen commonly in Shetland Sheepdogs and Persian cats). Nongenetic causes of malocclusions include trauma or systemic influences such as severe illnesses, nutritional disturbances, or endocrine diseases. In general, these nongenetic causes have historical or other clinical support.

Clinical Presentation

Patients often show no overt clinical signs but may present for oral pain, bleeding, ptyalism, aggression, "mouth shyness," halitosis, periodontal disease, or even an oronasal fistula.

Differential Diagnosis

Trauma, temporomandibular joint dislocation, mandibular fracture, normal bite for the breed.

Diagnosis

Diagnosis can usually be made with visual examination. Some malocclusions may require sedation for accurate and complete evaluation and diagnosis. Dental radiographs should be made to evaluate the involved teeth for periodontal or endodontic disease.

Management

Treatment depends on type and severity. If the malocclusion is purely cosmetic, intervention is neither warranted nor recommended, as orthodontic correction can be a long and uncomfortable process. If a malocclusion is diagnosed in the deciduous dentition, interceptive orthodontics can be attempted. This involves extraction of the deciduous dentition that is causing the trauma and/or resulting in an adverse dental interlock (not allowing the jaws to grow to their full genetic potential).

Malocclusions resulting in oral trauma or prevention of normal mandibular growth should be treated early and aggressively. This may be achieved by extraction of the offending tooth or teeth, coronal reduction and vital pulp therapy, or orthodontic appliances. All clients should receive genetic counselling. Orthodontic treatment should never be performed in patients destined for breeding or showing.

Prognosis

Successful treatment is dependent on early diagnosis and appropriate intervention. Clients should receive counselling on the genetic basis of most malocclusions. Neutering is generally recommended.

PERSISTENT PRIMARY (DECIDUOUS) TEETH

Definition/Overview

A deciduous tooth is considered persistent if it remains present in the oral cavity after the corresponding permanent tooth has erupted to any degree.

Etiology

The most common cause of this condition is an aberrant eruption path of the permanent tooth. Lack of a permanent tooth as well as nutritional or hormonal imbalances may also result in persistent deciduous teeth.

Pathophysiology

As the permanent tooth erupts along its natural path, the pressure it places on the apex of the root of the deciduous tooth results in resorption of the deciduous tooth root. As the permanent tooth continues its coronal advancement, the root continues to resorb and eventually exfoliates, and the permanent tooth assumes its place. When the permanent tooth fails to follow its natural path, the deciduous tooth root does not receive the proper pressure to result in adequate resorption for exfoliation.

Clinical Presentation

While they typically occur in toy and small breed dogs, persistent deciduous teeth may occur in any breed, as well as in cats. The condition is often bilateral and most commonly affects the canine teeth, followed by the incisors and premolars (Figure 5.15).

Differential Diagnosis

Supernumerary teeth, lack of associated permanent tooth, crown malformation.



FIGURE 5.15 A persistent deciduous maxillary incisor tooth (603) in an adult dog. Note the associated periodontal disease demonstrated by the placement of the probe.

Diagnosis

Conscious oral examination is usually sufficient for diagnosis of persistent canines and incisors; however, since the deciduous maxillary 4th premolars are palatal to the permanent ones, anesthesia may be required. Sedated or anesthetized examination and intraoral radiographs may be necessary to accurately distinguish between supernumerary teeth, crown malformation, and lack of permanent dentition (Figure 5.16).

Management

Early detection and extraction of offending teeth is critical. Two teeth of the same type should never occupy the same place at the same time, as periodontal and orthodontic damage can occur very quickly. The authors recommend enlisting clients in monitoring for the appearance of this condition, instructing them in home care from the time of the first puppy (or kitten) visit, and evaluating the oral cavity thoroughly at each vaccine booster appointment. The deciduous tooth should be extracted as soon as the permanent begins to erupt, unless the deciduous tooth is significantly mobile. Intraoral radiographs should be exposed prior to and following extraction, as these teeth can be quite difficult to remove because of their long roots and thin, fragile walls. In addition, partial and complete root resorption may further complicate extraction (Figure 5.16). Patience and great care must be taken to avoid damaging the unerupted permanent tooth. Root remnants should not be left behind if at all possible, as they may become infected and/or act as a foreign body and result in significant inflammation and discomfort (Figure 5.17).



FIGURE 5.16 Persistent deciduous maxillary canine tooth (604). Note the thin, fragile walls.



FIGURE 5.17 Dental radiograph of a persistent deciduous tooth root remnant with periapical lucency in an 8-year-old dog.

Prognosis

Prognosis is good if detected and treated very early and carefully. Permanent teeth damaged during extraction of deciduous teeth or retained roots may exhibit evidence of enamel defects. Orthodontic consequences may occur within 2 weeks of the first sign of eruption of secondary dentition, and irreversible periodontal disease may begin even earlier.

MISSING TEETH

Definition/Overview

Hypodontia is the congenital absence of one to five permanent teeth. Oligodontia is the congenital absence of six or more permanent teeth. Anodontia is the congenital lack of all permanent teeth.

Etiology

May be congenital or developmental.

Pathophysiology

Permanent teeth are formed from buds of the deciduous teeth with the exception of the molars and first

premolars, which have no corresponding deciduous. A truly missing deciduous tooth will result in lack of a permanent tooth. Hypodontia of deciduous dentition is extremely rare. More often, a deciduous tooth is prematurely lost to trauma.

Genetic conditions resulting in defects of tooth development are the most common cause of missing teeth. Developmental disturbances can also have a profound effect on tooth development. In addition, trauma, medications, and gestational problems can also result in significant tooth anomalies and defects.

Clinical Presentation

Most often an incidental finding, most patients are not clinically presented solely for missing teeth. However, they show signs of pain or discomfort, swelling, or mandibular fracture.

Differential Diagnosis

Previous tooth extraction, avulsion, or fracture; retained tooth root, impacted/embedded/unerupted tooth.

Diagnosis

Unless the practitioner has previous information from prior examination or surgery (including postoperative radiographs) that the tooth was extracted or otherwise not present, diagnosis must be confirmed with intraoral dental radiography. Missing teeth are generally diagnosed on conscious examination; however, sedation or anesthesia is often required to diagnose missing molars (Figures 5.18 and 5.19).

Management

All "missing" teeth should be radiographed to rule out impacted teeth or retained roots. These should be extracted once diagnosed unless the patient is geriatric, the tooth has undergone significant replacement resorption, and/or the extraction would be challenging, in which case referral to a veterinary dentist is recommended. A wait-and-see approach in a young patient is generally considered inappropriate. Congenitally missing teeth do not require intervention beyond intraoral radiography for diagnosis. Genetic counselling may be warranted.



FIGURE 5.18 Missing mandibular premolars in a 6-year-old male neutered Catahoula Leopard Dog.

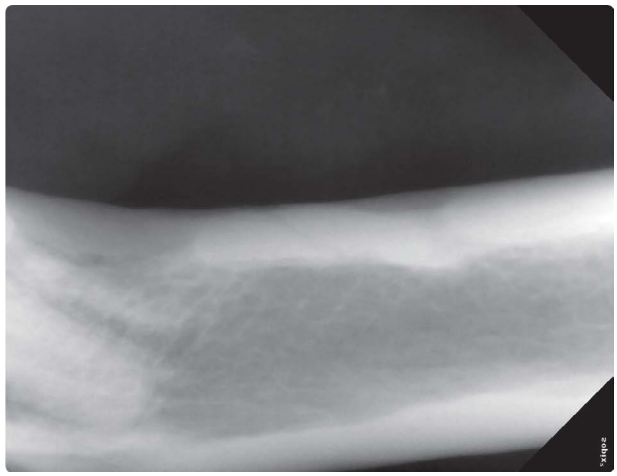


FIGURE 5.19 Congenital oligodontia was confirmed with intraoral radiography.

Prognosis

Prognosis is good if appropriate surgical intervention is taken when necessary. Impacted teeth that are not removed may develop dentigerous cysts, which can have significant consequences, such as tooth displacement, which may lead to malocclusion, tooth and/or bone resorption, or a pathologic fracture (see Case Examples: Cases 5.1 and 5.2 at the end of this chapter). Rarely, dentigerous cyst lining has been reported to undergo malignant transformation. Retained tooth roots can become infected and cause significant pain as well as local and systemic infection.

FRACTURED TEETH

Definition/Overview

Fractured teeth are classified by location of the fracture (crown, root, or both) and whether or not the pulp is exposed. Tooth fractures that result in pulp exposure are referred to as complicated. Those that do not result in pulp exposure are termed uncomplicated.

Etiology

Tooth fractures occur as a result of excessive force applied to a tooth or stresses that act on a tooth in a nonphysiological direction. They commonly occur secondarily to biting or chewing on rocks, bones, hard chew toys, and even hard rawhides. They may also be the result of impact trauma (e.g., automobile accidents, running into walls, horse kicks, falls) (Figures 5.20 and 5.21).

Pathophysiology

Enamel is the extremely hard, smooth, impervious substance covering the crowns of normal teeth. Underlying the enamel is dentin, a softer, rougher substance made





FIGURE 5.20 and **FIGURE 5.21** Complicated crown fractures of the right maxillary 4th premolar (108) and mandibular canine (404). Note the darkened, necrotic pulp and the explorer within the pulp cavity of 108 (**Figure 5.20**) and the fresh, hemorrhagic pulp of 404 (**Figure 5.21**).

up of millions of microscopic dentinal tubules that lead directly to the dental pulp.

When a crown fractures and the pulp is directly exposed, it is exceedingly painful. In addition, an open path to the blood vessels and nerves of the tooth is created, leading quickly to pulpitis, infection, and pulp necrosis. Following pulp necrosis, bacterial invasion of the periapical area occurs, which may create systemic spread of the infection.

Uncomplicated crown fractures result in direct dentinal exposure, which is considered indirect pulp exposure, as the dentinal tubules contain extensions of the root canal system called odontoblasts. These fractures also create significant pain for the patient. Furthermore, there is an opportunity for eventual infection of the pulp through the dentinal tubules. In fact, a recent study found that 24.3% of uncomplicated crown fractures in maxillary 4th premolars in dogs were endodontically infected, necessitating root canal therapy or extraction. How long that process takes is unknown and is likely affected by the amount of damage inflicted on the pulp and other tissues during the initial insult. Typically, the tooth will eventually respond to this exposure and seal off the tubules via tertiary dentin, but this process takes months and may not be effective. Finally, all fractures result in a roughened tooth surface increasing plaque adhesion and hastening the onset of periodontal disease.

Clinical Presentation

If the inciting cause is significant traumatic impact (i.e., hit by car/fall), patients may be presented with other injuries (e.g., facial or jaw fractures, head trauma, pulmonary contusions, or abdominal bleeding). These patients must be stabilized and treated appropriately prior to complete oral examination, assessment, and treatment. Owners may notice swelling or drainage in the area of the affected tooth, most commonly in the maxilla just ventral to the eye, but it may also occur in the ventral mandible.

The majority of the time tooth fractures are incidental findings, as pets very rarely show outward signs of oral pain. However, it is known that these conditions are very painful. Animals may present with some degree of pain, halitosis, reluctance to chew, or changes in eating behaviors (bear in mind that cats and dogs generally do not stop eating because of dental disease, except in very limited cases such as caudal stomatitis).

Differential Diagnosis

Abrasive wear, attrition (tooth on tooth wear), developmental malformation, oral tumor.

Diagnosis

Fractured teeth can typically be diagnosed on conscious examination or incidentally during a professional dental cleaning. Freshly fractured teeth are identified by an abnormally shaped area of the tooth and a roughened surface (dentin) compared with the surrounding tooth (enamel), if uncomplicated, and by a central area of pink or red (pulp) if complicated (**Figure 5.21**).

Older fractures may be more difficult to identify if they have been covered with calculus. Pulp necrosis may be evident as a dark brown, gray, or black central area of the tooth in an older, complicated crown fracture (**Figure 5.20**). Root fractures may not be apparent until sedated examination and radiographs are possible.

Management

All fractured teeth should be radiographed to evaluate for evidence of endodontic disease. Fractured deciduous teeth should be extracted urgently to prevent damage to the underlying permanent tooth bud. Uncomplicated crown fractures should be managed with bonded sealants if there is no radiographic evidence of endodontic disease and the pulp chamber cannot be accessed with a fine dental explorer. This will relieve the pain, block off the pathway of infection, and smooth the tooth. Crown/root fractures that are uncomplicated may be treated with a bonded sealant if the gingiva is



FIGURE 5.22 This is a slab-type fracture of the left maxillary 4th premolar (208). This particular tooth has a complicated crown-root fracture, but slab fractures are very common in dogs and may be complicated or uncomplicated.

first repositioned apically so that the sealant does not extend below the gingival margin (Figure 5.22). Some root fractures may be managed with benign neglect if no portion of the fracture extends into the oral cavity, the tooth is stable, and there is no evidence of endodontic disease. Complicated crown fractures and uncomplicated crown fractures with evidence of endodontic disease on intraoral radiographs must be treated either with root canal therapy or by complete extraction. Root fractures and teeth treated with bonded sealants or root canal therapy must be rechecked radiographically at 9–12 months and annually thereafter. Toys and chews should be evaluated for hardness, in order to avoid risk of tooth fracture. Proper items should be easily indented with a fingernail. Owners must be warned about the causes of tooth fractures and changes implemented at home if fractures are secondary to chew toys, treats, or housing. The inciting cause should be removed and replaced with softer, less dangerous options if at all possible. Veterinary Oral Health Counsel (VOHC) approved products may be recommended when evaluating proper chews and toys. Owners should also be counseled that bonded sealants are only effective for as long as they remain on the tooth; in other words, until the tooth breaks again. Referral to a veterinary dentist for crown placement should be considered, especially for working dogs and those extreme chewers that are at high risk for recurrent tooth fractures.

Prognosis

Early, appropriate treatment after complete examination, probing, and intraoral radiography provides the best outcome. Referral to a veterinary dental specialist for endodontic treatment, crown therapy, or to manage complicated or multiple tooth fractures when necessary is recommended. Fractured teeth are painful to the patient, although they will not complain. Recovery from surgical extraction is approximately 2 weeks; recovery from endodontic treatment is nearly immediate. In either case, prognosis is very good if the pet receives timely, appropriate treatment.

TEMPOROMANDIBULAR JOINT LUXATION

Definition/Overview

Temporomandibular joint (TMJ) luxation is usually a rostrodorsal displacement of the condylar process of the mandible from the articular surface of the mandibular fossa of the temporal bone. The TMJ may sometimes separate caudally, and this displacement is usually accompanied by a fracture of the retroarticular process.

Etiology/Pathophysiology

TMJ luxation is uncommon in cats and rare in dogs. It is usually traumatic in nature. It is, therefore, also often accompanied by other oromaxillofacial injuries. It may also be a result of TMJ dysplasia or disease.

Clinical Presentation

Patients often present with an open or dropped jaw appearance, an inability to close (or sometimes to open) the mouth, and lateral deviation of the lower jaw towards the side opposite the luxation. Joint pain, dysphagia, or ankylosis may accompany chronic TMJ luxation, as well as TMJ fractures or ramus fractures.

Differential Diagnosis

Mandibular fracture, maxillary fracture, TMJ dysplasia/fracture, periodontal disease, foreign body, idiopathic trigeminal neuritis, craniomandibular osteopathy.

Diagnosis

The classical dropped jaw appearance and inability to close the mouth is suggestive, although this may also be seen with idiopathic trigeminal neuritis or bilateral caudal mandibular fracture. Properly positioned dorsoventral radiographs may show an increased TMJ space. CT is the preferred imaging modality to diagnose TMJ issues. Radiographs should be exposed to evaluate for concurrent maxillary or mandibular fractures.

Management

Under general anesthesia, a fulcrum of an appropriate size for the patient (e.g., pencil, dowel, toothbrush, or syringe) is placed between the maxillary 4th premolar and mandibular 1st molar teeth on the affected side, and the mouth is gently forced closed to lever the condylar process back into the mandibular fossa. A return to normal dental occlusion is indicative of successful reduction. The joint should then be stabilized with a loose-fitting nylon or tape muzzle or with interarcade wiring for 1–2 weeks, especially if it easily reluxates. Unstable, refractory, or chronic luxations can be treated with open reduction and suture imbrication of the joint or, more commonly, with a condylectomy procedure.

Prognosis

Acute, uncomplicated luxations that are properly reduced and managed have a good prognosis. Those associated with chronicity, recurrence, underlying disease, dysplasia, or ramus fractures carry a less favorable prognosis and frequently result in condylectomy.

MAXILLOFACIAL/JAW FRACTURES

Definition/Overview

Oromaxillofacial fractures are usually the result of traumatic injury but may also occur secondary to a pathologic process. In the case of trauma, patients may have significant injury to other body systems or other serious complications and should be stabilized prior to treatment for oromaxillofacial injury. Pathologic fractures can be difficult to treat because of issues related to delayed healing or underlying neoplastic or infectious conditions.

Etiology/Pathophysiology

There is a wide variety of types and causes of maxillofacial and mandibular fractures. In the cat, symphyseal separation is the most common oral fracture, and mandibular ramus fractures are more common than those of the mandibular body. Fractures to the body of the mandible are most commonly seen in dogs and may be termed stable (Figure 5.23a) or unstable (Figure 5.23b) depending on the angle of the fracture line, with stable fractures running in a caudodorsal direction. The large muscles of the jaw insert at the caudal aspect of the mandible and compress the fragments of favorable fractures. In the dog, mandibular ramus fractures are less common than either symphyseal separation or mandibular body fractures, and repair can be very difficult because of the large amount of overlying musculature. TMJ fractures are uncommon. Maxillary fractures are often minimally displaced because of the inherent stability of the maxilla. Midline palatal features are commonly a result of high-rise syndrome in cats. Like mandibular symphyseal separation, these are not true fractures but a separation of the interincisive suture or the median palatine sutures. Pathologic fractures are not uncommonly seen and are usually the result of chronic, severe, untreated periodontal disease or, rarely, a neoplastic process.

Clinical Presentation

Patients may present with an obvious malocclusion or fracture, particularly of the mandible, or with symphyseal separation. Swelling, pain, soft tissue trauma, and ptyalism are common. Inability to open or close the mouth may be noted. Maxillary fractures in particular may present more subtly, with minimal displacement. In some patients, the maxillofacial or mandibular fracture is not noticed for a day or several days after the initial traumatic incident when the owner notes that the animal is reluctant or unable to eat, drops food from the mouth, or is malodorous. Patients with pathologic jaw fractures tend to be non-painful and often lack an obvious history of trauma. This is because the weakened bone took minimal force to fracture. Further, these fractures are typically seen in the areas of the mandibular 1st molars or canines of small and toy breed dogs. This is because their teeth are proportionally larger than those of large breed dogs and comprise a significant amount of the mandible.

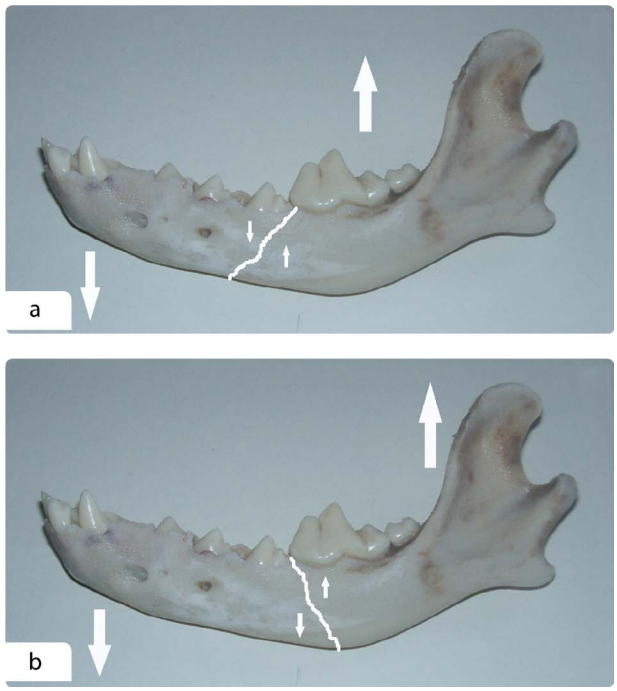


FIGURE 5.23 A left mandible demonstrating a stable (a) and an unstable (b) fracture line. The large white arrows indicate the directional pull of the masticatory muscles. Small white arrows illustrate the subsequent forces placed on the fracture line. In (a), the muscular forces keep the fracture in place. In (b), the unstable direction of the fracture leads to distraction of the fracture line.

Differential Diagnosis

Trauma, severe periodontal disease, neoplasia, TMJ luxation, osteomyelitis, hypoparathyroidism (rare).

Diagnosis

Careful examination under sedation or general anesthesia (if the patient is stable) combined with skull or, ideally, intraoral dental radiography may be utilized to determine the exact nature and extent of the injury. Depending on presentation, thoracic and abdominal radiographs, abdominal ultrasound, or CT may be indicated as well as complete blood count (CBC)/chemistry panel/urinalysis, T4, and parathyroid hormone level. Histopathology and bacterial culture and sensitivity may also be warranted in unusual cases.

Pathologic jaw fractures require intraoral dental radiographs to properly diagnose and treat. The subtle loss of bone is often not seen on skull radiographs. The classic appearance of a pathologic fracture is one located at the mandibular first molar or canine in a small breed dog with associated periodontal disease.

Management

Symphyseal separation can generally be treated with simple circumferential wire stabilization. Generally, mandibular body fractures are best repaired with intraoral splinting and either interdental or interosseous wiring techniques to recreate proper occlusion of the teeth. However, unstable or comminuted fractures may require more rigid fixation. Plates and external fixation techniques are occasionally indicated, but great care must be taken to avoid damaging tooth roots and neurovascular structures. Fractures of the mandibular ramus, condylar, coronoid, and angular processes are usually managed conservatively due to the great difficulty in performing internal repair. Many of these fractures are managed by interarch bonding or with loose nylon muzzles for 2–3 weeks (if a unilateral fracture dorsal to the condylar process) or 4–5 weeks (if below the condylar process). Maxillary fractures are often minimally displaced and more stable than mandibular fractures and require no more than digital reduction and soft tissue repair. However, more significant fractures require reduction and stabilization, typically an acrylic splint.

Pathologic jaw fractures carry a guarded prognosis for healing due to the lack of remaining bone, the low oxygen tension in the area, and the difficulty in rigidly fixating the caudal mandible. It is important to realize that a pathologic fracture will not heal (no matter how good the fixation is) if the diseased tooth root is not removed from the area of the fracture line. This is because a diseased root acts as a nidus of infection, which prevents healing. Extraction of the diseased root associated with the area of fracture is necessary but, unfortunately, creates a large defect in the bone, which makes alignment more challenging and increases healing time.

Prognosis

Oromaxillofacial fractures often occur concurrently with other serious injuries, and patients must be well stabilized prior to treatment of maxillary or mandibular fractures. Malocclusion is a serious potential complication of oromaxillofacial fracture and repair. Invasive fixation methods are only rarely necessary and often result in further damage to surrounding oral structures such as teeth and neurovascular tissues. There is a concern with mandibular ramus fractures for callus formation, which results in restriction of normal jaw movement. In addition, there is often damage to teeth during the initial insult that may not be immediately apparent. Recheck examination and radiographs are always indicated for jaw fractures.

Pathologic fractures caused by severe periodontal disease or neoplastic processes carry a guarded prognosis. These can be extremely difficult if not impossible to repair and, especially in the case of neoplasia, often result in mandibulectomy or maxillectomy. The underlying cause of any pathologic fracture must be investigated and addressed prior to attempting fixation. Stabilization or fixation of fractures caused by neoplastic processes should not be attempted; mandibulectomy, maxillectomy, radiation, and/or chemotherapy may be appropriate in such situations. Consultation with a veterinary dentist, surgeon, and/or oncologist is recommended.

ORAL MASSES AND NEOPLASIA

Definition/Overview

Oral masses are quite common in dogs and cats. In fact, the oral cavity is the fourth most common location for a tumor/neoplasm in the body in both canine and feline patients. Oral masses may be either benign or malignant. Like masses elsewhere, gross examination is generally insufficient for accurate diagnosis. All oral masses, no matter how small, should be biopsied and evaluated histopathologically. While most oral masses in dogs are benign, aggressive neoplasms are fairly common in the oral cavity.

Etiology

Oral tumors may be odontogenic or nonodontogenic, but a true etiology is unknown in most cases. An exception is canine squamous cell carcinoma (SCC), which is sometimes associated with papillomavirus.

Clinical Presentation

Presentation is variable depending on the type of tumor. Many masses are found incidentally during routine oral examination. Others may be erosive or ulcerated and secondarily infected or inflamed, causing discomfort, dysphagia, halitosis, or ptyalism.

Differential Diagnosis

Gingival hyperplasia (enlargement), granuloma, dentigerous cyst, abscess, eosinophilic granuloma.

Diagnosis

Intraoral dental radiographs and histopathology are required for accurate diagnosis of any oral mass. Palpable lymph nodes should be aspirated or excised in cases of malignant neoplasia. If cytopathology or histopathology is consistent with malignancy, standard clinical staging should be performed, including 3-view thoracic radiography, CBC, chemistry panel, urinalysis, +/– abdominal ultrasound.

Management

In general, surgical excision is the treatment of choice, with required margins and follow-up chemotherapy or radiation treatment dependent on histopathologic diagnosis.

Prognosis

Prognosis for benign tumors is excellent with adequate surgical resection. Malignant oral tumors may have a good prognosis if diagnosed and definitively treated very early. Advanced malignancies carry a poor to grave prognosis even with radical surgical excision and chemo or radiation therapy. (Note: Individual tumor types are discussed later.)

PERIPHERAL ODONTOGENIC FIBROMA/ FOCAL FIBROUS HYPERPLASIA (PREVIOUSLY TERMED EPULIS)

Epulis is not a diagnosis but a clinical description that includes neoplasia, fibromas, and odontogenic tumors. It refers to *any* swelling of the gingiva. Peripheral odontogenic fibroma is a benign neoplasm, previously classified as fibromatous or ossifying epulis. These are slow growing and usually found around maxillary premolars. They exhibit no evidence of bony involvement on radiographs but may show mineralized areas. The majority of gingival growths are histopathologically focal fibrous hyperplasia, frequently seen in Boxers. Marginal surgical excision of the tumor is generally curative.

CANINE ACANTHOMATOUS AMELOBLASTOMA

Previously known as acanthomatous epulis, these masses are now termed canine acanthomatous ameloblastoma (Figure 5.24). They most often occur around the mandibular incisors in large breed dogs (though may occur anywhere in either jaw) and are fleshy and proliferative masses. These tumors are locally aggressive but do not metastasize. Radiographs typically reveal local bone infiltration and tooth displacement. Local recurrence with marginal excision is common, so a minimum 0.5–1 cm of normal tissue surgical excision is recommended. Another treatment option is radiation therapy, which has a 90% control rate.

PAPILLOMATOSIS

These are generally pedunculated or cauliflower-like in appearance and white, gray, or flesh colored. Further, their appearance is benign mucosal thickening with finger-like projections. They may be solitary or multiple. They are of viral origin (papillomavirus) with a 2- to 6-month incubation and are spread usually through direct but sometimes indirect contact. Generally self-limiting, they resolve in weeks to months, and the patient is generally immune in the future. They are only cause for concern if they are large enough to interfere with mastication, are infected, or inflamed. They can mimic more aggressive tumors, and there are reports of transformation to SCC. No treatment is usually recommended; however, atypical appearance, failure to regress in the expected time period, and infection all are indications for excisional biopsy and histopathology. Removal may also be indicated if they are large enough to interfere with mastication. Excision may be accomplished with standard sharp excision, cryosurgery, electrocautery, or laser surgery. Vaccination, traumatic crushing, and chemotherapy have also been utilized but are generally no longer recommended.



FIGURE 5.24 Canine acanthomatous ameloblastoma associated with the maxillary left 3rd incisor (203) and affecting the 2nd incisor (202) and canine tooth (204).

ORAL MALIGNANT MELANOMA

Oral malignant melanoma (OMM) (Figure 5.25) is the most common malignant oral cavity tumor in dogs. They may be pigmented or amelanotic and are highly aggressive, with early metastasis to lymph nodes (less frequently to lungs and other organs). Palpable lymph nodes should be aspirated or excised at the time of diagnosis. Standard clinical staging after confirmatory cytopathologic or histopathologic diagnosis (3-view thoracic radiographs, CBC, chemistry panel, urinalysis, +/– abdominal ultrasound) should be performed prior to wide surgical excision (2–3 cm normal tissue). Follow-up chemotherapy, immunotherapy, or radiation therapy may also be indicated, as distant dissemination of disease is common, as is local recurrence. If complete resection is not possible, radiation therapy should be considered as a primary treatment. Prognosis is generally poor, but a fair to good response may be achieved with early diagnosis and aggressive treatment and follow-up.



FIGURE 5.25 Malignant melanoma affecting the left maxillary 4th premolar and molar teeth of a dog. Note the irregular, pigmented appearance. These are highly aggressive tumors that may or may not be pigmented.

FIBROSARCOMA

This is a malignant mesenchymal tumor, most often seen in young (4- to 5-year-old) large breed dogs and older (~8-year-old) small breed dogs. Fibrosarcomas are locally invasive with a high postsurgical recurrence rate. Prognosis is variable depending on location, size, grade, and stage at time of diagnosis. The maxilla is the most common site. This tumor can present as an innocuous, lobulated, sessile mass or, alternatively, as a rapidly growing, hemorrhagic, ulcerated lesion. They are often noted at dental margins and the palate but may also originate from nasal cartilages and the lateral surface of the maxilla or palate. Well-differentiated masses are best treated with wide surgical excision (2–3 cm margin). Poorly differentiated tumors require radical excision and postoperative radiation treatment.

A subcategory of fibrosarcoma, termed histologically low grade, biologically high grade, is most common in large breed dogs, particularly Golden Retrievers. These tumors are characterized by rapid growth, bony invasion, and high metastatic potential. Treatment for these tumors has not yet been optimized, and local recurrence is very common.

SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma (SCC; Figure 5.26) is the most common oral neoplasm in cats and the second most common in dogs. These are large, locally aggressive tumors that exhibit lymph node and lung metastasis late in the course of disease. Feline maxillary and lingual SCC carries a poor prognosis, mandibular tumors a somewhat better prognosis, and rostral mandibular locations a fair prognosis. Cure is possible with very early lesions and wide surgical excisions. Papillomavirus DNA has been associated with canine oral SCC. These are erosive, fleshy lesions, and with local bony invasion, dental displacement may occur. There may be chronic,

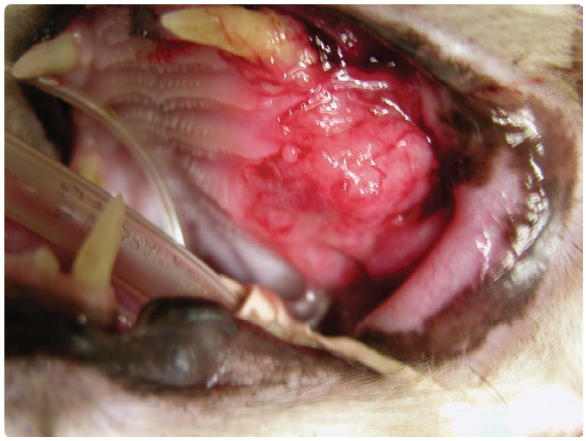


FIGURE 5.26 Squamous cell sarcoma in the left maxilla of a cat.

nonhealing ulcers of the associated skin. Wide surgical excision (2 cm) is recommended, including glossectomy for dogs with lingual tumors. Radiation treatment may be considered for local control or palliation but is fairly ineffective in cats. Chemotherapy is also an option for microscopic disease.

OSTEOSARCOMA

Osteosarcoma (OSA) may occur in either the mandible or maxilla. It is much less common in cats than in dogs. These tumors are locally aggressive but have less metastatic potential than appendicular OSA. Mandibular OSA carries a more favorable prognosis than maxillary, with a reported median survival time of 7 months, whereas the median survival of maxillary OSA is 5 months. It may be identified as a fleshy, expansile mass that may or may not be ulcerative in the early stages. The significant tissue destruction and locally aggressive bony swelling frequently lead to subsequent facial swelling and may be associated with pain and discomfort on opening or closing the mouth. Wide or radical surgical excision is recommended depending on stage, and radiation treatment should be considered for microscopic disease.

TOOTH RESORPTION

Definition/Overview

Previously called neck lesions, cervical line lesions, feline odontoclastic resorptive lesions, and several other names, these lesions are currently referred to as tooth resorption (TR). They represent noncarious odontoclastic destruction of teeth. There are two types of feline TR: Type 1 and type 2. Type 1 resorptions do not result in the replacement of roots by bone (Figure 5.27), while in type 2 resorptions, the lost root structure is replaced by bone (Figure 5.28). An individual tooth may exhibit both type 1 and type 2 resorption and is then classified as type 3. TR typically begins externally and may



FIGURE 5.27 Radiograph of the right mandible of a cat, demonstrating type 1 tooth resorption in all three teeth. Note the varying degrees of lucency, most obvious in the molar tooth (409). Complete extraction of crowns and all roots is the recommended treatment.



FIGURE 5.28 Type 2 tooth resorption in the right mandibular 3rd premolar of a cat. Note the lack of a visible periodontal ligament and how the roots have an appearance similar to that of the surrounding bone.

occur in the crowns, roots, or both (see Table 5.4 for American Veterinary Dental College [AVDC] classification). TR occurs in dogs and humans but is most commonly seen in cats and may represent different disease processes or etiologies in the different species. (Note: Internal resorption can also occur but is rare and more common in dogs than cats.)

TABLE 5.4 American Veterinary Dental College tooth resorption classification

Tooth resorptions are classified by radiographic type as well as stage of resorption:

- **Type 1.** Focal or multifocal radiolucency is present in the tooth with otherwise normal radiopacity and normal periodontal ligament space.
- **Type 2.** Radiographic narrowing or disappearance of the periodontal ligament space in at least some areas and decreased radiopacity of part of the tooth.
- **Type 3.** Radiographic features of both type 1 and type 2 are present in the same tooth. A tooth with this appearance has areas of normal and narrow or lost periodontal ligament space, and there is focal or multifocal radiolucency in the tooth and decreased radiopacity in other areas of the tooth.

- **Stage 1.** Mild dental hard tissue loss (cementum or cementum and enamel).
- **Stage 2.** Moderate dental hard tissue loss (cementum or cementum and enamel with loss of dentin that does not extend to the pulp cavity).
- **Stage 3.** Deep dental hard tissue loss (cementum or cementum and enamel with loss of dentin that extends to the pulp cavity); most of the tooth retains its integrity.
- **Stage 4.** Extensive dental hard tissue loss (cementum or cementum and enamel with loss of dentin that extends to the pulp cavity); most of the tooth has lost its integrity:
  - **Stage 4a.** Crown and root are equally affected.
  - **Stage 4b.** Crown is more severely affected than the root.
  - **Stage 4c.** Root is more severely affected than the crown.
- **Stage 5.** Remnants of dental hard tissue are visible only as irregular radiopacities and gingival covering is complete.

Etiology

Although there are several theories, the cause of tooth resorption remains unknown. Different theories have suggested either excess levels of dietary vitamin D or that feline teeth were not developed to masticate hard, dry kibble diets, leading to abfraction injuries. Type 1 TRs in cats are more commonly associated with oral inflammation (gingivitis, periodontitis, or stomatitis) than are type 2, but no clear cause and effect has been shown. Type 2 TRs are not as commonly associated with significant oral inflammation, but the lesion itself may create mild gingivitis. Neither form of TR has been shown to be related to the retroviral status of cats. In humans, abfraction (lateral forces that result in microflexure of the crown of the tooth) is a proposed cause of TR, and although not proven, this could also be a cause of TR in cats and other species.

Pathophysiology

As stated previously, type 1 TRs are typically associated with oral inflammation, especially in younger cats. There is an increasing likelihood for developing TRs (especially type 2) with age. Odontoclastic destruction of cementum usually begins in the apical third of the root

and generally extends into dentin. The dentinal destruction may eventually extend under the enamel and undermine it, at which point the enamel flakes off exposing the underlying dentin. This creates a significantly painful area of exposed tooth structure. Clinically, they are generally first noticed in the area of the cementoenamel junction. The tooth structure is damaged and eventually weakened to a point at which the crown of the tooth fractures, leaving roots behind. In type 1 lesions, these roots have intact endodontic systems and can create pain and/or infection, whereas in type 2 lesions, the roots have partially or completely been replaced by bone. In cases of complete replacement by bone, they are known as "ghost roots." It is possible that type 1 TRs are an early form of type 2 and that some type 1 lesions may progress to type 2 resorptions. However, the exact cause of TR is unknown at this time. In cats, it has also been proposed that type 2 lesions commonly seen in their canine teeth may not be related to inflammation but rather to ankylosis and age-related bone replacement.

Clinical Presentation

Type 1 lesions are often, but not always, accompanied by oral inflammation (gingivitis, stomatitis, and/or periodontal disease). In both type 1 and type 2 resorptions, there is often an associated area of gingival enlargement, which may or may not be inflamed, that covers or fills the lacuna that results from the resorption (Figures 5.29 and 5.30). Cats typically show no clinical signs even with advanced lesions, but they rarely may exhibit pain, dysphagia, decreased appetite, halitosis, depression, or other signs. (Note: One author [ER] has treated a cat whose only clinical sign was inappropriate urination that resolved with definitive treatment of the TR.) The mandibular 3rd premolars are often the first teeth affected, but TRs can occur in any tooth. Cats with one/any TR are at increased risk for developing future lesions. Dogs may present for pain or suspected tooth fracture or resorptions, but typically, TRs are incidental findings during routine dental prophylaxis or intraoral radiographs.



FIGURE 5.29 Tooth resorption of the left maxillary 3rd premolar (207) in a cat. Although the mandibular 3rd premolar is the most common location for tooth resorptions, they may occur in any tooth.



FIGURE 5.30 Tooth resorption in the left mandibular canine tooth (304) of a cat.

Differential Diagnosis

Gingivitis or periodontitis (without resorption), bone loss/furcation exposure in multi-rooted teeth, gingival hyperplasia or mass, fractured tooth, caries.

Diagnosis

Visual examination and subgingival exploration are often sufficient for identifying a clinical TR. However, intraoral radiography is essential for proper classification of the type and stage of the lesion and appropriate therapeutic planning, as well as finding incipient subgingival lesions.

Management

Extraction is the treatment of choice for TR. Crown amputation is only appropriate for type 2 lesions under the following conditions:

- No evidence of caudal stomatitis.
- No clinical or radiographic evidence of periodontal disease in the area of the root to be left.
- No identifiable tooth root structure, periodontal ligament, or root canal.
- There must be no evidence of endodontic disease.

If any of these criteria are not met, complete extraction is required. This may be very difficult due to root ankylosis. Radiographs must be obtained prior to and following extraction or crown amputation. Resorption that is completely subgingival and does not extend into the oral cavity may be monitored if there is no evidence of periodontal or endodontic disease, no stomatitis, and the patient is not showing clinical signs of pain, dysphagia, or inappetence. While there are no studies to this effect, crown amputation may be recommended for extremely advanced cases of TR in dogs. However, if at all possible, teeth and roots should be removed completely and complete extraction verified radiographically.

Prognosis

With appropriate diagnosis and treatment, prognosis is good. However, animals with TR lesions are at greater risk of developing lesions in other teeth. Some cats require full or near-full mouth extractions to alleviate their discomfort.

FELINE CAUDAL STOMATITIS

Definition/Overview

Stomatitis refers to inflammation and proliferation of the oral mucosa, while gingivitis more specifically refers to inflammation and proliferation of the gingival tissues. Gingivostomatitis is a clinical descriptive term, while lymphoplasmacytic stomatitis is the histopathologic diagnosis most commonly associated with this condition. It may range from mild to severe and generally increases with chronicity. The current terminology for this condition is caudal stomatitis, which is when the inflammation extends to the caudal oral tissues (caudal mucositis).

Etiology

The cause of caudal stomatitis is unknown and is possibly multifactorial. Suggested inciting causes or cofactors include an exaggerated inflammatory response to plaque, viral infection (particularly calicivirus), *Bartonella henselae* infection, and altered immune status.

Pathophysiology

Feline calicivirus (FCV) has been isolated from cats with caudal stomatitis, and cats exhibiting signs of the disease are more likely to be shedding FCV and feline herpesvirus-1 (FHV-1) from the oral mucosa. However, there is no evidence that FCV causes caudal stomatitis. Additional research is being done to more fully understand the role of FCV in chronic caudal stomatitis. Neither are feline leukemia virus (FIV) and feline immunodeficiency virus (FeLV) implicated directly in cases of caudal stomatitis, but infection with either virus may contribute to its development in individual cats. While cats that are positive for FIV and *B. henselae* exhibit increased levels of mandibular lymphadenopathy and gingivitis compared with non-infected cats, *B. henselae* is not currently believed to be a significant contributing factor in caudal stomatitis. An exaggerated response to bacterial plaque has been speculated to play a role in this disease, as cats with chronic caudal stomatitis exhibit significantly lower salivary IgA and higher serum IgA, IgG, and IgM levels than healthy cats. It has been proposed that the decreased salivary IgA in affected cats may have a contributing role in the development of chronic caudal stomatitis.

Clinical Presentation

It is not uncommon for affected cats to present for anorexia (complete or partial), dysphagia, pain, and ptyalism. They may also exhibit halitosis, pawing at the mouth, weight loss, vocalization, and an unkempt appearance due to lack of grooming (Figure 5.31). Paws and perioral areas may be stained with saliva, blood, and/or purulent material. Affected cats may have undergone behavior changes, becoming either more aggressive or more withdrawn than usual. Chronic caudal stomatitis is the oral disease most likely to result in anorexia. These patients are often extremely painful, and oral examination may prove very difficult, as opening the mouth can cause great discomfort. If oral examination is possible, the practitioner may note varying amounts of tissue inflammation, ulceration, and proliferation. The key clinical sign that differentiates this condition from periodontal disease is the caudal location of the stomatitis (Figure 5.32).

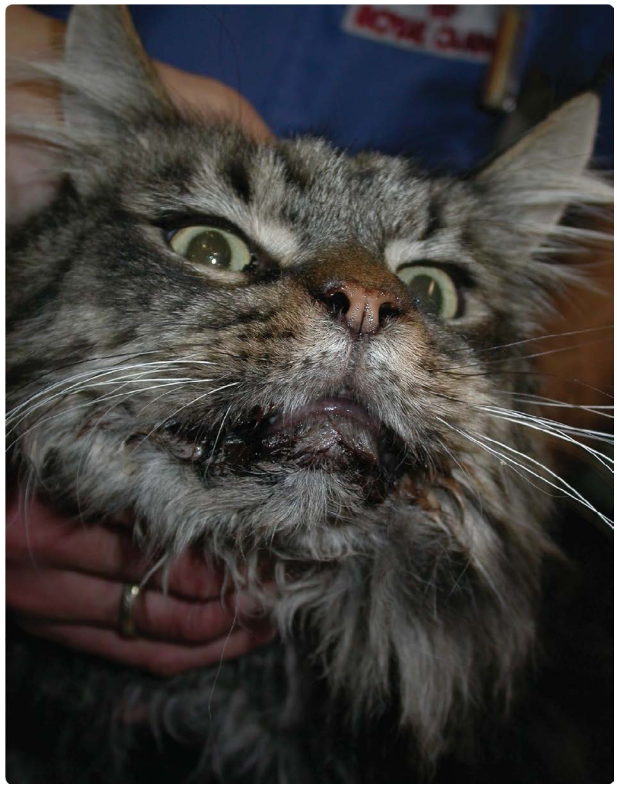


FIGURE 5.31 A cat with caudal stomatitis. Note the excessive ptyalism and unkempt coat.

Differential Diagnosis

Neoplasia (especially SCC), periodontal disease, eosinophilic granuloma complex (EGC), autoimmune disease, foreign body mucosal entrapment.

Diagnosis

As described previously, caudal stomatitis represents a clinical syndrome rather than a specific etiology or diagnosis. Therefore, diagnosis of caudal stomatitis is primarily a clinical one based on visual identification and testing for underlying contributing factors. A thorough visual examination under anesthesia, as well as dental radiographs to identify any retained root tips, periodontal disease, or any bony changes consistent with neoplasia,

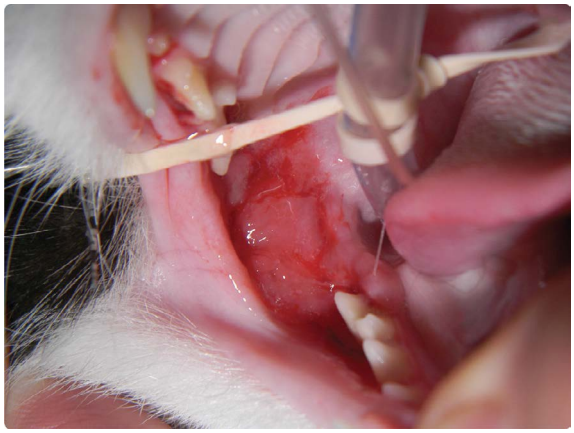


FIGURE 5.32 Caudal stomatitis in a cat. The severe erythema and inflammation in this area is pathognomonic for this condition.

is crucial. In addition, CBC and blood chemistry screening, including retroviral testing for FeLV and FIV status, are all indicated. Hyperglobulinemia may be present as a result of chronic antigenic stimulation. In addition, biopsies for histopathology should be collected if there is asymmetry in inflammation or ulceration, a nonclassical appearance to the inflammation, or if radiographs are suspicious for neoplasia.

Management

The goal of treatment is complete resolution of the oral inflammation. It has now been fairly well established that prolonged medical treatment with extensive or chronic use of steroids or nonsteroidal anti-inflammatory drugs (NSAIDs) results in poorer long-term responses than when early, aggressive surgical treatment is performed. Many, if not most, cats will respond best if all teeth and tooth remnants caudal to the canines are removed early in the course of the disease. Extraction of the canine and incisor teeth should also be considered, especially if the inflammation extends to the gingiva covering them. Aggressive management of periodontal disease is vital to treatment success. Some veterinary dentists are advocating CO_2 laser ablation of proliferative tissues following caudal mouth extractions; however, there is minimal research to support this procedure at this time. Patients may require some medical therapy with steroids or NSAIDs during the course of treatment, but these drugs are not a replacement for caudal to full-mouth extractions. Esterified fatty acid complex supplements have also shown some promise.

Prognosis

Extraction of all teeth and tooth remnants caudal to the canines (or full-mouth extractions if canine and incisor teeth are clinically abnormal) results in improvement in approximately 80% of affected cats. Of these, about 20% still show some signs of inflammation but do not demonstrate evidence of pain. The remaining 20% require additional care, which may include laser or surgical ablation, interferon therapy (used often in Europe but not widely available in the United States), or medical therapy (typically cyclosporine but also possibly steroids, NSAIDs, or fatty acid supplementation [1-TDC]). Early tooth extractions are indicated. Prolonged, repeated use of steroids not only has many undesirable side effects, but it also decreases the likelihood of resolution and worsens outcomes.

EOSINOPHILIC GRANULOMA COMPLEX

Definition/Overview

Eosinophilic granuloma complex (EGC) is, as the name suggests, a group of conditions that share a common etiology and some histopathological features. Seen most frequently in cats, EGC can also occur in dogs (Cavalier King Charles Spaniels, Siberian Huskies, and Malamutes, in particular).

Etiology

The true etiology remains unknown, but it is suspected to be a hypersensitivity or immune-mediated reaction. Most likely, EGC occurs in response to flea and/or food allergy or atopy. However, it should be noted that lesions have also been found in cases where infectious and allergic diseases have been essentially ruled out. Finally, there may be a genetic predisposition to EGC.

Pathophysiology

Inflammation and necrosis are seen and thought to be the result of the inflammatory agents released by accumulations of eosinophils in the lesions.

Clinical Presentation

The most common presentation is an indolent or rodent ulcer seen as a reddish brown lesion at the philtrum or around the maxillary canine teeth (Figure 5.33).



FIGURE 5.33 Typical rodent ulcer. This lesion is highly suggestive for eosinophilic granuloma complex in a cat.

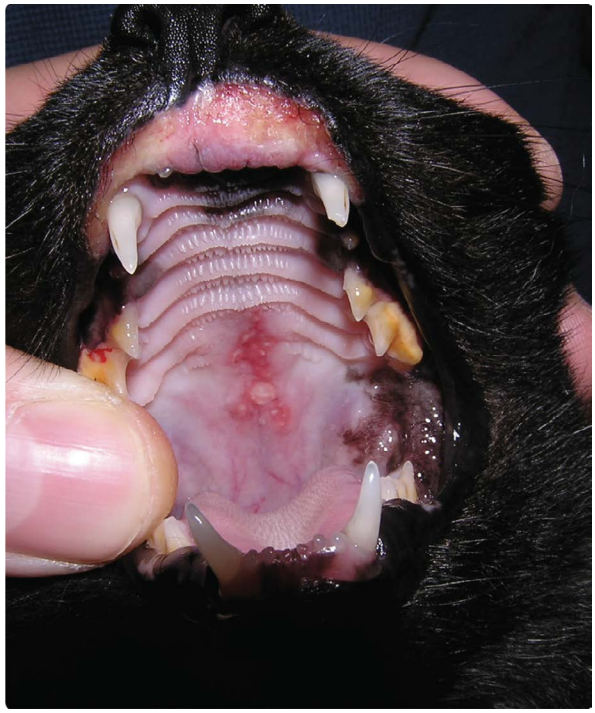


FIGURE 5.34 Palatal linear granuloma associated with eosinophilic granuloma complex. A rodent ulcer is also visible at the rostral maxillary lip. This is the same cat as in Figure 5.33.

Indolent ulcers may be unilateral or bilateral, and females appear to be overrepresented. Linear granulomas (Figure 5.34) are the second most common presentation and may be single or multiple. They are typically found on the lips, tongue, gingiva, and palate but can occur in any location in the mouth. These granulomas are yellow-pink, lobulated, raised masses and are generally nonpainful, although they may become secondarily infected and/or ulcerated. Occasionally, they can severely damage oral mucosa and even bone. There are reported cases of severe periodontal disease, oronasal fistulas, and even pathologic fractures as a result of eosinophilic granulomas. These lesions should not be taken lightly and should be on the differential list for any aggressive-appearing oral lesion. Another manifestation of EGC is the collagenolytic granuloma, a firmly swollen, rostral mandibular lip lesion most commonly seen in young female cats. Eosinophilic plaques may also be found (rarely) in the oral cavity where they appear much like a linear granuloma. These are more commonly seen as a dermatologic lesion. In fact, oral EGC very often occurs concurrently with dermatologic manifestations of the syndrome.

Differential Diagnosis

Neoplasia; gingival hyperplasia; uremic stomatitis; immune-mediated disease; trauma; periodontal disease; thermal, electric and chemical burns; foreign body mucosal entrapment.

Diagnosis

A minimum database (CBC, biochemical profile, urinalysis) should be obtained to rule out underlying disease. Histopathology should be performed to confirm the diagnosis. A thorough allergy evaluation (diet trial, serum, or intradermal testing) should be performed on histologic confirmation.

Management

Treatment is directed at the underlying cause of the disease, generally by controlling allergies. This may include strict flea control, hypoallergenic diets, and short-term (for acute control) steroids, but most often, long-term medical management is with cyclosporine or corticosteroids. Cyclosporine has proven effective for therapy of oral eosinophilic diseases, and a veterinary product is approved for use in dogs and cats for allergic disease. Weaning to the lowest effective dose at the longest interval that provides patient relief and disease control is recommended. Surgical removal has been occasionally successful, including cryosurgery and laser surgery. Finally, radiation therapy has been used in some cases.

CANINE CHRONIC ULCERATIVE STOMATITIS

Definition/Overview

Canine chronic ulcerative stomatitis (CCUS), also termed chronic ulcerative paradental stomatitis, or CUPS, is a painful, ulcerative condition seen in dogs. Like feline caudal stomatitis, this is one oral condition that will commonly cause anorexia in dogs. CCUS/CUPS is a severe form of inflammation and ulceration that extends beyond focal contact ulceration or "kissing" lesions and other forms of canine stomatitis.

Etiology

Etiology is unknown, but it is suspected to be a hypersensitivity or immune-mediated reaction to plaque or other allergen, drug administration, or other concurrent disease. Greyhound breeds appear to be overrepresented.

Pathophysiology

Various stages of ulceration and inflammation may be seen, with epithelial hyperplasia in nonulcerated areas. Plasma cells and lymphocytes may be predominant with intraepithelial neutrophils.

Clinical Presentation

Affected dogs may present for halitosis, difficulty eating, salivation/drooling, dropping food, pain, or general malaise. Awake exam is often sufficient to conclude CCUS as a likely diagnosis, but milder cases or patients with recent history of dental prophylaxis may be more difficult



FIGURE 5.35 Example of contact ulceration typical of CCUS/CUPS in a 7-year-old F/S Shih-Tzu.

to diagnose in the exam room and require anesthetized exam and even biopsy for reliable diagnosis. Contact ulcers or kissing lesions are usually easily diagnosed on awake exam and are recognizable as depigmented areas of erosion/ulceration in the buccal mucosa, in the shape of the tooth it contacts (Figure 5.35). Erosive or ulcerative lesions are also commonly seen on the lateral margins of the tongue where it contacts the lingual surfaces of the teeth and associated plaque. Gingival, palatal, and labial mucosa may also be significantly inflamed with severe redness, swelling, and/or ulcers, even if not in direct contact with tooth surfaces.

Differential Diagnosis

Eosinophilic granuloma complex; neoplasia; uremic stomatitis; immune-mediated disease; trauma; periodontal disease; thermal, electric and chemical burns; foreign body mucosal entrapment.

Diagnosis

A minimum database (CBC, biochemical profile, urinalysis) should be obtained to rule out underlying disease. Histopathology should be performed to confirm the diagnosis.

Management

Conservative treatment is directed at the strict control of plaque. This requires a significant commitment by pet owners: Daily home care, including tooth brushing; and regular, frequent anesthetized professional scaling and polishing, as often as every 3–4 months. Strategic, focused extractions may be performed in areas of ulceration and inflammation to provide relief in difficult-to-brush areas. Clients should be counselled that many dogs with CCUS eventually require complete, full-mouth tooth extractions, which is usually curative.

FELINE JUVENILE GINGIVITIS/ PERIODONTITIS

Definition/Overview

Feline juvenile gingivitis and periodontitis are separate entities from, though often mistaken for, feline caudal stomatitis. It occurs in cats less than 1 year of age and may be either destructive or hyperplastic (Figure 5.36). Hyperplastic gingivitis may precede or result in destructive periodontitis. Left untreated, it often leads to significant tooth loss. Cats may be able to outgrow the less aggressive form of the condition by approximately 2 years of age with appropriate professional treatment and home care.

Etiology

Etiology is unknown, but some pure breeds are overrepresented (Burmese, Siamese, and Maine Coon).

Pathophysiology

Various stages of ulceration and inflammation may be seen with epithelial hyperplasia in nonulcerated areas. Plasma cells and lymphocytes may be predominant with intraepithelial neutrophils.

Clinical Presentation

Kittens and juvenile cats may present for halitosis or bleeding but generally not pain. Juvenile gingivitis generally outlasts eruption gingivitis, which is associated with the eruption of permanent dentition and is usually short lived. Persistent, severe gingivitis with either hyperplasia or gingival recession requires complete anesthetized exam and dental radiographs.

Differential Diagnosis

Periodontal disease, feline caudal stomatitis, eosinophilic granuloma complex, neoplasia.

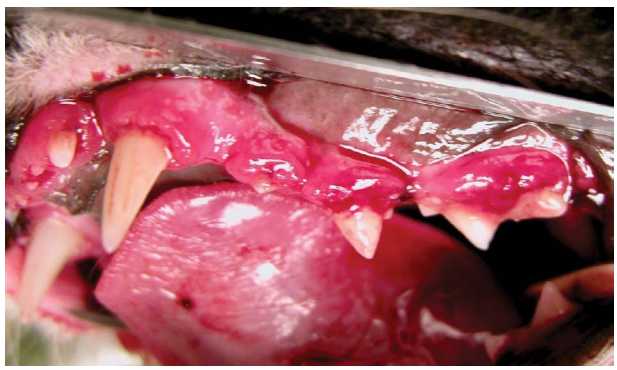


FIGURE 5.36 Feline juvenile gingivitis in a 9-month-old Domestic Shorthair cat. Note the significant erythema and swelling of the gingival tissues.

Diagnosis

A minimum database (CBC, biochemical profile, urinalysis), and viral testing (FIV, FeLV) should be obtained to rule out underlying disease. Complete anesthetized exam with full-mouth dental radiographs, complete prophylaxis, and implementation of strict home care should be performed. A positive response to treatment is consistent with diagnosis of juvenile periodontitis/gingivitis.

Management

Early (6–9 months of age) thorough exam, dental radiographs, and complete supra- and subgingival scaling are necessary to determine extent of the disease and implement treatments. Hyperplastic gingiva should be excised to reduce pseudopockets and risk of bone loss. In cases of destructive periodontitis, loose teeth, teeth with furcation defects, or significant periodontal pocketing should be extracted, or advanced periodontal surgical techniques may be attempted to maintain strategic teeth. Strict home care should be implemented, as well as frequent professional cleanings every 3–6 months regardless of quantity of visible plaque. Early, aggressive treatment and home care may allow patients to outgrow this condition and enjoy normal periodontal health in the future.

CASE EXAMPLES

Case 5.1

A 7-year-old female/spayed Maltese was referred for evaluation of missing teeth noted during routine dental prophylaxis approximately 3 months earlier.

Clinical Examination

On exam "Lea" was bright, alert, responsive and hydrated. Heart and lungs auscultated within normal limits. Preanesthetic lab work was unremarkable. Conscious oral exam revealed missing right (105) and left (205) maxillary first premolars, left mandibular canine (304) and first premolar (305), right mandibular first incisor (401), and a partially erupted right mandibular canine (404) (**Figure 5.37**). During anesthetized exam and probing, the left maxillary 2nd molar (210) and right and left 3rd molars (311, 411) were also discovered to be missing. In addition, the right maxillary 2nd incisor (102) was mobile and discolored, the left mandibular incisors (301–303) were mobile, and the remaining right mandibular incisors (402, 403) were crowded. Scant or mild tartar was noted throughout the mouth. The left mandibular first molar (309) was partially erupted, and a 4-mm periodontal pocket was probed at this tooth.

Questions

- What are the 4 differentials for missing teeth?
- What are the possible sequelae for impacted teeth?



FIGURE 5.37 Photograph of the rostral left mandible. The left mandibular canine (304) and 1st premolar (305) are missing.

Differential Diagnoses

Missing tooth: Congenitally missing permanent tooth, previously extracted tooth, fractured below the gingiva, impacted tooth. Partially erupted teeth: Congenital, developmental.

Provisional Diagnosis

Impacted tooth with possible dentigerous cyst formation, partially erupted permanent mandibular canines

Diagnostic Testing

Intraoral radiographs of the entire mouth were obtained. The left mandibular canine and 1st premolar teeth were impacted, and an associated dentigerous cyst was seen radiographically (**Figure 5.38**). Intraoral dental radiographs are a necessity for proper diagnosis of "missing" teeth.

Treatment

Full dental prophylaxis – scaling and polishing – was performed. A gingival incision was made over the area of the missing canine and premolar teeth and the tissue gently elevated from the bone with periosteal elevators to create a large envelope flap. Bone was carefully removed using a 701 cross-cut taper fissure bur on a high-speed, air-driven hand piece to expose the impacted teeth. Gentle luxation and elevation were performed to ease the teeth out of the mandible so as not to damage vital structures or fracture the jaw (**Figure 5.39**). The partially erupted right mandibular canine was treated with an apical repositioning flap to expose the enamel, lengthen the crown of the tooth, and prevent future periodontal pocketing. The left mandibular 1st molar was treated with closed root planing and a perioceutic to prevent further progression of periodontal disease. All mandibular incisors were removed as well as the right maxillary 2nd incisor, which was found to have an unstable root fracture on radiograph.

Conclusion

Impacted teeth are frequently diagnosed, particularly in small breed and brachycephalic dogs, and should

(*Continued*)



FIGURE 5.38 Radiograph of the rostral mandibles. Note the minimal amount of bone adjacent to the impacted left canine (304) compared with the right (404).



FIGURE 5.39 Intraoperative photograph showing the impacted left mandibular canine (304) and first premolar (305).

always be radiographed. Dentigerous cysts are a fairly common sequela of impacted teeth and, left untreated, can lead to serious consequences such as pathologic jaw fracture. Partially erupted teeth can lead to development of periodontal disease and should be treated with appropriate periodontal surgical techniques.

Case 5.2

A 9-year-old male neutered Poodle cross was presented for a nonhealing caudal mandibular fracture.

History

The patient had been first seen by a general practitioner for the fracture 4 months previous following a fight with a larger dog. According to referring veterinarian (RDVM) history, the pet was minimally painful on presentation and continued to eat following the injury. However, the pet was having increased difficulty chewing from the mandibular drift and was getting palatal trauma from the canine.

The patient was referred immediately to a surgeon at a local referral clinic for reduction and fixation. Surgery was performed the following day. The fracture was reduced and fixed with a bone plate and the patient discharged 48 hours later.

The patient initially did well. However, approximately 3 weeks following the initial surgery, the fixation failed, and the pet was returned to the referral center. The reduction and fixation was repeated and the patient again discharged. This time, the fixation only lasted 10 days when it broke down again. This process was repeated two more times. Following four plating procedures, the RDVM recommended that the pet be brought to a dental specialist for a second opinion.

Clinical Examination

Upon presentation, the jaw was misaligned, and there was purulent discharge from the surgery site.

Differential Diagnosis

Pathologic fracture secondary to periodontal disease, neoplasia, osteomyelitis (bacterial or fungal); nonunion.

Diagnostic Testing

The patient was placed under general anesthesia and dental radiographs exposed. These revealed the significant alveolar bone loss associated with the distal root of the mandibular first molar (**Figure 5.40**). This was conclusive evidence that this was indeed a pathologic fracture, and the infected distal tooth root was the reason for the nonunion.

Treatment

The plate was removed, and the right mandibular 1st molar was extracted (**Figure 5.41**). The fracture was reduced and stabilized with intraosseous wire (**Figure 5.42**). Intermittent rechecks confirmed that the patient was doing very well. Six weeks later, the patient was represented for wire removal. The dental radiographs revealed adequate healing. The splint/wire was removed and the soft tissues closed (**Figures 5.43** and **5.44**).

Conclusion/Discussion

Pathologic fractures are the result of a weakened area of bone secondary to a disease process. The most common etiology of these weakened areas is periodontal disease; however, fungal osteomyelitis and neoplasia can also degrade the bony integrity. Periodontal disease is the most commonly diagnosed problem in veterinary medicine. Bacteria and their by-products cause inflammation, which in combination with the patient's immune defenses leads to bony destruction. Over time,

(*Continued*)



FIGURE 5.40 Intraoral radiograph of nonhealing fracture site; attempted fixation with bone plate.

this chronic periodontal loss loosens the tooth support, resulting in exfoliation of the tooth. In the majority of teeth, this occurs before severe bone weakening. In some situations, however, the size of the tooth roots in relation to the mandible can cause significant bone weakening prior to tooth exfoliation. This scenario most commonly occurs in small breed dogs for several reasons. First, small dogs tend to have more severe periodontal disease than medium-to-large breed dogs.



FIGURE 5.41 Intraoral radiograph of pathologic fracture site after removal of bone plate.

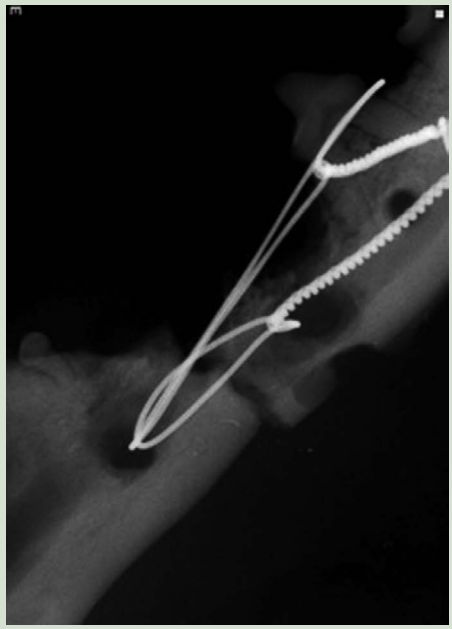


FIGURE 5.42 Intraoral radiograph after repair with interosseous wiring technique.

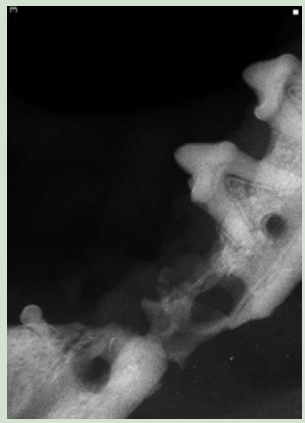


FIGURE 5.43 Intraoral radiograph after removal of interosseous wire, demonstrating healing.



FIGURE 5.44 Intraoral photograph of fracture site, caudal right mandible.

(*Continued*)

In addition, small dogs tend to live longer. Finally, and most importantly, small and toy breed dogs have proportionally larger 1st molars than do larger breeds. Consequently, the root apex of the mandibular 1st molar (especially the mesial root) lies within millimeters of the ventral cortex of the mandible. Another vulnerable area involves the mandibular canines, which comprise 60%–70% of the strength of the rostral mandible. Thus, the mandible weakens to the point of fracture before the tooth exfoliates. Pathologic jaw fractures typically happen as a result of just mild trauma, such as jumping off a bed, a dog fight, or quite commonly during dental extraction procedures. However, dogs can even break their jaw while simply eating.

Although this is typically thought of as a disease of older patients, the authors have treated a few cases in dogs less than 3 years of age. Therefore, it is of critical importance that these small patients have regular dental examinations (under anesthesia and ideally including dental radiographs) from an early age.

A pathologic fracture should be suspected in any case of a mandibular fracture, especially in the area of the mandibular 1st molar of small breed dogs. Additional supportive history is lack of obvious trauma, a nonpainful or mildly painful appearing patient, periodontal disease elsewhere in the mouth, and lack of response to adequate fixation.

Diagnosing a pathologic fracture is only possible with dental radiographs. In general, skull films are not detailed enough to diagnose periapical disease. The classic radiographic appearance is bone loss around the involved roots and/or a periapical lucency in the area of the fracture. Additionally, a periapical lucency may be seen on another root of a multi-rooted tooth.

It is important to realize that a pathologic fracture will not heal if the diseased tooth root is not removed. This is because a diseased root acts as a nidus of infection, which prevents healing. Extraction of the diseased root is necessary but, unfortunately, creates a large defect in the bone, which much be bridged.

All pathologic jaw fractures are typically difficult to heal due to the lack of remaining bone, the low oxygen tension in the area, and difficulty in rigidly fixating the caudal mandible.

This case demonstrates the importance of dental radiology when treating mandibular fractures. Skull films are generally not detailed enough to reveal the pathologic nature of these fractures. Referral of mandibular fractures to a facility with this capability is recommended.

RECOMMENDED FURTHER READINGS

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CHAPTER

6

Respiratory Disorders

Cécile Clercx

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INTRODUCTION

Respiratory diseases are common clinical problems in small animal practice. Some are readily diagnosed on the basis of history and clinical signs while others can prove difficult to diagnose. Upper airways generally refer to the nasal cavities and frontal sinuses, nasopharynx and laryngopharynx, larynx, and extrathoracic trachea, while lower airways include organs inside the thoracic cage, including (1) the intrathoracic part of the trachea, the airways or "conducting pipes" (i.e., the bronchi and bronchioli) and (2) the lung parenchyma, composed of functional units (i.e., the alveoli surrounded by capillaries, where gas exchange takes place, and interstitial tissue). Pleural disorders and diseases involving other intrathoracic organs, such as the heart and vessels, and mediastinal organs will cause clinical signs similar to those encountered in parenchymal diseases.

Clinical history is of great importance, since a good description of the complaints can help determine the segment of the respiratory tree involved. A physical examination is essential and will often be very helpful in the diagnosis of upper airway diseases, while in respiratory diseases of intrathoracic origin, diagnosis is much more challenging, and several ancillary diagnostic tests, mainly imaging, will always be needed.

The clinical signs encountered in disorders of the different affected areas are summarized in Table 6.1.

UPPER AIRWAY DISORDERS

NASAL, SINUS, AND/OR NASOPHARYNGEAL DISORDERS

Nasal, sinus, and/or nasopharyngeal diseases will be presented together, since differentiation, based on clinical signs alone, is challenging and because in most diseases all three regions can be involved. Although the clinical signs (e.g., sneezing, discharge, reverse sneezing, stertor) localize the disease to this area, confirmation of the etiology depends on additional diagnostic tests, primarily imaging (mainly high-resolution computed tomography or HRCT) and rhinoscopy (direct and retrograde). Direct rhinoscopy can be performed using a rigid scope (Figure 6.1a, b), but investigation of the frontal sinus and nasopharynx usually requires a flexible endoscope (Figure 6.2a, b). These procedures require general anesthesia. When HRCT is indicated, it should preferably precede rhinoscopy, if performed during the same anesthetic procedure. During rhinoscopy, other procedures such as brushing, biopsies, nasal lavage, and sampling for microbiologic examination can be performed.

Disorders of the nasal cavities must be differentiated from nasal planum (planum nasale) disorders. Indeed, some disorders of the nasal cavities induce changes on the nasal planum (e.g., hyperkeratosis, erosions, and ulcerations together with local oozing or bleeding) that can be confused with nasal discharge. However, diseases of the nasal cavities are most often accompanied by sneezing and discharge coming from inside the nasal cavity, which is not the case in planum nasale disorders. These include skin or mucocutaneous junction disorders (e.g., tumors, immune-mediated diseases, or leishmaniasis), which can be associated with coagulopathy in addition to being associated with epistaxis unrelated to coagulopathy. In these cases, a full clinical examination must be performed before considering other diagnostic procedures such as rhinoscopy, nasal/sinus radiographs, or HRCT under anesthesia.

Stenosis of the nares (Figure 6.3) causes a decrease in the intranasal opening, resulting in a stertorous breathing during normal attempts to breathe. The noisy respiration can be associated with some degree of serous nasal discharge and sometimes sneezing. This pathology

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TABLE 6.1 Clinical signs in respiratory tract diseases

	Major signs	Less common signs
Upper airway disorders		
Nasal cavities, sinuses, nasopharynx	– Sneezing – Nasal discharge – Reverse sneezing – Alterations of the nasal plane – Change in nostril patency – Stertor	– Facial deformity (tumor) – Systemic signs of illness (aspergillosis) (e.g., lethargy, inappetence, weight loss) – Seizures
Pharynx	– Stertor – Open-mouth breathing – Sneezing, nasal discharge – Cough	– Upper digestive symptoms – Gagging, retching – Dysphagia – Ptyalism
Larynx	– Exercise intolerance – Stridor – Difficult breathing/respiratory distress – Cough – Hypoxemia/cyanosis	– Modified barking sounds – Gagging or coughing with eating
Extrathoracic trachea	– Cough (mainly in dogs, not in cats) – Stridor (mainly in cats) – Retching, gagging	– Exercise intolerance – Dyspnea (when severe obstruction)
Lower airway disorders		
Intrathoracic trachea	– Cough (mainly in dogs, not in cats) – Stridor – Gagging	– Exercise intolerance – Difficult breathing (when severe obstruction)
Bronchi	– Cough – Dyspnea	– Exercise intolerance – Systemic signs of illness
Pulmonary parenchyma	– Exercise intolerance – Tachypnea – Dyspnea (obstructive or restrictive)	– Systemic signs of illness (depending on the cause) – Hypoxemia
Pleural space	– Exercise intolerance – Orthopnea – Dyspnea	– Varies with cause
Mediastinal	– Exercise intolerance – Orthopnea – Dyspnea	– Cough – Digestive signs

is encountered mainly in brachycephalic breeds of dogs and is often associated with the clinical signs reported in dogs with brachycephalic airway obstructive syndrome (BAOS).

In cats, although BAOS is appreciated less commonly than in dogs, stenotic nares area component which appears to play a major role.

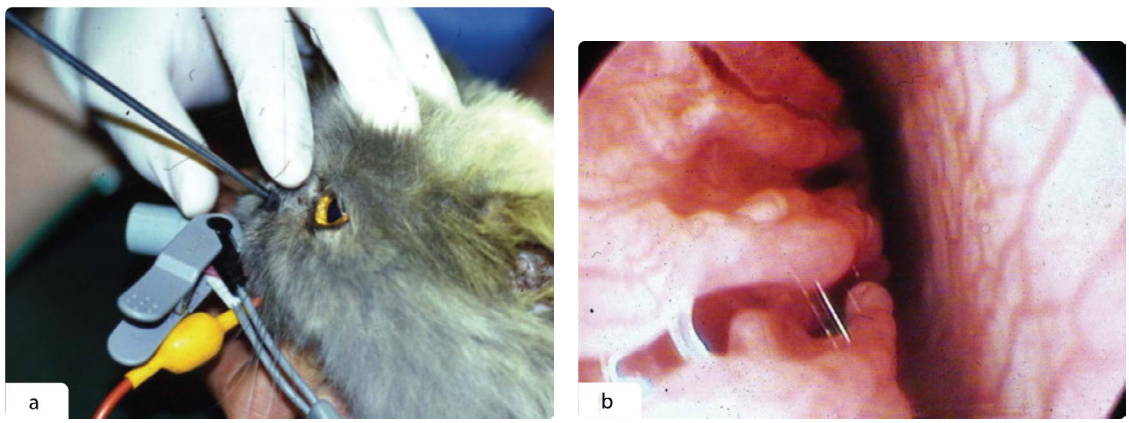


FIGURE 6.1 Direct rhinoscopy. **(a)** Use of a rigid scope in a Persian cat. **(b)** Rhinoscopic view of the turbinates in a dog.

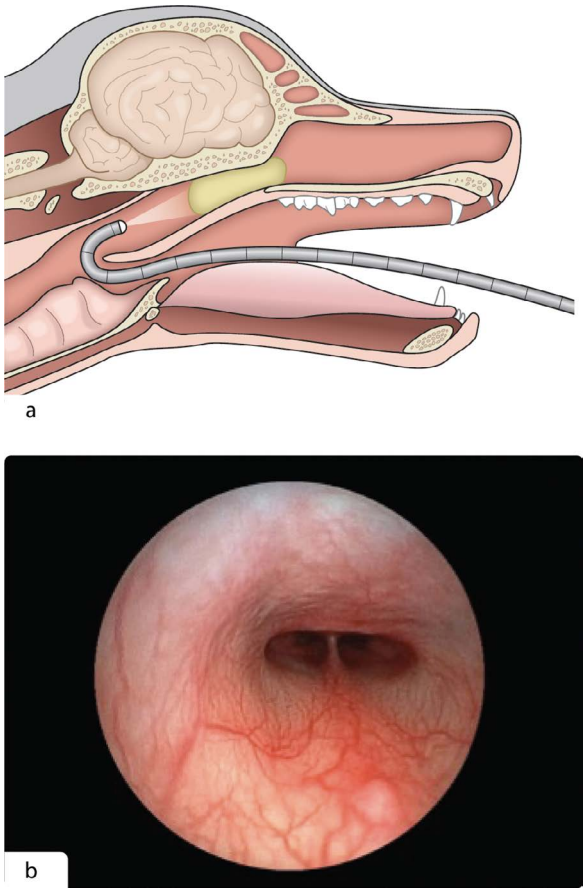


FIGURE 6.2 Retrograde rhinoscopy. **(a)** Diagram showing the use of a flexible endoscope. **(b)** Normal aspect of the choanae in a dog.

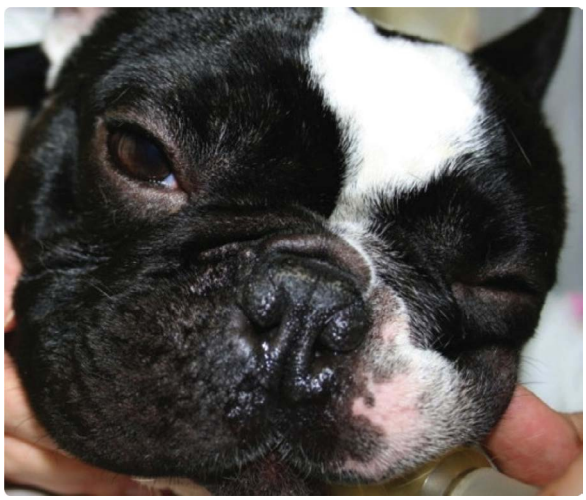


FIGURE 6.3 Stenotic nares in a French Bulldog.

MYCOTIC RHINOSINUSITIS (DOGS)

Definition/Overview

Sinonasal aspergillosis (SNA) is a common disease and affects between 12% and 34% of dogs evaluated for chronic sinonasal disease. The term "nasal aspergillosis," which was used in the past to describe this condition, is better replaced by the term sinonasal aspergillosis, since the infection involves the nasal cavity and frontal sinus in most cases. Aspergillosis in dogs typically causes destructive rhinitis and sinusitis. Most affected dogs are young to middle aged and of mesocephalic and dolichocephalic breeds.

Etiology

In most instances, *Aspergillus fumigatus* is the etiologic agent, but *A. niger, A. nidulans, A. flavus*, as well as *Penicillium* spp. may also be involved. *A. fumigatus* is a filamentous saprophyte and ubiquitous fungus.

Pathophysiology

Despite numerous investigations, the pathogenesis is, to date, poorly understood. As the disease usually affects systemically healthy dogs, and as *A. fumigatus* is a ubiquitous fungus, a local immune deficiency in affected dogs has been suggested. The fungus invades the nasal cavity and sinus and causes necrosis of the turbinates, which is painful. The fungus can also induce lysis of the medial septum and invade the contralateral nasal cavity/sinus or cause lysis of the cribriform plate.

Clinical Presentation

Clinical signs associated with the disease include, in decreasing frequency:

- Profuse nasal discharge, unilateral when the disease begins, then possibly bilateral when the disease progresses due to septal erosion. The discharge can be mucopurulent, although more often it is sanguinopurulent or bloody.
- Sneezing and reverse sneezing.
- Signs of nasal and frontal sinus pain, as evidenced by restriction of head movements, lethargy, and decreased appetite.
- Hyperkeratosis of the planum nasale and ulceration of external nares (Figure 6.4).

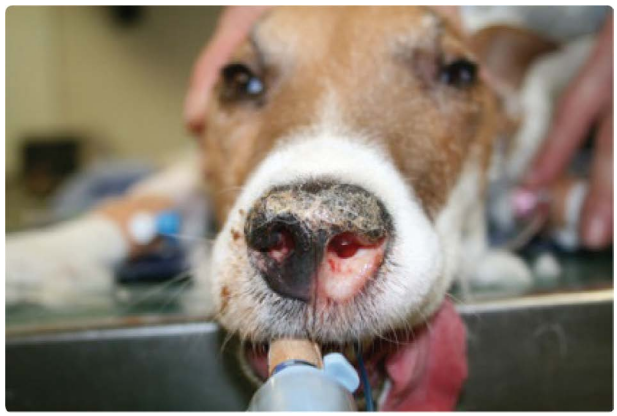


FIGURE 6.4 Ulceration of the external nares, hyperkeratosis, and discharge in a dog with sinonasal aspergillosis.

- Increased nasal airflow, as shown by placing a thin piece of cotton wool in front of each nostril alternately, related to the destruction of the turbinates (this abnormality is easily demonstrated from early in the course of the disease).
- Enlarged mandibular lymph node(s).

In advanced cases, other clinical abnormalities that can occur include facial deformity due to frontal bone hyperostosis, epiphora secondary to extension of the pathologic process into the orbit, or signs of forebrain dysfunction (e.g., seizures, dullness) if there is significant cribriform plate destruction.

Differential Diagnosis

Includes lymphoplasmacytic rhinitis, early nasal tumor, chronic nasal foreign body, bacterial rhinitis due to dental disease, and fungal rhinitis.

Diagnosis

SNA may be suspected based on signalment, history, and clinical signs, but reaching an early definitive diagnosis remains a clinical challenge. Medical imaging (HRCT or magnetic resonance imaging [MRI]), endoscopy, cytology/histology, fungal culture, serology, and fungal DNA quantification have been reported to help in the diagnosis of canine SNA. However, there is no single consistently reliable diagnostic method, as false-positive and false-negative results can occur with each test. Direct rhinoscopy may detect turbinate lysis in the affected cavity (or cavities) in addition to any fungal plaques with their associated accumulation of necrotic material in the affected cavity (Figure 6.5a–c). In early cases, rhinoscopy may not detect the presence of typical fungal colonies because the plaques might not yet be formed or because they are hidden inside the frontal sinus, which cannot easily be explored in the absence of severe nasal turbinate lysis in smaller dogs.

Radiographic signs of fungal rhinitis consist of a loss of the normal intranasal trabecular pattern together with an increased lucency of the affected nasal cavity (or cavities). High-resolution CT is much more useful. Typical features of nasal aspergillosis include cavitary destruction of the turbinates with abnormal soft tissue within the nasal cavity, a rim of soft tissue along the frontal and sinus bones, and thick, reactive bone (Figure 6.6a–c). The value of MRI for the diagnosis of aspergillosis is very similar to that provided by HRCT because of the greater detail they provide compared with radiography.

Rhinoscopy is required for a definitive diagnosis because it is the only technique that is able to show the presence (active overt aspergillosis) or absence of fungal colonies. It also allows access to the plaques for surgical debridement.

Direct endoscopic visualization of fungal plaques along with biopsy of the pathologic tissue and, preferably, positive culture and/or quantitative polymerase chain reaction (qPCR) results have become accepted as the gold standard for the diagnosis of SNA. Referral of suspect patients to veterinary centers that have the diagnostic expertise can be a great service for practices that are not equipped for such diagnostic testing.

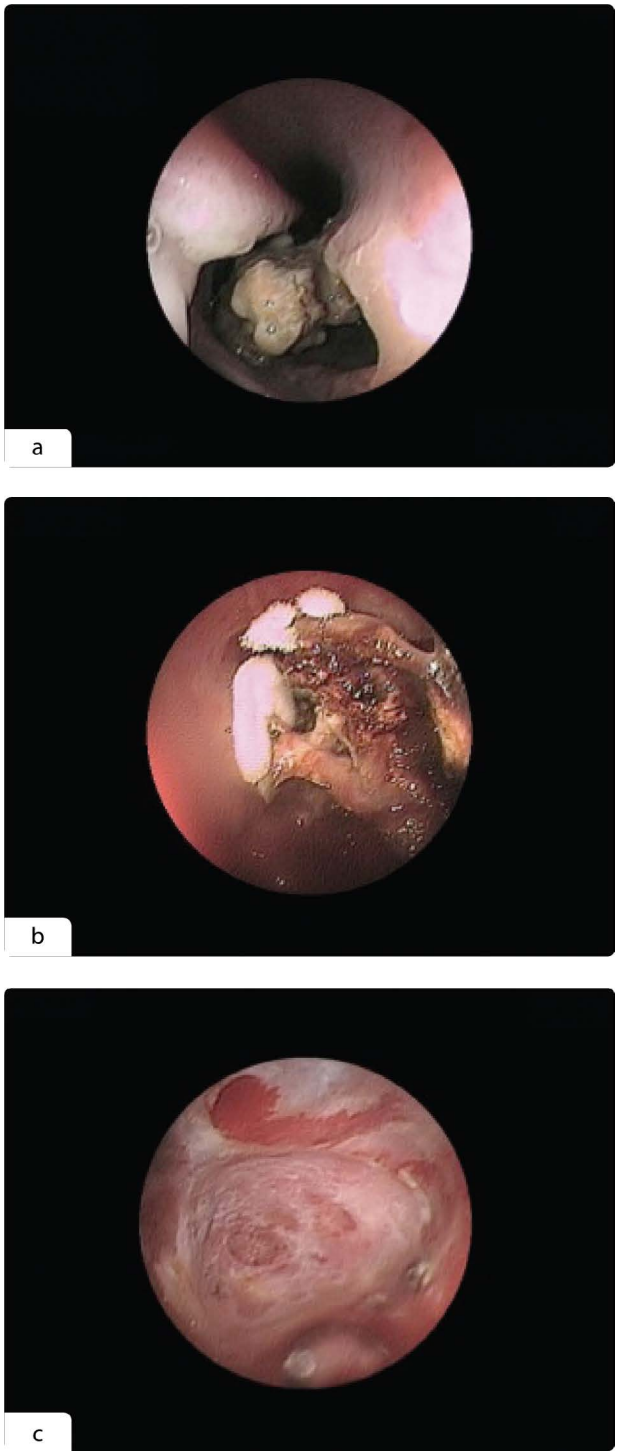


FIGURE 6.5 Rhinoscopy in a dog with SNA showing **(a)** important turbinate lysis and presence of necrotic material in the nasal cavity; **(b)** presence of typical fungal plaques and collection of necrotic material in the nasal cavity; and **(c)** a cleaned frontal sinus after debridement.

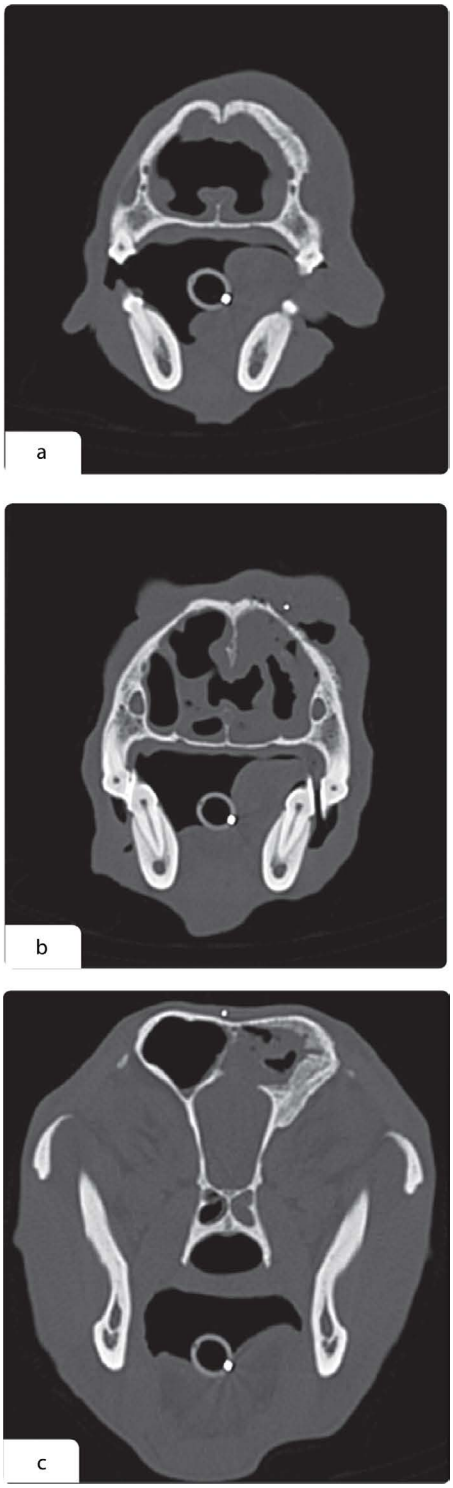


FIGURE 6.6 Transverse high-resolution CT images of a dog with severe nasal aspergillosis, showing **(a)** bilateral cavitary destruction of the turbinates with abnormal fluid/soft tissue within the nasal cavities and L>R frontal sinuses; **(b)** thickening of the mucosa along the inner surface of the bones of the left frontal sinus and nasal cavities; and **(c)** thick, reactive maxillary, incisive, nasal, and frontal bones (hyperostosis) as well as lysis of the maxillary, nasal, and incisive bones, nasal septum, frontal crest, and cribriform plate. Note the swelling of the dorsal subcutaneous tissue on the left side. (*Courtesy of G. Bolen.*)

Agar gel double immunodiffusion (AGDD) is the most commonly used serologic test for diagnosing SNA. Enzyme-linked immunosorbent assay (ELISA) techniques have at least similar performances but are not yet widely/commercially available. Serology is cheap, simple, and easy to perform and offers good specificity but moderate sensitivity. Although fungal culture of nasal specimens is highly specific for the diagnosis of SNA, nasal secretions sampled blindly with swabs are an unreliable source for fungal culture in contrast to fungal plaque and mucosal biopsy samples. Incubating samples for fungal culture at 98.6°F (37°C) improves the chance of fungal isolation in the laboratory.

Rarely, hyphae or conidia can be seen on cytologic or histopathologic preparations.

Management

Effective treatment of SNA in dogs is very challenging. Treatment options include systemic oral therapy, topical antimycotic therapy, and more invasive surgical procedures. The reported success rates, and short-term and long-term outcomes are variable.

Systemic oral treatments (ketoconazole, 5 mg/kg q.12h. or itraconazole 5 mg/kg q.12h.) are noninvasive but require prolonged administration (more than 4 weeks in all cases) because of poor efficacy and may have significant side effects, especially on liver function.

Currently, the most rewarding therapies include topical treatments. They have been associated with greater success and have improved the management of SNA. Various procedures have been developed to administer medication topically, and these procedures vary in invasiveness and ease of performance. Extensive debridement prior to infusion is a critical and essential step. Topical therapy includes mainly the use of enilconazole and clotrimazole at a concentration of 1%–2%. These methods have shown good efficacy and reach success rates of up to 80%–90%. Although the use of topical agents via noninvasive methods is well tolerated and shows a high success rate, these procedures are time-consuming and require general anesthesia. Infusion of 1% clotrimazole cream through bore holes into the frontal sinus, which acts as a depot agent to minimize anesthesia time while providing an extended period of drug contact, has been described.

Prognosis

Despite all these treatment procedures, some dogs remain refractory to any treatment, and the prognosis is then very poor. The inability to predict first-treatment success rate is frustrating. Severity of disease, experience of the treating clinician, and the ability and extent to which debridement is performed are contributing factors to treatment response. Recurrence after apparent remission is not uncommon and has been demonstrated to occur several years after an initial successfully treated episode of SNA.

MYCOTIC RHINOSINUSITIS (CATS)

Definition/Overview

In contrast to canine SNA, aspergillosis in cats is rare but is considered an emerging condition. In cats, upper respiratory tract (URT) aspergillosis can be divided into SNA and sino-orbital aspergillosis (SOA), with SOA being the most invasive form and also the most common. In contrast to canine SNA, purebred brachycephalic cats, predominantly of Persian or Himalayan breeds, account for most cases. The disease affects young to middle-aged cats, with evidence of immunocompromise in some cases but not in most. Previous viral URT infection or recurrent antimicrobial therapy might be additional risk factors.

Etiology

A diverse range of *Aspergillus* species has been identified in cats with URT aspergillosis.

Clinical Presentation

Feline SNA is characterized by more local signs of chronic nasal infection (e.g., sneezing, unilateral or bilateral serous to mucopurulent nasal discharge) and, sometimes, epistaxis. Soft tissue masses protruding from the nares and bone lysis are less frequent abnormalities. SOA probably represents an extension of SNA to orbital and subcutaneous tissues, caused by more invasive *Aspergillus* species. It is characterized by signs of orbital and surrounding tissue invasion, including unilateral exophthalmos, third eyelid prolapse, conjunctival hyperemia, and keratitis. In some cases, a mass in the pterygopalatine fossa or an ulceration of the hard palate can be seen. The CNS can also be involved, leading to neurologic signs.

Differential Diagnosis

Includes mainly viral upper URT infections, neoplasia (lymphoma, carcinoma), and severe chronic rhinosinusitis (idiopathic or secondary to polyp, nasopharyngeal stenosis or atresia, or palatal defect), cryptococcosis, foreign body.

Diagnosis

Confirmation of the diagnosis relies on advanced imaging (CT or MRI) and rhinoscopy. Biopsy or a nasal lavage specimen can be used for histology, cytology, culture, and even molecular identification when a negative fungal culture is suspected. In SOA, CT-guided biopsy of orbital or other paranasal mass lesions can be performed.

Management

Evidence-based treatment protocols are not available. Only small numbers of reported treated cases exist, and very little follow-up information is available. Successful treatment regimens have been described using systemic antifungal therapy alone or with topical intranasal antifungal infusion. As with canine SNA, debridement of fungal lesions appears to be a very important step in any treatment protocol. To date, optimal treatment regimens have not been investigated, confirmed, or identified.

Prognosis

SNA carries a favorable prognosis with treatment, whereas the prognosis for SOA is poor.

CRYPTOCOCCOSIS

Definition/Overview

Cryptococcosis is a dimorphic fungus that exists in the yeast form in the animal. In nature, it is found in bird guano. Various species exist (*Cryptococcus neoformans* var. *grubii* or var. *neoformans*, *Cryptococcus gattii*) with various geographic distributions. Feline cryptococcosis is most prevalent in Australia, Western Canada, and the Western United States and occurs sporadically in other countries. Cryptococcal infection is reported more commonly in cats than in dogs, with the disease being less frequently reported compared to aspergillosis.

Clinical Presentation

Clinical signs include facial distortion, sneezing, and chronic mucopurulent nasal discharge and can be accompanied by skin lesions, chorioretinitis, or CNS signs such as seizures.

Diagnosis

Diagnosis involves cytologic identification of the organism in nasal smears, exudates, aspirates, or impression smears. The organism is characteristic (3–8 microns round, surrounded by a clear capsule ranging in size from 10 to 30 microns). There is also a serum latex agglutination test that has shown reliable accuracy in detecting the cryptococcal antigen.

Management/Prognosis

Itraconazole (50–100 mg per cat per day) is reportedly efficacious in most cases.

TUMORS (DOGS)

Definition/Overview

Nasal and paranasal tumors account for 1%–2% of canine neoplasms. Dolichocephalic breeds and medium to large breeds of dogs are more often affected. Older

dogs are predominantly affected. The tumors are mostly malignant and include mainly carcinomas, but sarcomas also occur. Nasal lymphomas are infrequent in dogs but are not rare in cats. Benign tumors are very rare. Nasal tumors are locally invasive; systemic metastasis is infrequent, while local lymph node involvement can be seen.

Clinical Presentation

Dogs exhibit chronic nasal discharge, which is at first unilateral and can then become bilateral. The discharge is serous to mucopurulent and/or hemorrhagic. Epistaxis is common. Other clinical features include stertor, sneezing, and reverse sneezing. Ocular discharge, facial deformity, alteration of the nasal plane, weight loss, and CNS signs are less frequently encountered.

Diagnosis

History and clinical signs lead to a presumptive diagnosis in most cases. A very easy and interesting test is the airflow passage test, which is measured by placing a thin piece of cotton wool in front of each nostril alternately. Airflow passage is always decreased or absent when associated with nasal cavity tumors. Diagnostic imaging is useful to define the extent of the disease and provide a presumptive diagnosis. CT is the imaging modality of choice for diagnosing nasal neoplasia, although radiographs are often adequate. CT is superior for staging and is required before any surgical and/or radiation therapy treatment is started. MRI is more sensitive for identifying intracranial involvement.

Rhinoscopy is an important diagnostic procedure because it allows not only visualization of the mass but also the opportunity to take selective biopsies in order to confirm the diagnosis and determine the histopathologic type of the tumor.

A number of different techniques have been described for obtaining cytology or biopsy tissue samples from the nasal cavity. These include nasal flush, traumatic core biopsy, and rhinoscopy-assisted biopsy. Retrograde rhinoscopy allows for visualization of the posterior nasal cavity (Figure 6.7a). Imprint and/or brush cytology can be diagnostic for nasal tumors, but deep biopsy and histopathology are recommended, since biopsies that are too superficial may fail to confirm the neoplastic nature of the mass. Fine-needle aspiration of the submandibular lymph node is a simple, inexpensive, minimally invasive technique that can help detect metastasis.

Differential Diagnosis

Includes inflammatory rhinitis, aspergillosis, and intranasal foreign bodies.

Diagnosis

The diagnosis of intranasal neoplasia is complicated by the difficulty in obtaining a representative biopsy, and neoplasms are sometimes initially diagnosed as inflammatory disease.

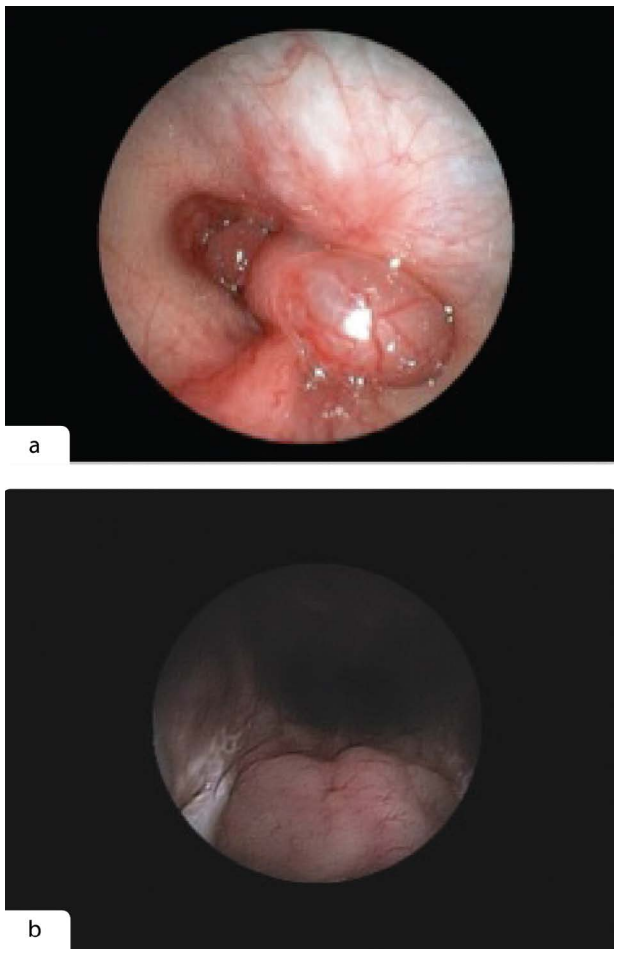


FIGURE 6.7 (a) Retrograde rhinoscopy in a dog, showing a nasal tumor invading and obstructing both choanae. **(b)** Retrograde rhinoscopy in a cat, showing an enlarged nasopharyngeal tonsil, infiltrated with a lymphoma.

Management/Prognosis

In dogs, regardless of the chosen therapeutic procedure, prognosis is poor. Chemotherapy will provide varying results with nasal lymphoma in dogs and cats but otherwise is not highly recommended with other tumor types.

Surgery alone is ineffective since local recurrence is a consistent outcome, resulting in survival times comparable to those observed in untreated dogs. However, surgery may be used to achieve cytoreduction, but it must be associated with other treatment modalities. Radiation alone or after cytoreductive therapy has been the standard of care for treating nasal tumors. The most common therapy currently used in veterinary medicine is high-voltage radiotherapy using megavoltage x-ray or cobalt-60 because this method has reportedly improved outcomes compared with other treatments. In order to minimize acute radiation

toxicity, palliative (hypofractionated) protocols are preferred to definitive ones.

Various treatments have been used in dogs for nasal tumors, including cryosurgery, iridium-192 brachytherapy, cisplatin chemotherapy, cyclo-oxygenase inhibitors (piroxicam), tyrosine kinase inhibitors, hydropulsion and some others, that all might have a role in a multimodality or palliative approach, since they showed some efficacy in scarce reports. However, results are difficult to interpret (different protocols, staging systems, tumor types, small number of dogs included, lack of control groups) and further research is needed to evaluate their efficacy.

TUMORS (CATS)

Overview

Lymphoma in cats normally carries a guarded prognosis; however, nasal lymphoma is prognostically the best variant, with a good chance of long-term remission and even a possibility of cure. Response rates to treatment (chemotherapy and/or radiation therapy) average 66%–75%, with reported median survival times of 12–30 months, even when chemotherapy is delivered intraperitoneally. The disease is often localized (**Figure 6.7b**), and the cats are often still eating well and are usually FeLV negative. Negative prognostic factors for nasal lymphoma include anorexia, anemia, and involvement of the cribriform plate, as seen with CT.

FOREIGN BODY

Etiology

Most intranasal foreign bodies are of vegetal origin. Foreign material can be inhaled into the nasal cavity. It can also be stopped at the entrance of the larynx or regurgitated from the esophagus and misdirected toward the nasopharyngeal area where it lodges in the nasopharynx above the soft palate behind the choanae (**Figure 6.8**). Dogs are more commonly affected than cats, and young animals are more frequently affected than older dogs, but the disease can be found in any breed and at any age.

Clinical Presentation

Clinical signs are quite suggestive and include sudden onset of sneezing bouts, nasal pruritus (the animal rubs his nose against the ground or with his paw), and a serous nasal discharge, which can become mucopurulent or even bloody with time. When the foreign body is blocked in the nasopharyngeal area, clinical signs will occur suddenly and consist of reverse sneezing, stertor if the choanal opening is reduced, ptyalism, and gagging. Later, nasal discharge, sneezing, anorexia, and halitosis can occur.

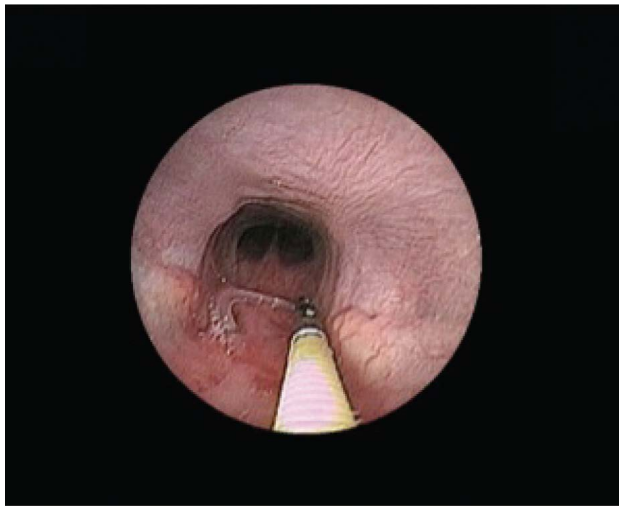


FIGURE 6.8 Retrograde rhinoscopy showing a foreign body in the nasopharynx.

Diagnosis

Diagnosis is confirmed by direct or retrograde rhinoscopy. If performed very early, the nasal foreign body can sometimes be visualized in the anterior nasal cavity and retrieved with the help of an otoscope. This approach will not be feasible if the foreign body has migrated to the caudal nasal cavity. In this case, a rhinoscope is needed. For detection and retrieval of nasopharyngeal foreign bodies, retrograde rhinoscopy is essential.

Management/Prognosis

Early removal is advised. No other treatment is warranted unless severe inflammation and/or turbinate lysis have occurred. In this case, nasal drops containing antibiotics can be prescribed and given intranasally 3–4 times a day for 1 week. Antibiotics can also be administered orally.

Unless the foreign body has caused chronic mucosal inflammatory changes, the prognosis is excellent. However, nasopharyngeal ulceration can potentially lead to secondary nasopharyngeal stenosis.

PARASITIC RHINITIS ("NASAL MITE")

Etiology

This is a rare disease associated with the presence of the nasal mite *Pneumonyssoides caninum*. This nasal cavity parasite of dogs has been reported worldwide; however, details of the parasite's life cycle remain to be elucidated.

Clinical Presentation

Clinical signs include daily repeated episodes of reverse sneezing, sneezing, and mild nasal discharge.

Diagnosis

Diagnosis is based mainly on clinical signs and rarely on visualization of the mites during retrograde or direct rhinoscopy. There is no valid serologic test to confirm the diagnosis, although antibodies were recently demonstrated by ELISA in naturally and experimentally infected dogs.

Management

Treatment is with milbemycin oxime (0.5–1.0 mg/kg p.o. once a week for 3 consecutive weeks). Selamectin (6 mg/kg SC) or ivermectin (0.2 mg/kg SC or p.o. given twice during 3 weeks) is generally successful as well.

NASOPHARYNGEAL STENOSIS AND CHOANAL ATRESIA

Definition/Overview

Nasopharyngeal stenosis is acquired and results from excessive formation of scar tissue in the nasopharynx secondary to a local inflammatory process of infectious, caustic (e.g., passage of acid gastric fluids during regurgitation and vomiting), or traumatic (e.g., foreign body, surgery) origin.

Choanal atresia is a congenital anomaly that results from failure in the development of the communication between the posterior nasal cavities and the nasopharynx (i.e., the formation of the choanae). Atresia can be unilateral or bilateral, partial or total, and bony or membranous.

Clinical Presentation

Both nasopharyngeal stenosis and choanal atresia lead to decreased nasal patency (obstruction of airflow through the nose). Progressive stertor and possibly secondary nasal discharge are present; sometimes, open-mouthed breathing is observed with subsequent respiratory discomfort and inappetence.

Diagnosis/Management/Prognosis

Retrograde rhinoscopy is required for both diagnosis and treatment.

The best therapeutic approaches include balloon dilation of the stenosis and stenting with a metallic stent or silicone tubing (**Figure 6.9a–d**). Balloon dilatation has been reported to result in an immediate improvement or resolution of clinical signs but with high recurrence rates, while stent placement would be associated with a higher success rate but also with a higher complication rate. This gives favorable results for nasopharyngeal stenosis and less favorable prognosis for choanal atresia.

NASOPHARYNGEAL POLYP

Etiology/Pathophysiology

Nasopharyngeal polyps usually affect young cats. Their etiology is unknown. They are made of pedunculated fibrous inflammatory tissue that originates in the eustachian tube and invades the nasopharyngeal area. The polyp may also grow into the middle ear and invade the external auditory tube. In dogs, aural and nasopharyngeal inflammatory polyps are rare.

Clinical Presentation

Because they can lead to unilateral or bilateral nasal obstruction, polyps in the nasopharynx cause stertorous breathing and inspiratory dyspnea. A chronic serous or mucopurulent nasal discharge may be present. Polyps in the middle ear may cause vestibular signs and Horner syndrome. In advanced cases, permanent open-mouthed breathing progressively leads to inappetence and poor general condition.

Diagnosis, Management, and Prognosis

The rostral part of the soft palate may be depressed by the polyp, which can be visualized under anesthesia after rostral retraction of the soft palate. Retrograde rhinoscopy can facilitate polyp visualization in the posterior nasal cavity. Ear canal examination will identify any polyp in this particular location. This is important since surgery, along with tympanic bulla curettage, is the preferred treatment option, leading to cure without recurrence. Radiographic examination of the bullae or high-resolution CT of the skull should be performed if the polyp cannot be visualized on direct examination prior to planning surgery (**Figure 6.10**).

RECURRENT INFECTIOUS RHINITIS IN DOGS

Definition/Overview

Primary acute rhinitis is rare in dogs. Canine distemper virus is the only virus able to induce rhinitis in dogs and is always accompanied by other, more severe, clinical signs.

Etiology, Clinical Presentation, and Differential Diagnosis

A primary etiology should be looked for when clinical signs of mucopurulent rhinitis improve with antibiotic therapy but recur after discontinuation of therapy. Tooth root infection as well as silent bacterial pneumonia

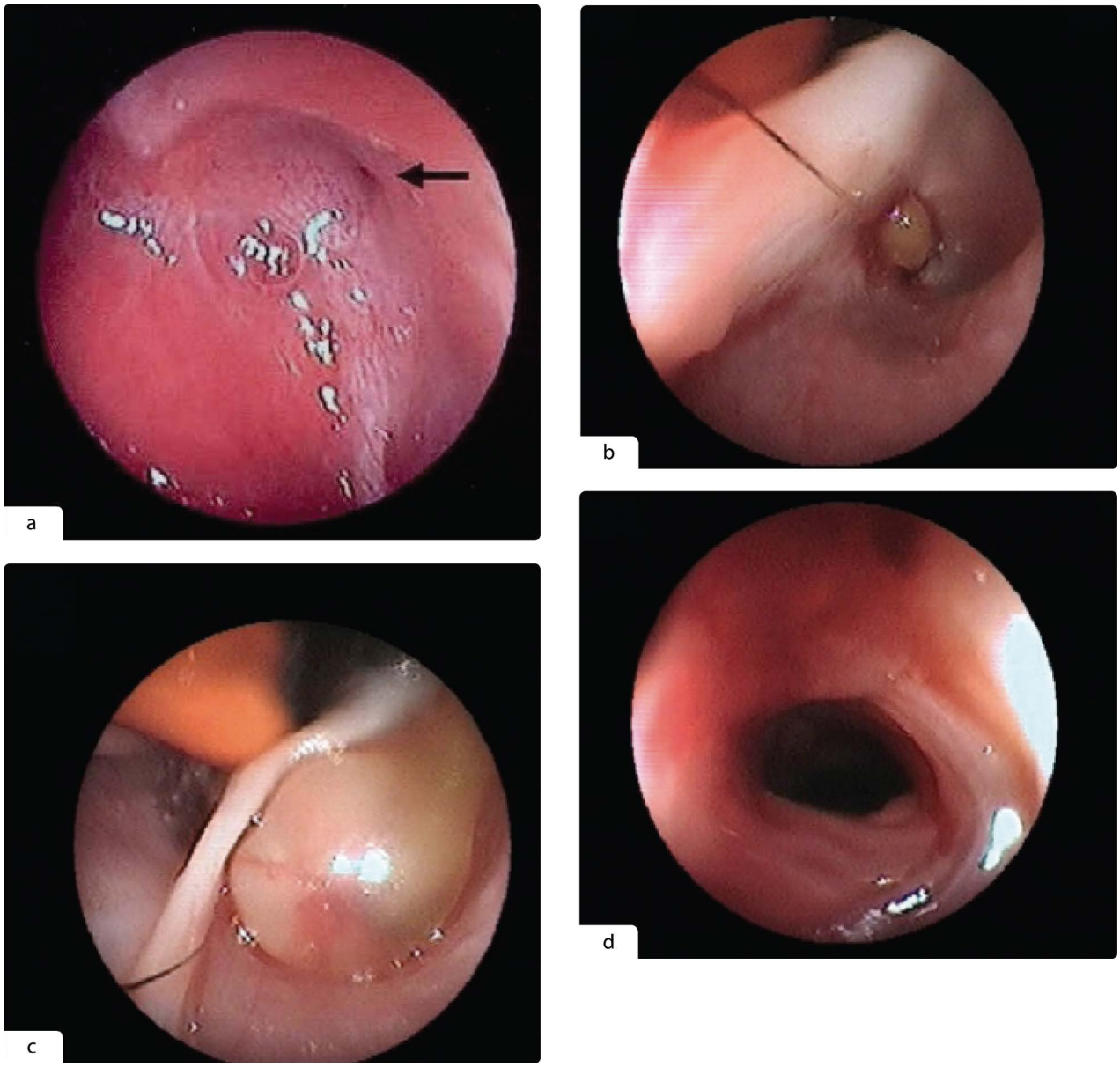


FIGURE 6.9 Retrograde rhinoscopy in a cat with left nasopharyngeal stenosis before **(a)**, during **(b, c)**, and after ballooning **(d)**.

must be ruled out as possible causes. Tooth root infection leading to chronic or recurrent mucopurulent rhinitis is most commonly encountered in middle-aged to old small breed dogs (e.g., Poodles, Yorkshire Terriers) with stomatitis associated with dental tartar. An oronasal fistula can be found in some cases, and the discharge can be malodorous and have a whitish, granular appearance. If clinical signs appear at a very young age, a severe metabolic problem such as immune deficiency (e.g., rhinitis/bronchopneumonia syndrome in Irish Wolfhounds) or a primary ciliary defect should be suspected. In such cases, the nasal discharge is mostly associated with other clinical signs, mainly related to lower airway recurrent infection.

ACUTE FELINE UPPER RESPIRATORY TRACT DISEASE

Definition/Overview

Acute feline URT disease is very common in cats. Young kittens are most commonly affected, but older cats can become infected when exposed to high concentrations of pathogens (e.g., in a shelter environment).

Etiology/Pathophysiology

The most commonly implicated organisms include feline herpesvirus type 1 (FHV-1), feline calicivirus (FCV),

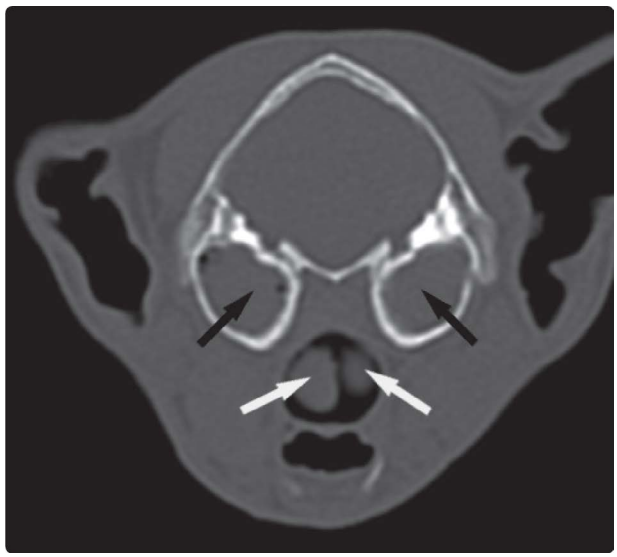


FIGURE 6.10 Transverse CT image of the skull of a cat with bilateral nasopharyngeal polyps showing both tympanic bullae totally filled with soft tissue attenuating masses (black arrows) and the presence of two soft tissue images in the nasopharyngeal lumen (white arrows). (*Courtesy of G. Bolen.*)

Chlamydophila felis, *Bordetella* spp., *Mycoplasma felis*, and influenza virus. Viral infection predisposes to bacterial infection, which can also act as a primary pathogen. Viral infection usually resolves within 10 days, but it is highly contagious, since viral shedding can persist for up to 3 weeks. Moreover, affected cats can become carriers, and viral shedding may be reactivated during periods of stress. FHV-1 is an important cause of morbidity and sometimes mortality. Virulent strains of FCV have been described, leading to pneumonia with a high mortality rate.

Clinical Presentation

Clinical signs are dominated by sneezing and a serous to mucopurulent oculonasal discharge, while fever and systemic illness (lethargy, anorexia, dehydration) are common. *C. felis* is often associated with unilateral or bilateral conjunctivitis and chemosis, and FCV causes lingual ulcers and sometimes pneumonia.

Diagnosis

Viral and bacterial confirmation using isolation or PCR or bacterial cultures are rarely necessary in acute cases in practice unless the disease is associated with high morbidity and mortality in a community of cats (shelters, cattery, or multihouse environments).

Management and Prognosis

Supportive care and systemic antibiotic therapy against secondary bacterial infection are indicated. Many antibiotics can be used. *Chlamydophila* is best treated with doxycycline (10 mg/kg per day for 6 weeks). The efficacy of novel treatments such as lysine and antiviral therapy have not yet been proven in large clinical settings, although the efficacy of some specific antiviral therapies such as oral administration of famciclovir has recently been reported.

Most kittens survive, but mortality is still quite high. Vaccination against viruses may reduce the clinical signs and limit the spread of the disease.

CHRONIC NONSPECIFIC LYMPHOPLASMACYTIC RHINITIS IN DOGS

Definition/Overview

Idiopathic lymphoplasmacytic rhinitis is a common, chronic, and gradually progressive inflammatory nasal disease of unknown etiology associated with varying severity of clinical signs. It is characterized by lymphoplasmacytic to mixed inflammation of the nasal mucosa.

Etiology

The pathogenesis of this disease remains unknown. An aberrant immune response to inhaled organisms or allergens but not to fungi is suspected.

Pathophysiology

In chronic conditions, persistent inflammation of the mucosa leads to loss of epithelium and squamous metaplasia, which reduces the population of ciliated cells present in the distal third of each nasal cavity. Furthermore, hyperplastic subepithelial glands secrete increasingly viscid mucus, which also impedes normal ciliary clearance. As a consequence, mucus plugs accumulate and entrap inhaled bacteria and irritating particles within the nasal cavities, thus perpetuating the inflammation. When this material accumulates in the distal part of the nasal cavities, it obstructs the choanae and tends to induce reverse sneezing as well as heavy efforts to clear the throat and nose.

Clinical Presentation

Clinical signs include sneezing, reverse sneezing, and chronic unilateral or bilateral serous or mucopurulent nasal discharge that is characterized as tenacious and sometimes hemorrhagic in nature. The patient's general condition is usually unaffected.

Differential Diagnosis

Before a diagnosis of chronic nonspecific lymphoplasmacytic rhinitis can be made, other underlying causes such as a nasal or nasopharyngeal foreign body, soft palate defects (where an increased opening between the oropharynx and the nasopharynx leads to misdirection of food/saliva), nasopharyngeal atresia or stenosis, or nasopharyngeal cysts or polyp must be excluded.

Any chronic inflammatory disease of the nasal cavities caused by bacteria or fungi can give rise to progressive chronic lymphoplasmacytic rhinitis. Xeromycteria (dry nose) can also cause mild signs of chronic rhinitis.

Diagnosis

Diagnosis cannot rely on clinical signs. Diagnostic imaging and gross rhinoscopic findings are variable and nonspecific. A nasal mucosal biopsy taken during rhinoscopy shows epithelial and glandular hyperplasia, lymphoplasmacytic infiltration, and sometimes fibrosis. It is important to perform these examinations in order to eliminate other potential causes, such as aspergillosis, tumors, chronic foreign body, tooth root infection, or anatomic abnormalities, which could be treated specifically.

Management

In all chronic nasal diseases with epithelial hyperplasia and glandular hyperplasia, treatment should include local therapy with saline and mucolytics, since the physiological mucociliary clearance protective mechanism is impaired. This can be administered intranasally or by aerosol therapy. Nebulization devices used in human medicine can be used. Treatment entails the intranasal instillation of saline or mucolytic drops 2–4 times daily. Sometimes, the addition of nasal antibiotics becomes necessary in case of secondary bacterial infection. Improvement should occur after 1–3 weeks in most cases; other cases can remain refractory. Some authors advise treatment with prednisone (1 mg/kg q.12h. for 1–2 weeks, followed by a gradual taper) in refractory cases, although this recommendation will vary among different authors.

Prognosis

Although the condition is benign, treatment is unrewarding in some dogs, where clinical signs will fluctuate and require prolonged treatment.

FELINE IDIOPATHIC CHRONIC RHINOSINUSITIS

Definition/Overview

Chronic rhinitis or rhinosinusitis is one of the most common chronic disorders in cats and is characterized by chronic and/or recurrent nasal discharge and sneezing.

Etiology

Although the underlying pathogenesis is unclear, the disease is likely multifactorial. Some chronic forms are presumed to be caused by FHV-1, FCV, *Chlamydophila felis*, or a combination of these agents. FHV-1 is most commonly implicated in the chronic form of disease, since more than half of the cats exposed to the virus remain latent carriers. Secondary bacterial infections and poorly regulated or improper immune responses also play a role in the pathogenesis. There is some evidence that *Bordetella bronchiseptica* is also a cause of chronic respiratory disease in cats. The low prevalence of FeLV and FIV infection in affected cats suggests that these viruses are not responsible for the disease.

Clinical Presentation

Clinical signs include sneezing and chronic unilateral or bilateral nasal discharge of a serous to mucopurulent nature, stertor, and intermittent open-mouthed breathing. The cat's general condition can be affected.

Diagnosis

Rarely, a primary defect can be identified (nasopharyngeal foreign body, soft palate defects, nasopharyngeal stenosis, or nasopharyngeal cysts or polyps). Imaging and/or rhinoscopy can reveal mild-to-severe turbinate remodeling. Microbiologic identification of microorganisms does not usually help manage the disease since they are usually secondary infections. The signs are mostly related to irreversible remodeling of intranasal lesions rather than to bacterial infections.

Management

Currently, treatment is supportive and aims at the consequences of nasal and sinus dysfunction, decreasing inflammation, and eliminating secondary bacterial infections. Cats with chronic rhinosinusitis often have a transient response to antimicrobial treatment. Many antibiotics can be used orally for prolonged periods (from 3 weeks up to 8 weeks or more). When *Chlamydophila* is suspected, doxycycline (10 mg/kg per day for 6 weeks) can be used. The use of azithromycin (10–15 mg/kg q.24h. followed by 5 mg/kg q.48h. or even q.72h.) is helpful for treating cats that are difficult to pill and need prolonged treatment. Intranasal administration of drugs is difficult in most cases because cats are usually intolerant of this treatment method.

Prognosis

Chronic rhinosinusitis is frustrating to manage. Owners must be informed that definitive cure is unlikely, and clinical signs will probably not resolve. Treatment aims at reducing the frequency and severity of clinical signs.

BRACHYCEPHALIC AIRWAY OBSTRUCTIVE SYNDROME

Definition/Overview

The term brachycephalic airway obstructive syndrome (BAOS) refers to a disorder resulting from multiple anatomic abnormalities commonly found in brachycephalic canine breeds, mainly the English and French Bulldog and the Pug. It is also recognized in Persian cats.

Etiology

Conformational anomalies in brachycephalic dogs are related to breeding selection of "hypertypes," which leads to progressive shortening of the face and nose, with subsequent shortening of the bony structures of the skull without concurrent reduction in surrounding soft tissues.

Pathophysiology

Primary inherited abnormalities include stenotic nares (Figure 6.3), elongated soft palate, hypoplastic trachea, and sometimes protrusion of the nasal turbinates into the nasopharynx. In some dogs, the soft palate can be too long in addition to being exceptionally thick; macroglossia can also occur. Secondary lesions develop as a consequence of increased pressures on the pharyngeal, laryngeal, and intrathoracic structures during breathing. These lesions include everted laryngeal saccules, progressive laryngeal collapse, and probably bronchial collapse (mainly collapse of the left main bronchus). In addition, subepiglottic cysts, severe edema of the dorsal aspect of the laryngopharynx, and laryngeal granulomas ("kissing lesions") all further narrow the air passage at the laryngeal inlet. The severity and the combination of these abnormalities will vary. To complicate matters even further, these same dogs can have various accompanying gastrointestinal abnormalities involving the distal esophagus, stomach, and duodenum, including inflammatory disease with coexisting functional or anatomic anomalies (cardiac atony, gastroesophageal reflux, gastric retention, pyloric mucosal hyperplasia, and pyloric stenosis).

BOAS shares some features with obstructive sleep apnea (OSA) in humans, a syndrome characterized by recurrent collapse of the upper airway during sleep leading to intermittent hypoxia. Like OSA, BAOS can also be associated with sleep apnea and decreased survival as a result of cardiovascular and thromboembolic disorders, metabolic derangements, and liver disease.

Clinical Presentation

The abnormalities associated with the BAOS impair air flow through the upper airways and cause clinical signs of upper airway obstruction, including noisy respiration, stridor, stertor, exercise and heat intolerance, respiratory distress, cyanosis, syncope, gagging and retching, and sometimes sleep apnea. The clinical signs are exacerbated by exercise, excitement, and high environmental temperatures. As a result, some dogs can be presented with life-threatening clinical signs of airway obstruction. Digestive signs such as regurgitation and vomiting are common. Secondary aspiration pneumonia is also a common associated finding and must be addressed.

Diagnosis

A tentative diagnosis can be based on the breed and clinical signs. Laryngoscopy (Figure 6.11a–e) and radiography (Figure 6.12) are essential diagnostics. Other procedures such as retrograde rhinoscopy, bronchoscopy, and gastroscopy might be necessary in order to assess the full scope of the existing abnormalities and will be helpful in providing an accurate prognosis and the best treatment recommendation. Additionally, HRCT of the skull and measurement of respiratory function using plethysmography allow to make a quantitative assessment of several causal anatomical lesions and can be used to both help predict severe disease and select the best surgical approach.

Management

Animals presented with life-threatening upper airway obstruction should be cooled, oxygenated, sedated, and if necessary anesthetized and intubated. A tracheotomy might be indicated in cases of severe upper airway occlusion. In other cases, medical therapy consisting of anti-inflammatory doses of short-acting glucocorticoids (prednisone, 0.5 mg/kg q.12h.) will suffice. Surgical widening of stenotic nares and surgical removal of excessive soft palate (Figure 6.13) and everted laryngeal saccules are classically performed if there are no complicating abnormalities, such as laryngeal or tracheal hypoplasia, which would impair treatment success.

Since computed tomography together with anterior and posterior rhinoscopy allow evaluation of the level endonasal obstruction, laser-assisted turbinectomy (LATE) using a diode laser can be used to remove nasal conchae that are causing airway obstruction and can be performed as part of a multilevel surgery. Additionally, isolated LATE of caudal aberrant turbinates (CAT) can be used for the treatment of brachycephalic dogs with obstructing CAT.

Corrective surgical procedures should be done as early in life as possible in order to decrease the consequences of long-term negative pressure on the airway structures (laryngeal cartilage collapse). Once severe laryngeal dysfunction occurs, successful management is much more difficult. Cricoarytenoid lateralization combined with thyroarytenoid caudolateralization, arytenoid laryngoplasty, or permanent tracheostomy might be necessary in the setting of severe laryngeal pathology. If tracheal hypoplasia with its associated ventilation impairment is still severe after reaching adult size (at 1 year of age), there is nothing else that can be done to remedy the situation. Stress, excitement, and weight gain must be avoided in these animals.

Digestive tract medical treatment combined with upper respiratory surgery appears to decrease the complication rate and improve the prognosis of dogs presented for upper respiratory syndrome.

Prognosis

Prognosis depends on the severity of the abnormalities and the ability to surgically correct them. Laryngeal collapse and tracheal hypoplasia are poor prognostic indicators.

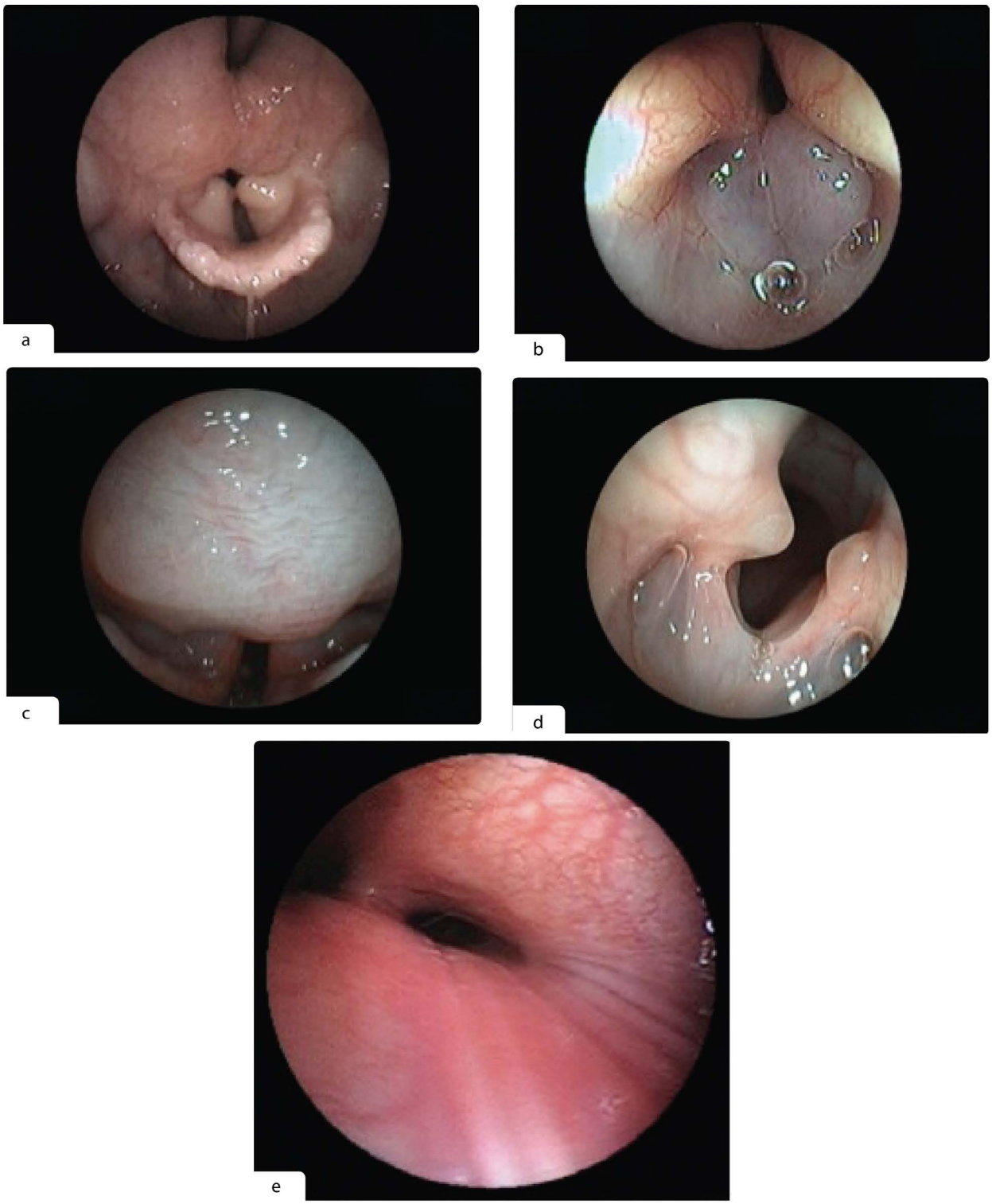


FIGURE 6.11 Laryngoscopic features of BAOS. **(a)** Elongated soft palate; **(b)** everted laryngeal saccules; **(c)** severe edema of the dorsal part of the laryngopharynx; **(d)** intralaryngeal granuloma ("kissing lesion"); **(e)** localized bronchomalacia at the level of the left mainstem bronchus.

A combination of primary and secondary changes can progress to life-threatening laryngeal collapse in many brachycephalic dogs. Early recognition of the primary anatomic abnormalities is essential, since it allows the clinician to make early recommendations for medical and surgical management, which can improve the quality of life in affected animals. Factors that may increase the risk and further complicate the condition include obesity, overexcitement, and exercise.

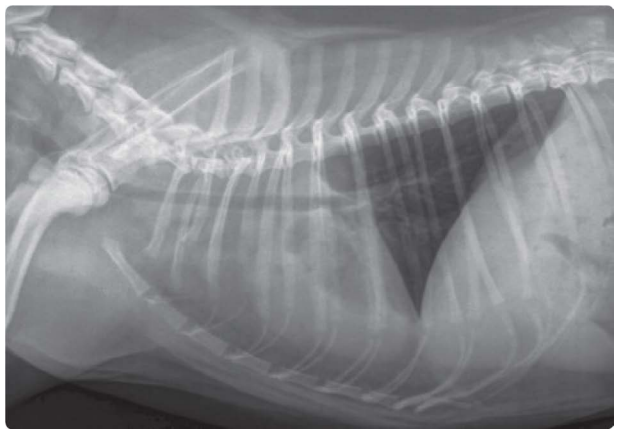


FIGURE 6.12 Thoracic radiograph (lateral projection) of a non-Bulldog brachycephalic dog showing tracheal hypoplasia with a ratio of 0.14 (tracheal diameter/thoracic inlet diameter ≥0.16 for Pugs) and ventral distribution of an alveolar pattern consistent with an aspiration pneumonia. (*Courtesy of G. Bolen*.)



FIGURE 6.13 Laryngoscopic view of a BAOS dog after surgery (soft palate and ventriculectomy), showing persistence of laryngeal collapse.

LARYNGEAL DISEASES

LARYNGEAL PARALYSIS (DOGS)

Definition/Overview

Laryngeal paralysis (Figure 6.14) refers to lack of abduction of the arytenoid cartilages during inspiration due to loss of innervation of the intrinsic musculature of the larynx through the recurrent laryngeal nerves and resulting in inspiratory dyspnea.

Etiology

Laryngeal paralysis is most often of unknown cause and is named idiopathic laryngeal paralysis, although some of the affected dogs may then develop a progressive generalized neuropathy. This is most commonly observed in middle-aged to old, large breed animals (Labrador Retrievers seem to be predisposed). Congenital laryngeal paralysis appears to be inherited and has been reported in breeds such as the Bouvier des Flandres and Husky. Young Dalmatians, Rottweilers, and Great Pyrenees can acquire laryngeal paralysis as part of a polyneuropathy complex. Masses or trauma involving the ventral neck region or the anterior thoracic cavity can damage the recurrent laryngeal nerves and cause unilateral or bilateral paralysis or paresis. Laryngeal paralysis has also been reported in dogs as a manifestation of various peripheral neuropathies or polyneuromyopathy complex, resulting from immune-mediated diseases (such as myasthenia gravis), endocrinopathies (such as hypothyroidism), or other systemic disorders.

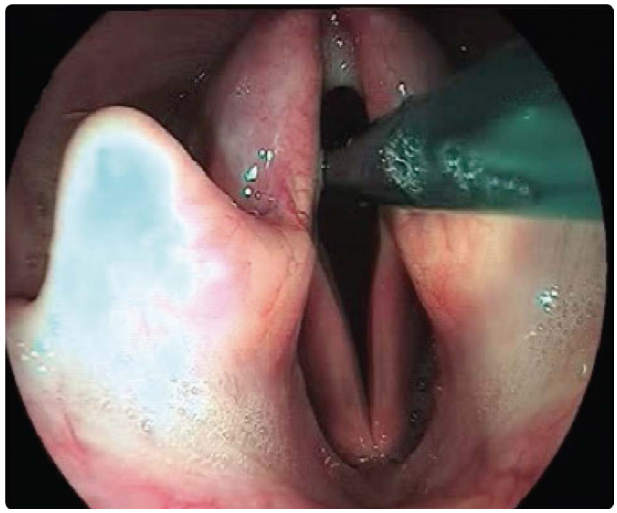


FIGURE 6.14 Laryngeal paralysis. Endoscopic image of the larynx during inspiration, showing a lack of abduction.

Clinical Presentation

The clinical signs vary in severity. The characteristic signs of dyspnea and stridor result from increased airflow resistance occurring during inspiration. They are initially prominent during the inspiratory phase of respiration in association with exertion, excitement, or exposure to high environmental temperatures. As the reduction in laryngeal diameter worsens, the signs can occur during both inspiration and expiration and even at rest. Changes in bark can also occur. Cyanosis and syncope are observed in advanced cases when secondary edema further narrows the glottis, exacerbating the signs and creating a vicious circle. As a result, some dogs may present with life-threatening upper airway obstruction. Some dogs with laryngeal paralysis exhibit gagging or coughing while eating. Secondary aspiration pneumonia is a possible complication.

Diagnosis

The clinical features of laryngeal dysfunction are easily identified. Direct laryngoscopic examination under light anesthesia allows for visualization of this disorder and differentiation from laryngeal edema,

laryngeal tumor, or collapse. Weak, fluttering movements of the arytenoid cartilages and vocal folds may be observed due to changes in airway pressure and airflow and should not be confused with normal movements. Since anesthesia impairs laryngeal motion (moderate-to-deep planes of anesthesia result in cessation of all laryngeal movement), administration of doxapram hydrochloride (1.1–2.2 mg/kg IV), a potent respiratory stimulant, during laryngeal examination is useful for differentiating normal dogs from dogs with laryngeal paralysis. Electromyographic studies of the intrinsic laryngeal muscles done under general anesthesia and ultra-sonographic evaluation of the larynx have also been used to assess laryngeal function. Once a diagnosis of laryngeal paralysis is established, additional diagnostic tests should be considered to identify an underlying cause.

Management/Prognosis

Animals presented with life-threatening upper airway obstruction should be cooled, oxygenated, and sedated. Some may require general anesthesia and intubation, while other extreme cases require a tracheotomy. In less severe situations, initial therapy can begin with anti-inflammatory doses of short-acting glucocorticoid drugs (prednisone, 0.5 mg/kg q.12h., followed by progressive tapering). This reduces the inflammatory reaction and alleviates some of the clinical signs. Surgery is inevitable and should be done as soon as possible. The recommended procedure is unilateral arytenoid lateralization. Aspiration pneumonia is the most common postoperative complication. Suture breakdown is another postoperative complication. However, most owners are ultimately pleased with the outcome. Poor outcomes are associated with underlying diseases causing a more generalized polyneuropathy.

LARYNGEAL PARALYSIS (CATS)

Laryngeal paralysis appears to be infrequent in cats. Both unilateral and bilateral dysfunctions have been documented, although left-sided unilateral paralysis is predominant. This condition can result from trauma or some other destructive process of the recurrent laryngeal nerves or in cases where the cause is idiopathic. Conservative management (weight loss, minimization of excitement, and anti-inflammatory therapy) and surgical treatment are mostly successful.

LARYNGEAL TUMORS

Definition/Overview

Laryngeal neoplasms are rare (Figure 6.15a–c). They are mainly carcinomas, which affect middle-aged to older dogs. However, younger dogs, especially Labrador Retrievers, can be affected with rhabdomyoma, which is a benign tumor. Tumors of tissues surrounding the larynx, such as thyroid carcinomas and lymphomas,

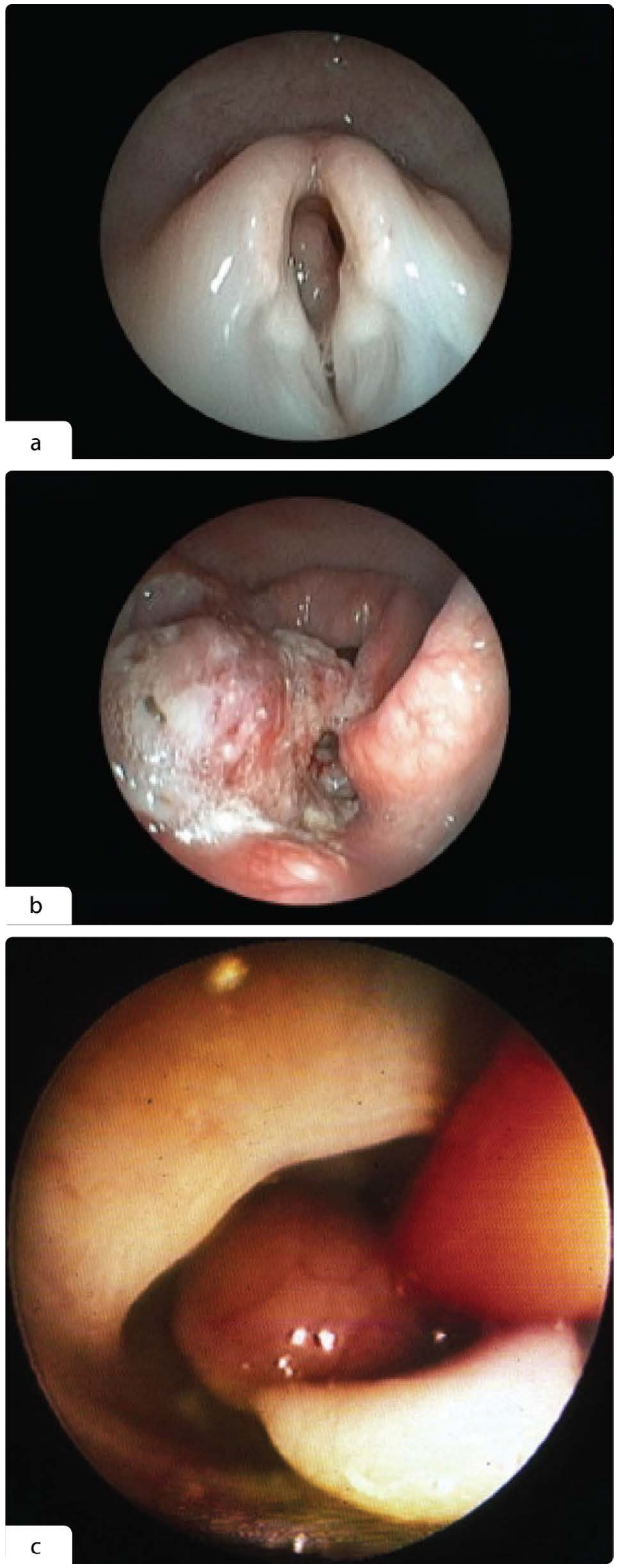


FIGURE 6.15 Laryngeal tumors in a cat **(a)** and two dogs [**(b)** adenocarcinoma; **(c)** rhabdomyoma].

can also compress and invade the larynx, causing similar signs of upper airway obstruction.

Clinical Presentation

The clinical features of laryngeal tumors are similar to those of other laryngeal diseases and include stridor, dyspnea, changes in bark, and cyanosis.

Differential Diagnosis

Includes laryngeal paralysis, foreign body, abscess, and traumatic granuloma.

Diagnosis

Primary laryngeal tumors are best identified by laryngoscopy. It is very important to make the diagnosis on the basis of histopathologic examination of a biopsy of the mass rather than on the gross appearance alone, since some tumors are benign, and some growths are actually granulomas. CT can be helpful in assessing the extent of the mass and in making a decision for surgery.

Management/Prognosis

Benign tumors should be excised surgically, and, in case of rhabdomyoma, the prognosis is excellent when surgical excision is complete. In cases of malignant tumors, complete surgical excision is rarely achievable, and complete laryngectomy and permanent tracheostomy are the only surgical options.

LARYNGEAL EDEMA

Definition/Overview/Etiology

Edema or infiltration of the larynx with inflammatory cells occurs frequently. It can be secondary to paralysis, tumor, or trauma and is seen in brachycephalic dogs with BAOS. In cats, the larynx is very sensitive, and edema can develop after faulty intubation technique or following an excessive application of local anesthetic agent. In some cases, the cause is not determined.

Clinical Presentation

Clinical signs are those typical of an upper airway obstruction and identical to those observed in laryngeal paralysis. They range from exercise intolerance and stridor after excitement to life-threatening respiratory distress.

Differential Diagnosis

Apart from the primary causes (paralysis, tumor, trauma, BAOS, intubation), chronic laryngitis, due to excessive and repeated barking, and laryngospasm ("glottis cramp") can also cause some degree of laryngeal edema. In cats, severe edema and laryngeal neoplasms can appear similar.

Diagnosis

Laryngoscopy shows irregular proliferation, hyperemia, and swelling of the larynx. Additional diagnostic procedures, such as biopsy or brush cytology or fine-needle aspiration, should not be performed when the laryngeal opening is severely reduced unless a temporary tracheostomy is in place, especially in cats. It is prudent to first treat the patient medically before instituting any interventional procedures.

Management/Prognosis

Most animals respond to glucocorticoid therapy within a couple of days. Prednisone (0.5–1.0 mg/kg q.24h. to q.12h.) is used initially. The dose can be gradually tapered over the next 3 weeks once the signs have resolved.

The prognosis is good unless the response to medical treatment is poor. In such cases, tracheostomy should be considered.

TRACHEAL DISORDERS

TRACHEAL COLLAPSE AND MALACIC AIRWAYS

Definition/Overview

Tracheal collapse is a very common disorder characterized by dorsoventral flattening of the tracheal rings with laxity of the dorsal tracheal membrane. Bronchial collapse, essentially of the left cranial lobar bronchus, is often present as well. The syndrome is encountered in middle-aged to older toy or miniature breeds (Yorkshire Terrier, Miniature Poodle, Chihuahua, Pomeranian, Shih Tzu, Lhasa Apso). The sound of the cough is a characteristic "honking noise" or "goose honk."

Etiology/Pathophysiology

The cause is complex and is best regarded as multifactorial. The development of the clinical condition requires the presence of a primary cartilage abnormality, resulting in intrinsic weakness of the tracheal rings, together with secondary factors capable of initiating progression to the symptomatic stage. These potential triggering factors include obesity, cardiomegaly, inhalation of irritants and allergens, periodontitis, respiratory infections, and recent endotracheal intubation. The dynamic changes of tracheal collapse may be confined to either the cervical or thoracic region of the trachea or both and are frequently more pronounced at the cervicothoracic junction. In dogs with tracheal collapse, concurrent bronchomalacia is frequently encountered.

Once clinical signs occur, the syndrome is perpetuated by the cycle of chronic inflammation of the tracheal mucosa and the accompanying cough reflex.

Clinical Presentation

Clinical signs include chronic cough, mild-to-severe panting, and varying degrees of inspiratory and expiratory dyspnea (respiratory distress). Cyanosis can occur in extreme cases. The cough is harsh, followed by a terminal retch, and is generally described as "goose honk," which is precipitated by activity, excitement, tracheal pressure (such as caused by pulling on a leash), or drinking. This characteristic cough can be easily elicited by palpation of the trachea.

Differential Diagnosis

Includes chronic mitral valvular heart disease, which can be a concurrent disease, chronic bronchitis, chronic tracheitis (both possibly secondary to tracheal collapse), and chronic pulmonary parenchymal disease such as idiopathic pulmonary fibrosis.

Diagnosis

Radiographic examination of animals with a collapsed trachea can be done with both still and motion studies. The most useful radiographic examinations include lateral projections of the thoracic inlet, a tangential (rostrocaudal) projection of the thoracic inlet, and fluoroscopic investigation to demonstrate movements of the dorsal membrane during the respiratory cycle. On lateral radiographs, a redundant dorsal tracheal membrane that invaginates into the tracheal lumen can be seen as a soft tissue opacity along the dorsal aspect of the caudal cervical tracheal lumen. During inspiration, it will cause an increased tracheal diameter. This condition can be seen in both small and large breed dogs as a consequence of coughing and must be differentiated from a superimposed esophagus. Therefore, lateral radiographs made during both the maximal inspiratory and expiratory phases (Figure 6.16) of the respiratory cycle are needed to demonstrate a dynamic collapse. Collapse of the cervical tracheal segment occurs in inspiration because of decreased pressure within the trachea, whereas the thoracic portion tends to collapse during the expiration phase as a consequence of increased intratracheal pressure. These dynamic changes are best viewed in real time using image-intensified fluoroscopy. In the skyline projection, the trachea is seen as an oval, "C" or crescent shape.

Tracheoscopy, although rarely needed to confirm the diagnosis, reveals a decreased dorsoventral diameter due to flattening of the cartilaginous rings, with a pendulous dorsal membrane. A severe collapse can cause complete obstruction of the tracheal lumen (Figure 6.17a, b). Tracheobronchoscopy is helpful in determining the degree of severity of the tracheal and, especially, the bronchial collapse, as well as in assessing concomitant airway disease. Radiographs greatly underestimate the incidence of bronchomalacia. Therefore, bronchoscopy is recommended in all cases of suspected tracheal collapse before stent placement is considered because the presence of severe bronchomalacia and/or lower airway disease may impact on the prognosis after stent placement.



FIGURE 6.16 Lateral thoracic radiograph of an 8-year-old Yorkshire Terrier showing probable tracheal collapse with a decreased inspiratory cervical tracheal diameter. (*Courtesy of G. Bolen.*)

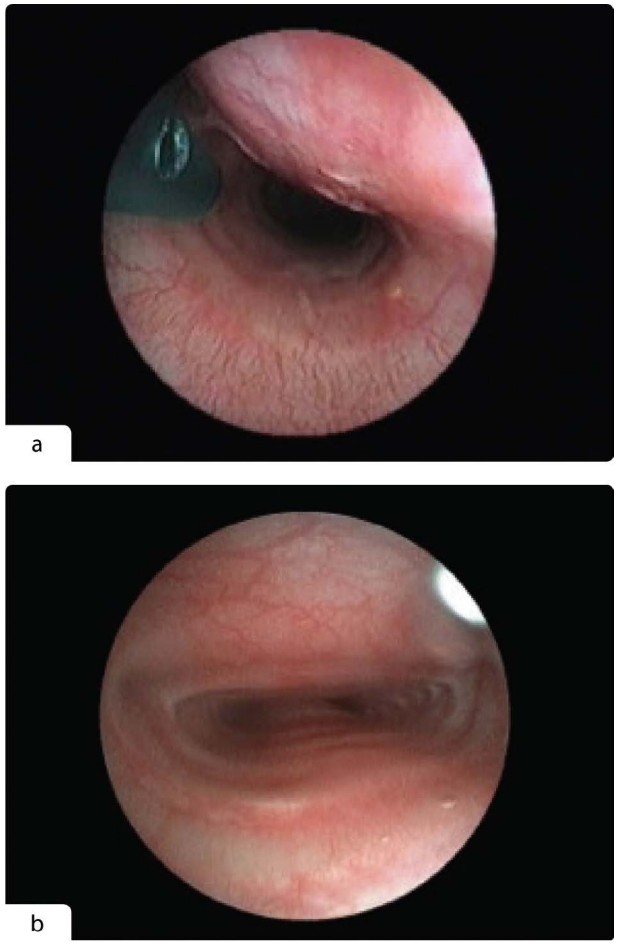


FIGURE 6.17 Endoscopic views of the trachea showing grade 2 **(a)** and grade 4 **(b)** tracheal collapse.

Management

In animals with marked respiratory difficulty, oxygen supplementation should be provided along with sedation and antitussive agents. Butorphanol (0.05–0.2 mg/kg q.4–6h.) and acepromazine (0.01–0.1 mg/kg) can be injected SC in order to alleviate anxiety, and prednisolone sodium succinate (15–30 mg/kg IV) can be administered to decrease acute inflammation.

Long-term treatment aims principally at decreasing potential promoting factors and the level of inflammation of the tracheal mucosa. Weight reduction in obese animals is essential. Weight loss alone can sometimes be curative in terms of dealing with the clinical signs. Likewise, removal of the neck collar and its replacement by a harness can be helpful. Removing the dog from respiratory irritants such as noxious gases, smoke, and dust is essential. It is also important to detect and treat other diseases such as chronic airway disease, cardiac disease, or Cushing's disease.

Some authors recommend short- to long-term therapy consisting of very low-dose steroids orally (prednisone, 0.2 mg/kg daily for 2 days to 2 weeks, followed by the same dose every other day, then at 3-month intervals) or by inhalation (fluticasone, 120 µg puff q.12h. using a face mask and spacer). Short-term administration of sedatives such as acepromazine can be useful in very excited animals to break the cough/excitation/cough cycle. However, oversedation must be avoided because the animal will benefit from limited exercise as far as weight gain and airway clearance is concerned. Oral antitussive agents are effective in controlling symptoms (e.g., hydrocodone 0.22 mg/kg q.12h. or butorphanol 0.55 mg/kg q.12h.). Bronchodilators (methylxanthines or beta agonists) can also be used, their benefits being due to a reduction in bronchoconstriction, thereby reducing intrathoracic pressures and the associated collapse of the larger airways. Furthermore, they improve mucociliary clearance and reduce diaphragmatic fatigue.

In dogs that do not respond to medical management, intraluminal self-expanding stenting devices may be placed. Determination of the appropriate size and type of the stent is a critical step. In some dogs, this minimally invasive technique is the only successful treatment option. Tracheal prosthetic devices are very expensive, and their use is not without complications. These include stent displacement/migration, rupture, stent detachment with development of purulent pockets between the stent and the tracheal mucosa, and inflammatory granuloma (Figure 6.18). The inflammatory complications might respond to oral or nebulized glucocorticoid drugs. It is important to note that the tracheal stent might not benefit the dog if bronchial collapse and bronchomalacia are present together with tracheal collapse.

Prognosis

Most animals can improve with an individualized treatment plan, but the condition is generally progressive and the long-term prognosis poor, especially when irreversible airway collapse is present.

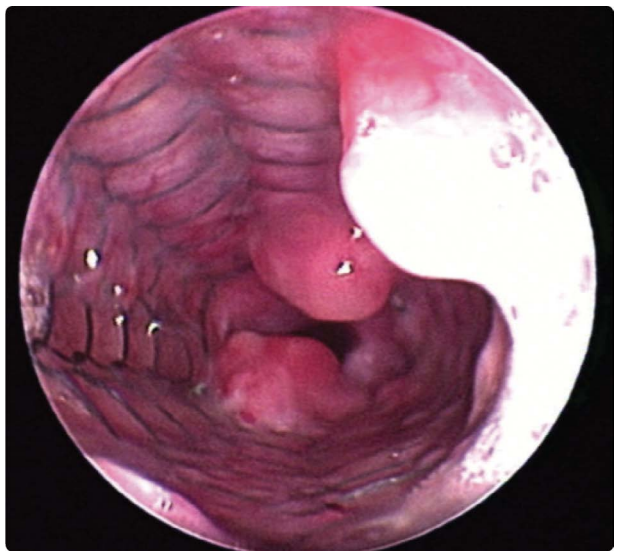


FIGURE 6.18 Endoscopic view of the trachea of a dog 6 months after stent placement, showing exuberant granulation tissue filling most of the tracheal lumen.

TRACHEAL INJURIES (CATS)

Definition/Overview

Tracheal injuries range from small lacerations to tracheal avulsions and can be caused by intraluminal or external trauma. Intraluminal trauma is mostly associated with endotracheal intubation, while external trauma is most commonly the result of blunt trauma to the thorax. Often the diagnosis and treatment are delayed, resulting in attempted surgical repair months or even years after the injury.

Etiology

Stenosis occurs after laceration, necrosis, or rupture following endotracheal intubation associated with over inflation of the endotracheal tube cuff. A blunt traumatic incident to the neck or thorax or both probably includes a hyperextension injury of the head and neck. This stretches the trachea and ruptures it intrathoracically.

Pathophysiology

After the avulsion injury, the airway lumen is thought to be maintained by either intact tracheal adventitia or by thickening of mediastinal tissue, leading to the development of a pseudoairway. Rupture and avulsion of the trachea result in stenosis of the lumen at both ends of the injury.

Clinical Presentation/Diagnosis

Apart from some possible cough, clinical signs of inspiratory distress and tracheal stridor are delayed and are due to tracheal obstruction. In acute cases, subcutaneous emphysema can be seen over the cervical and

thoracic areas due to air escaping from the trachea into the subcutaneous tissue.

Diagnosis is confirmed by thoracic radiography and tracheoscopy.

Management/Prognosis

Surgical management consists of resection of the stenosed end(s) of the injured trachea and subsequent repair by anastomosis. The prognosis is good.

TUMORS

Intratracheal tumors are rare. The tracheal lumen can also be reduced by an extrathoracic tumor, such as a mediastinal tumor, which will cause deviation or compression of the trachea.

LOWER AIRWAY AND LUNG DISORDERS

APPROACH TO PATIENTS WITH LOWER AIRWAY AND LUNG DISEASE

Diagnosis of lower airway disease is based on history, physical examination, blood testing, radiography, ultrasonography, CT, and on more invasive techniques (e.g., transtracheal aspiration, bronchoscopy and bronchoalveolar lavage [BAL], transthoracic fine-needle aspiration, transthoracic or open-chest lung biopsy). Pulmonary function tests are not commonly used.

Signalment, origin, present environment, vaccination, and prior medical problems must be assessed before detailing the current complaint and previous treatment. Signs typical of lower respiratory tract (LRT) disease include cough, exercise intolerance, dyspnea, hypoxemia, cyanosis, and systemic signs such as anorexia, depression, weight loss, and fever. Determination of the type of breathing pattern is provided by inspection of the thorax. Respiration should be observed for rate, depth, and regularity. Increased respiratory rate, which is sometimes the only visible sign, may be difficult to differentiate from stress-induced polypnea. Careful and symmetrical auscultation of the lung fields may indicate increased normal breath sounds, crackles, and wheezes as well as silent areas. The thorax should be percussed to assess resonance. A dull note will be obtained with significant lung consolidation and pleural effusion. Again, comparison of percussion notes obtained on the left and right sides is essential, especially in cases where there is a unilateral thoracic problem.

Noninvasive methods include radiography, ultrasonography, and CT. Radiography is still the preferred initial diagnostic test in respiratory medicine. Thoracic radiographs are absolutely essential for proper evaluation of dogs and cats with bronchopulmonary diseases. Thoracic radiographs should be obtained and interpreted before doing any other more invasive procedure. Correct radiographic technique, knowledge of thoracic anatomy, and skilled radiographic interpretation will maximize the amount of information derived from radiography.

Ultrasonography is used to evaluate pulmonary mass lesions adjacent to the body wall and consolidated lung lobes. The consistency of the lesions can often be determined (solid or fluid-filled), and vascular structures may be visible, which can help diagnose lung lobe torsion. It can also be used to guide biopsy instruments into solid masses for specimen collection. Point-of-care ultrasound (POCUS), including lung ultrasound (LUS), is gaining interest in veterinary medicine. Abnormalities found on LUS in dogs with various underlying causes of cough in the canine have recently been described. Echocardiography helps distinguish respiratory from cardiac diseases. High-resolution CT is used for evaluation of patients with intrathoracic diseases (e.g., interstitial pulmonary diseases such as idiopathic pulmonary fibrosis or lung lobe torsion) or for determining the extent of intrathoracic mass lesions before considering surgery.

More invasive techniques for cell and tissue sampling include transtracheal wash, endotracheal tube bronchial wash, bronchoscopy with BAL, percutaneous fine-needle aspiration, and lung biopsy obtained through surgical or endoscopic thoracic exploration.

Bronchoscopy allows for examination of the tracheobronchial tree and identification and localization of structural abnormalities of the major airways. It can detect the presence of mucus, pus, or hemorrhage in the airways. It is also used to assess for intraluminal foreign bodies, granulomas, neoplasia, and parasites. It allows for the detection of abnormal mucosal surfaces (Figure 6.19) as well as the presence of bronchiectasis and airway patency.

Specimen collection techniques performed in conjunction with bronchoscopy include BAL and various mucosal biopsy techniques. The latter include periendoscopic pinch mucosal biopsy, periendoscopic mucosal



FIGURE 6.19 Bronchoscopic view of a dog with eosinophilic bronchopneumopathy showing the thickened and polypoid appearance of the bronchial mucosa.

brush for cytologic smears, and transbronchial biopsy. A familiarity with the bronchoscopic anatomy of bronchopulmonary structures is helpful. An endobronchial nomenclature for a systematic evaluation of the canine and feline airway systems has been proposed. The nomenclature enables the bronchoscopist to locate the lesions, correlate bronchoscopic and diagnostic imaging findings, and assess the lesions throughout the course of the disease. The procedure also allows for photography of the lesions. Animals undergoing bronchoscopy require general anesthesia, even though they are at increased risk of anesthetic complications. Allowing for the delivery of oxygen before, during, and after the procedure helps avoid oxygen desaturation but does not remove the risk of iatrogenic pulmonary decompensation. Other concerns include the expense of the equipment and the need for proper training of the bronchoscopist. A pediatric bronchoscope (diameter of about 3.6–5.0 mm) is the preferred equipment for this procedure. Bronchoscopes are expensive, delicate, and fragile and need to be handled, used, and cleaned with the utmost care. Additional equipment for optimal sampling includes brush catheters and biopsy and retrieval forceps. If available, the endoscope should be connected to equipment with video projection capability.

In cats with chronic cough and/or dyspnea, the procedure is considered less safe than in dogs, mainly due to the small size of their airways and the greater degree of airway irritability. The procedure can be performed rapidly by a skilled, experienced endoscopist, which limits the risks to the patient.

The risk-to-benefit ratio should be evaluated before each endoscopy. BAL can be performed with or without an endoscope. The procedures require anesthesia, preoxygenation, and in cats premedication with a bronchodilator such as a single 100 μg puff of aerosolized albuterol, administered through an inhaler and a face mask, or terbutaline orally. Pulse oximetry should be available throughout the procedure until full recovery. When performing bronchoscopic BAL, several small aliquots of warmed sterile saline, using either weight-adjusted (2 mL/kg) or fixed-amount volumes of lavage fluid, are instilled either into the channel of the endoscope or through a sterile catheter passed into this channel. It is important that the endoscope is properly cleaned and disinfected, including the insertion and retrieval channels, prior to each procedure. Nonetheless, contamination of the endoscope by colonizing bacteria is not uncommon, and this possibility should always be kept in mind while interpreting microbiological results from BAL fluid analysis.

Alternatively, endotracheal tube bronchial washing or a tracheal wash (TW) can be performed to obtain a bronchial fluid specimen. A sterile catheter is passed through the endotracheal tube, or it can be inserted between two tracheal rings into the distal trachea. The recommended volume of fluid varies among different authors, with each aliquot ranging from 5 to 15 mL. A smaller volume consisting of 0.5 mL/kg is likely to cause less bronchospasm in cats and small breeds of dogs. For medium- to large-sized dogs, the lavage volume can range from 5 to 40 mL or approximately 2 mL/kg. The fluid is instilled through the catheter and immediately aspirated. The technique provides fluid and cells that can be used to identify diseases involving the major airways while bypassing the normal flora and debris of the oral cavity and pharynx. The advantages of this technique compared with BAL are that the procedure is inexpensive and minimally invasive. The procedure can be performed in awake or sedated animals. Potential complications are rare and include tracheal laceration, subcutaneous emphysema, and pneumomediastinum. Disadvantages are that the lesions and site of sampling cannot be visualized, and the TW fluid analysis is less likely to identify interstitial, alveolar, or focal disease processes compared with BAL fluid analysis.

Both BAL and TW fluids are evaluated cytologically and microbiologically and, therefore, should be collected before initiation of antibiotic treatment whenever possible. Semiquantitative bacterial culture allows for identification of organisms and antimicrobial susceptibility testing. Healthy dogs and cats have bacteria in their airways that can be cultured. Therefore, the significance of organisms must be interpreted in conjunction with the cytologic findings and other clinical data. Cells collected in BAL and TW fluids are fragile and must be quickly and meticulously processed. Nucleated cell counts and differential cell counts are performed. The cells are evaluated qualitatively for determination of the type of inflammation (neutrophilic, eosinophilic), evidence of macrophage activation, neutrophil degeneration, lymphocyte reactivity, characteristics of malignancy, and presence of infectious agents.

Transthoracic needle biopsy is very useful in identifying diffuse interstitial peripheral lesions and solitary lesions of the lung that are located adjacent to the thoracic wall. It also allows for sampling and identification of infectious agents. Samples can be collected using large-bore biopsy or fine-needle aspiration techniques. The site for sampling must be carefully selected radiographically, and the accuracy of sampling can be improved by using ultrasonograhic guidance. In most cases, this technique does not require general anesthesia and does not require expensive or sophisticated material. Potential complications with fine-needle aspiration, although rare, include pneumothorax, hemoptysis, and bleeding.

Open-chest biopsy is a diagnostic test of last resort because of the invasiveness, cost, degree of morbidity, and danger of mortality associated with this technique. It is advised when exploratory thoracotomy might also be therapeutic or when it will result in confirmation of a negative prognosis (diffuse metastasis) and justification for euthanasia during surgery.

Video-assisted thoracoscopy, allowing lung biopsy as well as therapeutic procedures, is a very helpful technique since it is much less invasive than open-chest procedures but offers the same advantages of direct visualization and sampling of the lesion. However, this technique requires special skills and expensive equipment, thus limiting its availability.

Pulmonary function tests can be useful in the diagnosis and evaluation of patients with pulmonary disease. LRT diseases can result in inadequate oxygenation due to decreased ventilation, improper matching of ventilation and perfusion within the lung (V/Q mismatching), and interference with the diffusion of gases across the alveolar membrane. Diseases in small animals can affect these two major physiological functions. Blood gas measurement and calculation of alveolar and arterial oxygen concentrations (A–a gradient) is currently available for assessment of impaired lung function with regard to gas exchange. Normal PaO_2 values range from 80 to 100 mmHg. Hemoglobin saturation with oxygen, and thus whole blood content, does not begin to decrease greatly until the PaO_2 falls below 60 mmHg. Other pulmonary function tests are difficult to apply in veterinary medicine because most of them depend on patient cooperation during the testing procedure or require expensive and sophisticated equipment. Among them, whole-body barometric plethysmography and tidal breathing flow volume loops have been used with some success in both awake, unrestrained cats and dogs. Pulmonary scintigraphy is another noninvasive technique used to assess pulmonary ventilation and perfusion. However, such tests are not routinely available to most veterinarians. Another noninvasive functional testing that is more readily available in practice is the 6-minute walk test.

CANINE INFECTIOUS RESPIRATORY DISEASE COMPLEX IN YOUNG DOGS ("KENNEL COUGH")

Definition/Overview

Canine infectious respiratory disease (CIRD) complex is also known as "kennel cough." The disease is commonly seen in young dogs that have been in boarding kennels. This contagious disease is often self-limiting in dogs, but a wide range of respiratory signs can be found.

Etiology

Although many agents have been implicated, CIRD usually results from infection by any one or more of the following pathogens: *Bordetella bronchiseptica*, canine parainfluenza virus, canine influenza virus, canine adenovirus, and canine respiratory coronavirus. *B. bronchiseptica* is a Gram-negative, aerobic coccobacillus that is recognized as a primary cause of respiratory disease in dogs. It can also be a serious complicating factor in dogs simultaneously infected with a viral pathogen. *Bordetella* and canine parainfluenza virus have commonly been described as the principal pathogens recovered from dogs involved in CIRD outbreaks.

Pathophysiology

Adherence of *B. bronchiseptica* to cilia via adhesion molecules, induction of ciliostasis, and damage to ciliated epithelium have been implicated in the pathogenesis of *Bordetella* infection. Given the ability of this bacterium to regulate its virulence and the likelihood that co-infected dogs tend to experience more serious clinical disease than dogs infected with single agents, viral coinfection could influence *B. bronchiseptica* virulence and clinical manifestations of CIRD in an individual patient.

Young dogs are more susceptible, especially those housed within a high population density environment, since the viruses and *Bordetella* are highly contagious. Despite the widespread availability of *Bordetella* vaccines, the disease is still common.

Clinical Presentation

CIRD is often self-limiting in dogs. In the typical infection, a mild dry cough is the only clinical symptom. However, infection with *Bordetella* can elicit a chronic cough that is more challenging to cure. Respiratory signs may range from mild illness to severe life-threatening pneumonia.

Diagnosis

Diagnosis of bordetellosis relies on positive bacterial culture or, more recently, on positive PCR from BAL fluid. Several laboratories offer PCR testing; however, studies investigating the reliability of this method are lacking. It is difficult to interpret the significance of a positive PCR test result for this disease because *B. bronchiseptica* can be commonly isolated from the URT of clinically healthy dogs, in addition to the fact that a recovered asymptomatic dog may still shed the organism for several weeks. Finding pleiomorphic cocci or coccobacilli adhering to the cilia of the epithelial cells is reported to be a characteristic cytologic feature (Figure 6.20).

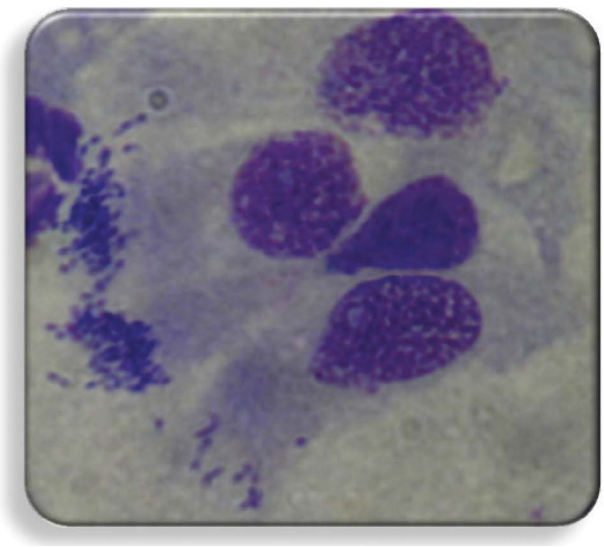


FIGURE 6.20 Pleiomorphic cocci or coccobacilli found adhering to the cilia of the epithelial cells in a dog with bordetellosis.

Management

Treatment generally consists of empirical antimicrobial therapy. Doxycycline is one of several drugs that can be used effectively. Dogs that are unresponsive to oral or parenteral antibiotics may respond to a nebulized form of administration. Aerosolized topically, nonabsorbable antibacterials such as gentamicin have been shown to be effective in reducing the population of *B. bronchiseptica* organisms in the trachea and bronchi of infected dogs.

BACTERIAL BRONCHOPNEUMONIA

Definition/Overview

Bronchopneumonia of bacterial origin is much more frequently diagnosed in dogs than in cats, although it might be underdiagnosed in cats. In dogs, many underlying problems can be associated with bacterial bronchopneumonia.

Etiology

A wide variety of bacteria can result in bronchopneumonia, mostly as opportunistic invaders. A single pathogen such as *Escherichia coli, Pasteurella multocida*, *Staphylococcus*, *Streptococcus*, or *Klebsiella pneumoniae* can be isolated in the majority of cases, but mixed infections are common. Bacteria enter the LRT primarily by inhalation or aspiration or by hematogenous routes. Whether or not a respiratory infection will develop depends on the complex interplay of many factors, such as interference with natural defense mechanisms. Multiple host defense mechanisms exist to protect the LRT from damage secondary to inhaled materials and from possible microbial invasion. These include the mechanisms of coughing and mucociliary clearance, local immunoglobulin (particularly IgA), and cellular and humoral defense mechanisms. Macrophages are responsible for phagocytosis and intracellular killing, and inhibition of macrophage function by viral infections, such as distemper, and corticosteroid use has a major role in the development of secondary bacterial infection.

Pathophysiology

The possibility of an underlying problem should not be overlooked, since bacterial infection can complicate nearly any other respiratory disease. There are many clinical conditions that predispose animals to bacterial pneumonia, and these include viral, mycoplasmal, or fungal respiratory infections; metabolic disorders; immunosuppressive therapy; therapy with specific drugs (aspirin, digoxin); functional and anatomic disorders (obstruction of upper airways, tracheal hypoplasia, primary ciliary dyskinesia); immunodeficiency (phagocyte or lymphocyte dysfunction); and contaminated indwelling catheters. Diseases causing dysphagia, vomiting, and reduced levels of consciousness can result in foreign material being inhaled into the lung and aspiration pneumonia (AP). In AP, pulmonary bacterial infection secondary to the aspiration of foreign contents is suspected but rarely confirmed, and AP is, therefore, rarely differentiated from sterile pneumonitis.

Clinical Presentation

Animals with bacterial bronchopneumonia can present with signs typical of lower respiratory disease such as cough, exercise intolerance, dyspnea, nasal discharge, and cyanosis in addition to systemic signs of anorexia, depression, weight loss, and fever, the degree of which will vary between patients. However, none of these signs can be used to confirm or rule out bacterial pneumonia. Animals with mild or localized disease show no obvious signs. Most dogs with bronchopneumonia will cough, but many will show only labored breathing. The severity of aspiration pneumonia will vary according to the characteristics of the inspired material and the patient's health status prior to aspiration.

Diagnosis

Diagnosis of bacterial bronchopneumonia is based on history, physical examination, blood testing, lung ultrasound (LUS), and radiographic findings. Other tests such as transtracheal aspiration, bronchoscopy and BAL, and transthoracic fine-needle aspiration are used if deemed necessary. Physical examination signs can include tachycardia and weak pulses, hyperemic oral mucous membranes, and dehydration. Determination of the type of breathing pattern is useful. An increased respiratory effort with an exaggerated abdominal component is common. Nasal flaring also occurs. Auscultation can detect absent or increased lung sounds depending on the degree of pulmonary consolidation.

Thoracic radiography is an essential component of the diagnostic evaluation. The radiographs may show only an interstitial pattern early in the disease. An alveolar pattern develops as the disease progresses. Distribution of lesions may also be helpful in identifying underlying problems. Focal lesions may be associated with foreign bodies. Involvement of the dependent lung lobes commonly occurs with pneumonia with or without aspiration (**Figure 6.21**). Hematogenous-borne infections may have a caudodorsal distribution. Diagnosis may be confirmed by microbiologic and cytologic examination of material from the tracheobronchial tree or lung through aspirates, washings, or brushing performed by transtracheal aspiration, bronchoscopy, or fine-needle lung aspiration.

A CBC may reveal neutrophilic leukocytosis and left shift with monocytosis. It is not uncommon to find only a stress response or even a normal leukogram.

Adequate bronchopulmonary sampling techniques for cytologic evaluation and culture of aspirates include tracheal washing, BAL or brushing, and percutaneous fine-needle aspirations. Bacterial culture is more sensitive than cytology for identifying organisms and also allows for susceptibility testing. However, bacteria

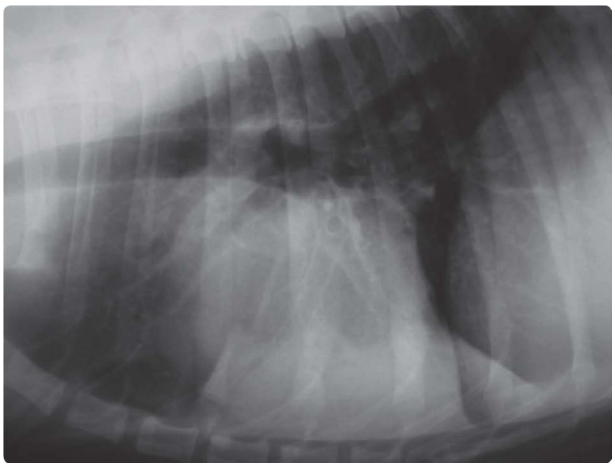


FIGURE 6.21 Thoracic radiograph of a dog with aspiration pneumonia showing ventral distribution of an alveolar pattern with air bronchograms and lobar signs.

can be cultured from the airways of healthy dogs. This microbial population has the potential to cause or complicate respiratory infections and clouds the interpretation of airway and lung cultures. Therefore, the significance of organisms must be interpreted in conjunction with the cytologic findings and other clinical data. Quantitative culture of BAL fluid is advised, since only a significant bacterial growth (1.7×10^3 colony forming units per milliliter of BAL) allows a diagnosis of LRT infection.

Management

Antimicrobial therapy is essential for the treatment of lower airway bacterial infections. The most important criterion for selection of an antibiotic is identification of the bacterial organism and the results of sensitivity testing. There appears to be much variability in the in-vitro sensitivity of common isolates in different countries, emphasizing the importance of culture and sensitivity testing for individual patients. Broad-spectrum coverage for life-threatening infections or sepsis can be obtained using combinations of either amoxicillin–clavulanic acid and enrofloxacin or amoxicillin–clavulanic acid and an aminoglycoside. Fluoroquinolones specifically achieve excellent concentrations within the lung.

Systemic oral or parenteral antibiotics should be administered in high doses for a minimum of 2 weeks and sometimes longer (up to 4–6 weeks is recommended according to the International Society for Companion Animal Infectious Disease) so that maximum concentrations are reached in lung tissue and airway secretions. Obvious clinical improvement will optimally be noted after 3–5 days of treatment. Ideally, the animal should be re-examined weekly in order to monitor the response to treatment based on clinical and radiographic findings. Therapy may be discontinued 1 week after resolution of all clinical signs and the disappearance of the radiographic infiltrates. In AP, several studies are presently investigating the validity of a much shorter course of antibiotics based on CRP values and LUS findings.

Maintenance of normal systemic hydration is very important for mucociliary clearance and secretion mobilization. Airway hydration can also be achieved using saline aerosol therapy followed by physiotherapy (mild forced exercise, increasing cough frequency by chest wall coupage or tracheal manipulation, and postural drainage). The use of aerosol administration of antibacterials or other drugs should be restricted to cases of bordetellosis.

Animals with severe tachypnea, dyspnea, or hypoxemia (PaO_2<60 mmHg) require oxygen therapy. The oxygen should be humidified to prevent drying of respiratory membranes. Oxygen can be administered by oxygen cage, mechanical ventilator, intratracheal cannula, or nasal catheter. Antitussives and antihistamines that inhibit mucokinesis and exudate removal are contraindicated with bacterial pneumonia.

Although the value of expectorant therapy (saline expectorants, guaifenesin, and inhaled volatile oils that are inhaled) has not been scientifically demonstrated, their use can be beneficial.

Pulmonary lobectomy can be an alternative in the management of pneumonia in dogs, especially if a diagnosis of abscessation is suspected or if a lesion does not resolve after several months of aggressive adequate antibiotic therapy.

Prognosis

Bacterial pneumonias are generally responsive to appropriate antibiotic therapy and supportive care. The severity and the chronicity of the infection, the presence of an underlying disease, and the development of complications can affect the long-term prognosis. Potential reasons for failure are many. They may be related to the organism involved (not sensitive to the antibiotic used or capable of developing resistance) or to the antibiotic itself. Failures attributable to the drug may relate to the dosage regimen, spectrum of activity, or ability to achieve effective concentration. Other causes of failure include inaccurate diagnosis or existence of an undiagnosed underlying disorder.

PRIMARY CILIARY DYSKINESIA

Definition/Overview

Primary ciliary dyskinesia (PCD), previously referred to as immotile cilia syndrome, results from a heterogeneous group of inherited diseases that cause defective ciliary motility mostly associated with ultrastructural abnormalities. It is a predisposing cause of recurrent bacterial pneumonia. In dogs, as in humans, the ineffectiveness and incoordination of ciliary function result in ineffective clearance of mucus from the airways, which in turn results in chronic mucus plugging and inflammation of nasal cavities and airways. Kartagener syndrome represents a triad of signs that includes bronchiectasis, complete transposition of viscera (situs inversus), and

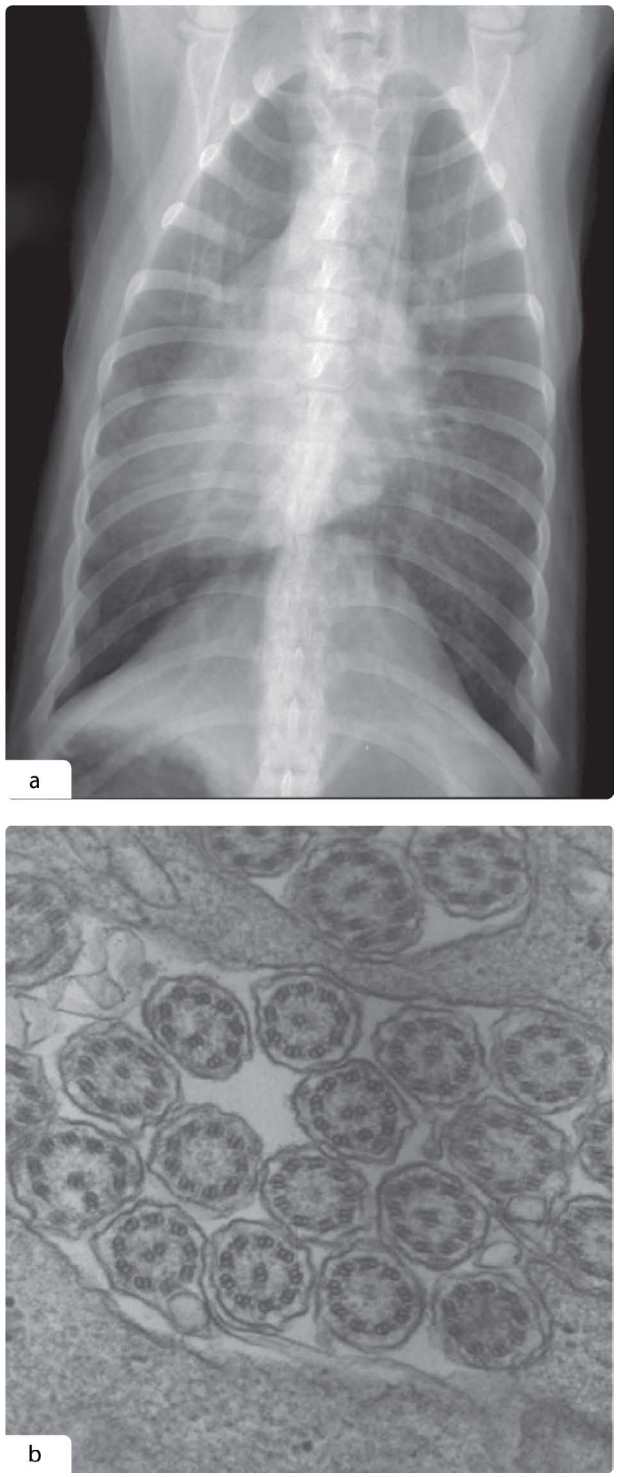


FIGURE 6.22 Old English Sheepdog with primary ciliary dyskinesia associated with situs inversus. **(a)** Dorsoventral thoracic radiograph. **(b)** Transmission electron microscope image of transverse sections of cilia showing a primary defect (absence of the central pair of doublets) and many secondary defects.

chronic rhinosinusitis (Figure 6.22a, b). This syndrome has been reported in humans and in dogs with PCD. In dogs, PCD is a rare disease that has been reported in more than 19 breeds.

Etiology

Currently, PCD-causing mutations have been identified in 20 human genes. Each causative gene can be associated with particular ultrastructural ciliary defects, and these 20 genes only explain 50% of human PCD cases; more genes need to be identified. In dogs, a recent mutation in a new causative gene (CCDC39) has been identified in the Old English Sheepdog. This new mutation is dispersed in a significant worldwide population and is responsible for PCD in this breed. A new genetic test has been developed and is currently available for breeding purposes.

Clinical Presentation

As a consequence of impaired mucociliary clearance, clinical signs include chronic respiratory abnormalities such as rhinosinusitis, bronchitis, bronchopneumonia, and bronchiectasis. Although the respiratory system signs are usually the presenting complaint, other signs related to pathology in other tissues with ciliated epithelia or microtubules can occur, such as otitis media, infertility in females, asthenoteratospermia in males, hydrocephalus, and renal fibrosis or dilation of renal tubules. The signs typically begin at an early age in a purebred vaccinated dog; however, some dogs have remained asymptomatic until several months to several years of age. Hallmark clinical features (i.e., recurrent bilateral nasal discharge and repeated episodes of bronchitis or bronchopneumonia since birth) should alert the clinician to include PCD in the differential diagnosis.

Diagnosis

Finding the hallmark clinical features in combination with situs in versus is even more suggestive. Most other potential possible causes should be excluded by a complete physical examination as well as currently available complementary tests. Confirmation of a diagnosis of PCD requires both in-vivo and in-vitro functional and ultrastructural analysis of cilia. Scintigraphy can be used for in-vivo functional analysis of mucociliary clearance. In-vitro functional analysis in PCD consistently demonstrates an uncoordinated or a dyskinetic ciliary beat. Transmission electron microscopy can reveal specific ultrastructural abnormalities, although regularly the distinction between PCD and secondary ciliary defects (caused by another primary disease) based on ultrastructural findings is difficult.

Other causes of recurrent bacterial infection of the lower airways should be investigated, such as the presence of an immune deficiency, a resistant bacterium, a bronchial foreign body, or any other predisposing cause. In Irish Wolfhounds, a rhinitis/bronchopneumonia syndrome characterized by transient to persistent mucoid or mucopurulent rhinorrhea, cough, and dyspnea since an early age has been described; so far, PCD has not yet been formally identified as the cause of the disease in this particular breed.

Management

Even though PCD is not a curable disease, it can frequently be managed for some years. A key element in successful management is adequate monitoring of infecting microorganisms and judicious use of antibiotics over time. Moreover, a regular routine consisting of good systemic and local hydration, daily coupage, and vigorous exercise will help to clear mucus from the airways.

Prognosis

The long-term prognosis is poor, since even in cases with adequate management the disease generally progresses over time, and the response to treatment worsens. It would be very useful to have a genetic test able to identify carriers in order to prevent their use for breeding.

PARASITIC BRONCHOPNEUMOPATHY IN DOGS, ANGIOSTRONGYLOSIS (FRENCH HEARTWORM DISEASE)

Definition/Overview/Etiology

The nematode worm *Angiostrongylus vasorum* is an emerging disease, with reported increases in both distribution and incidence in the United Kingdom, Europe, South Africa, and Canada. The expanding geographic range might be related to the influence of the climate on parasite distribution.

The worm infects dogs and foxes and is spread through ingestion of intermediate hosts, including slugs and snails harboring infective third-stage larvae. The adult parasites live in the pulmonary arteries and the right ventricle of the heart. The prepatent period is 40–60 days.

Respiratory disease results from the inflammatory response induced by migration of the larvae, causing granulomatous pneumonia and probably thrombotic disease.

Clinical Presentation

Infection seems more common in outdoor young dogs, especially those playing with/eating slugs. Dogs are presented for a combination of signs, including cough, exercise intolerance, respiratory distress, coagulopathy (hemoptysis, bleedings), lameness, neurologic signs, and syncope. However, clinical signs may be variable and range from subtle and chronic to more acute and severe.

Diagnosis

Eosinophilia, thrombocytopenia, and hyperglobulinemia are relatively common. Thoracic radiographs generally show an interstitial and/or alveolar pattern, most often present in the dorsocaudal lung fields. Definitive parasitologic diagnosis relies on observation of first-stage larvae (L1) in the respiratory tract or feces, using the Baermann test. L1 are sometimes observed on airway cytology. A major limitation of the Baermann test is that L1 excretion appears to be intermittent, and infected dogs might be negative on fecal examination. A single Baermann test is likely to detect at most 50% of infected dogs, although sensitivity can be increased by serial examination (e.g., of samples collected 3 days in succession, which is not always practical).

Improved diagnostic tests are likely to emerge. Parasite proteins or DNA can be detected in blood or BAL fluid using sandwich ELISA or PCR, respectively. Serologic ELISA tests to detect host antibodies to the parasite have also been developed.

Management

Fenbendazole (25–50 mg/kg p.o. q.24h. for 7–21 days) has been the most commonly used anthelminthic drug during the last decade. Milbemycin oxime and moxidectin (e.g., Advantage Multi, a spot-on combination formulation of moxidectin plus imidacloprid) both prevent establishment of adult parasites when given during the prepatent period and substantially reduce worm burdens. However, continued monitoring after treatment is advisable, with repeated treatment as necessary. Depending on the severity of clinical signs, additional therapy with corticosteroids, IV fluid support, and oxygen can be required.

Prognosis

Dogs carrying a low worm burden may remain subclinical. The prognosis is guarded in those animals with severe respiratory signs. The disease can be fatal if left untreated.

EOSINOPHILIC BRONCHOPNEUMOPATHY IN DOGS

Etiology/Pathophysiology

Canine eosinophilic bronchopneumopathy (EBP) is a disease characterized by eosinophilic infiltration of lung and bronchial mucosa, considered to be manifestations of immunologic hypersensitivity. Although the etiology of EBP is still unknown, the association of eosinophilic infiltration with $CD4^+$ T cells favors a likely Th2 immune response mounted in the lower airways. Suspected and known causes of pulmonary hypersensitivities in humans and animals include fungi, molds, drugs, bacteria, and parasites. However, in many cases, no underlying cause is found. The role of inhaled allergens in EBP is still unclear. EBP is mostly diagnosed in young dogs. Siberian Huskies and Malamutes are predominantly affected, but many other breeds also can be affected.

Clinical Presentation

Usually, the general condition of the animal is good unless the disease is associated with concomitant bacterial bronchopneumonia. Clinical signs include mainly

cough, gagging, and retching. In acute cases, gagging and retching are sometimes the main complaint, extending the differential diagnosis to dyspeptic problems. Dyspnea is a very frequent sign. Nasal discharge (about 50% of affected dogs) is less commonly encountered.

Differential Diagnosis

Several parasites including *Strongyloides* spp., *Ascaris* spp., *Toxocara canis*, and *Ancylostoma* spp. can lead to eosinophilic pneumonia in humans and probably in dogs as well. Respiratory symptoms are mild, and gastroenterologic signs usually predominate.

In the dog, occult heartworm disease caused by *Dirofilaria immitis* can cause eosinophilic pneumonitis. Migration of larvae of *Angiostrongylus vasorum* through pulmonary parenchyma may also result in eosinophilic pneumonia in dogs. Other bronchopulmonary parasites, such as *Capillaria aerophila, Oslerus osleri, Filaroides hirthi, Crenosoma vulpis*, or *Paragonimus kellicotti*, are also implicated in the migration of eosinophils into the airways (*O. osleri*) or lungs (other parasites) in dogs and can mimic EBP.

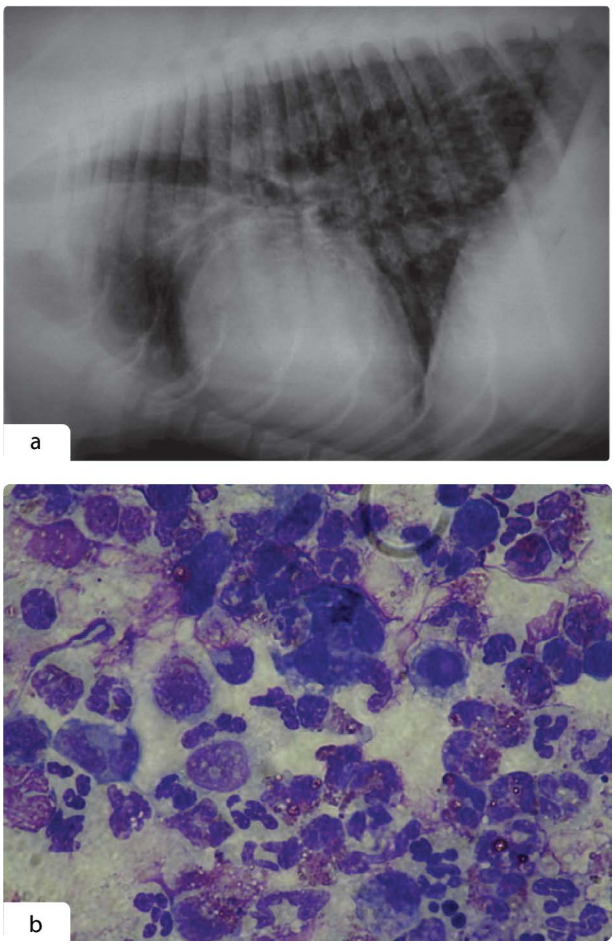


FIGURE 6.23 Four-year-old male Akita Inu with eosinophilic bronchopneumopathy. **(a)** Lateral thoracic radiograph showing a severe bronchointerstitial pattern with peribronchial infiltration. **(b)** Cytologic preparation (BAL fluid cytospin) showing 47% of eosinophils (total cell count = 7,000 cells/mL).

Diagnosis

The diagnostic workup of dogs with pulmonary disease should include a search for parasitic disease, using BAL fluid analysis or feces examination (fecal zinc sulfate centrifugation/flotation and Baermann sedimentation procedure). However, a single negative fecal examination by either method is not conclusive. The fecal examination should, therefore, be repeated, or, alternatively, the animal treated for potential parasites using a course of an appropriate anthelmintic (e.g., fenbendazole, thiabendazole, or levamisole). In endemic areas, it is strongly advised to run a heartworm antigen test to rule out occult heartworm disease.

The diagnostic criteria for the diagnosis of EBP include anamnestic factors (breed, young age, previous response to corticosteroids), clinical signs, radiographic and bronchoscopic findings, blood eosinophilia, tissue eosinophilic infiltration as demonstrated by cytologic and histopathologic examinations, response to adequate treatment, and the exclusion of other pulmonary conditions. The most common radiographic finding is a mixed moderate-to-severe bronchointerstitial pattern (**Figure 6.23a**), although some studies distinguish subgroups based on findings of thoracic imaging, from no changes to bronchial/peribronchial pattern or bronchointerstitial/interstitial/alveolar pattern. Bronchoscopy can reveal typical macroscopic features, which include the presence of abundant yellow–green mucus or mucopurulent material, severe thickening of the mucosa with irregular or polypoid surface (**Figure 6.19**), and in some cases partial airway closure during expiration. Peripheral blood eosinophilia is frequently found but not always observed. BAL fluid or brush cytology demonstrates a marked eosinophilic component (**Figure 6.23b**); frequently, more than 50% of the inflammatory cells are eosinophils. In most cases, eosinophilic infiltration of the bronchial mucosa can also be observed histopathologically in biopsy samples.

Management

The response to steroid therapy is generally very good (prednisone, initial dosage of 1 mg/kg q.12h. for the 1st week, then on alternate days during the 2nd and 3rd weeks, followed by a gradual decrease to the lowest possible maintenance dose) while achievement of long-term remission is only seen in about half of dogs.

Inhaled glucocorticoid therapy can be considered for long-term maintenance in order to help avoid the systemic complications of chronic glucocorticoid treatment, although this might not allow for complete clinical control of the disorder. This treatment modality is well tolerated, results in improvement in clinical signs and reduction in side effects, and allows for a reduction of oral steroid dosage in steroid-dependent animals.

Prognosis

Relapse frequently occurs within weeks to months after drug discontinuation, although some dogs may remain asymptomatic after discontinuing glucocorticoid treatment.

CHRONIC BRONCHITIS IN DOGS

Definition/Overview

Chronic bronchitis is mostly seen in middle-aged to old smaller breeds of dogs, but it can occur in larger breeds. It is a chronic inflammatory airway disease that results mainly in cough.

Chronic bronchitis in dogs is defined when three diagnostic criteria can be fulfilled:

- Chronic cough
- Evidence of excessive mucus or of mucus hypersecretion
- Exclusion of other chronic cardiopulmonary diseases (e.g., congestive heart failure, chronic infectious bronchopneumonia, pulmonary neoplasia, eosinophilic bronchopneumopathy)

Coexisting diseases (e.g., congestive heart failure and airway collapse) may be present and complicate diagnosis and treatment. The most common sequela is chronic airway obstruction, referred to as chronic obstructive pulmonary disease, a syndrome that is well described in humans.

ETIOLOGY

Many causes of chronic bronchitis are a result of chronic airway irritation and inflammation. The condition is usually diagnosed after a protracted period (> 2 months) of clinical signs that can result from exposure to passive smoking, excessive environmental perfumes, or atmospheric pollution.

Pathophysiology

Chronic bronchitis results in inflammatory changes within the bronchial mucosa, including increased mucus production. Bronchial wall thickening and progressive bronchomalacia contribute to airflow obstruction and further worsening of the inflammation and clinical signs, which consist mainly of a productive cough.

Clinical Presentation

Middle-aged to older smaller dog breeds are more often affected, although any dog that is exposed to chronic airway irritants or has suffered from smoke inhalation can be similarly affected. Most dogs with chronic bronchitis have a rather sonorous cough, which is followed by a retching movement.

Differential Diagnosis

Chronic cough related to specific causes should be ruled out, mainly tracheal collapse, lung fibrosis, EBP, parasitic lung diseases, bronchial or lung primary or secondary tumors, and mitral valve disease.

Diagnosis

Diagnostic tests are carried out to rule out other causes of chronic cough. The hemogram is usually normal, and thoracic radiographs show bronchial wall thickening or generalized increased airway-oriented interstitial density, or both. BAL cytology typically has excess mucus with hyperplastic epithelial cells and increased numbers of neutrophils, goblet cells, and macrophages. Echocardiography helps diagnose any concomitant disorders such as mitral valve disease and right heart enlargement associated with pulmonary arterial hypertension, which can occur secondary to chronic pulmonary disease.

Management

The bronchial alterations are not readily medically reversible. Therapy is based on an assessment of the nature and severity of the individual animal's problems and includes:

- Avoidance of airway irritants and neck compression.
- Control of body weight because obese dogs often show improvement associated with weight reduction.
- *Relief of airway inflammation:* Anti-inflammatory therapy using a low dose of glucocorticosteroids, which reduces mucus hypersecretion and mucosal bronchial wall thickening. Bronchodilators ($\beta_2$agonists, theophylline) are frequently used, although their effectiveness in the treatment of chronic bronchitis has not been widely addressed.
- Control of intractable cough (butorphanol 0.25–1 mg/kg b.i.d.).
- Control of infection and maintaining good dental hygiene.

Prognosis

Treatment can alleviate clinical symptoms, but ongoing airway disease will likely persist.

CHRONIC IDIOPATHIC PULMONARY FIBROSIS IN WEST HIGHLAND WHITE TERRIERS AND OTHER TERRIER BREEDS

Definition/Overview

Chronic idiopathic pulmonary fibrosis (IPF) in West Highland White Terriers and other terrier breeds is an emerging chronic and progressive pulmonary

condition. It has been described in middle-aged to old West Highland White Terriers but also in other young to middle-aged terrier dogs such as the Staffordshire Bull Terrier. A similar condition exists in humans. Very little is known about IPF prevalence, pathogenesis, and prognosis in dogs.

Etiology

As in humans, the etiopathogenesis of IPF in dogs is not known. There is emerging evidence for the role of genetic factors in the development of the disease. Most cases appear to be caused by an interaction between a specific environmental exposure and a genetic predisposition. In dogs, the predisposition of related terrier breeds combined with very low incidence within nonterrier breeds also strongly suggests an underlying genetic cause.

Pathophysiology

Current prevailing hypotheses for the condition focus on dysregulated epithelial–mesenchymal interactions promoting a cycle of continued epithelial cell injury and fibroblast activation leading to fibrosis. Multiple abnormalities in a myriad of biological pathways affecting inflammation and wound repair, including matrix regulation, epithelial reconstitution, the coagulation cascade, neovascularization, and antioxidants, modulate this defective process and promote fibrogenesis.

Clinical Presentation

The disease is clinically characterized by progressive dyspnea, exercise intolerance, and pronounced crackles on auscultation. General body condition is good, and dogs do not lose weight. Cough is described principally in the earliest phase of the disease. The condition might also be associated with some degree of tracheal collapse that develops secondarily in some dogs.

Differential Diagnosis

The disease is not easily distinguished from chronic bronchitis, which may coexist. In IPF, cough can be attributed to tracheal collapse, which is found in a proportion of affected dogs. Crackles might suggest cardiogenic edema; however, such a diagnosis is not compatible with other clinical findings.

Diagnosis

Radiographic, bronchoscopic, hematologic, or biochemical findings are nonspecific but help eliminate other possible disorders. Echocardiography may reveal signs of secondary pulmonary arterial hypertension. Arterial blood gas analysis shows low levels of $PaO_2$and a high alveolar–arterial oxygen gradient. Other noninvasive pulmonary function tests are rarely used in veterinary practice.

Lung imaging using high-resolution CT looks promising and is currently often used to evaluate IPF in humans. However, ultimate confirmation of the diagnosis requires (open chest) lung biopsy and histopathology. Histopathologically, the predominant changes include septal and interstitial fibrosis and pneumocyte hyperplasia.

Management/Prognosis

As the disease is a progressive condition, the long-term prognosis is poor. A mean survival time of about 18 months has been reported. The course of the disease is characterized by a slow progression together with episodes of worsening. Treatment of dogs with IPF is essentially symptomatic and supportive. Glucocorticoid drugs have been tried but have not proved beneficial, while subjecting the dog to potentially detrimental side effects.

BRONCHIECTASIS

Definition/Overview

Bronchiectasis is pathologically defined as an abnormal and permanent dilatation and distortion of subsegmental airways due to destruction of the elastic and muscular components of the bronchial walls. Several congenital or acquired conditions that lead to a cycle of chronic airway infection and inflammation may result in bronchiectatic changes.

Bronchiectasis can be accompanied by bronchomalacia, marked during the expiration phase.

Etiology/Pathophysiology

Focal bronchiectasis most often results from foreign body aspiration. Diffuse bronchiectasis often occurs subsequent to aspiration or inhalation injury, primary ciliary dyskinesis, infection with *Bordetella bronchiseptica* or *Pneumocystis carinii* (in relation to immune deficiency), eosinophilic bronchopneumopathy, and chronic bronchitis. Affected airways are usually partially obstructed by purulent or viscid exudates, since the dilation greatly interferes with normal airway clearance. Dysfunction of mucociliary clearance allows pooling of mucus, exudates, and microbes, which eventually leads to secondary infection and its accompanying inflammatory response, creating a vicious cycle of further damage to the airway wall and predisposition to recurrent bronchopulmonary infections.

Clinical Presentation/Diagnosis

There appears to be a breed predilection, since bronchiectasis is more prevalent in certain breeds such as the American Cocker Spaniel, Miniature Poodle, Siberian Husky, and English Springer Spaniel. Most dogs with bronchiectasis are 7 years of age or older. The clinical signs are typical of chronic bronchial disease and include cough, gagging, tachypnea, dyspnea, and occasionally fever.

Diagnosis

Bronchiectasis can be detected by thoracic radiography, high-resolution CT, or bronchoscopy.

Management

Treatment is the same as for chronic bronchitis, but the disease is more difficult to control. The goal of therapy is to control clinical signs and eliminate any bacterial infections. Removing any likely pulmonary irritants from the dog's environment is essential to slow the progression of bronchial wall destruction. Dogs with bronchiectasis may survive for years despite substantial clinical abnormalities. Patients with focal bronchiectasis might benefit from surgical resection of the pathologic lung lobe.

PULMONARY CONTUSIONS

Etiology

Pulmonary contusion is caused by blunt trauma. It is a common finding in dogs that have received thoracic trauma and can be associated with pneumothorax, pneumomediastinum, rib fracture, and many other adverse effects of the traumatic insult. Hemorrhage into the interstitium and alveoli occurs, usually in localized lung regions.

Clinical Presentation

Generally, there is historical and physical evidence of trauma. Increased respiratory efforts are usually obvious, but the clinical picture will depend on the effects of other ongoing injury.

Diagnosis

Alveolar infiltrates are seen on thoracic radiographs along with other signs of thoracic injury. They include large, localized areas of alveolar and interstitial opacities. Note that pulmonary hemorrhage can also occur from anticoagulant rodenticide ingestion. The history, absence of other signs of trauma, and abnormal blood clotting times will distinguish this from traumatic pulmonary contusions.

Management

Dogs should first be treated for life-threatening, trauma-related problems. Decreased physical activity and cage rest in a 40% oxygen-enriched environment is advised. Oxygen can also be provided with nasal cannulation. Pulmonary contusion will begin to show radiographic resolution after 3–5 days.

Prognosis

Prognosis varies from good to guarded depending on the extent of the injuries. Progression of pulmonary injuries to acute respiratory distress syndrome is an ominous complication.

FELINE BRONCHIAL SYNDROME

Definition/Overview

Cough is an infrequent clinical sign in cats. It is fairly specific for tracheobronchial disease in cats since cough of cardiac origin is rare. Feline bronchial disease (feline asthma or bronchitis) is characterized by inflammation of the lower airways without an obvious identifiable cause. Many other terms are found in the literature such as chronic bronchitis, allergic bronchitis, eosinophilic bronchitis, and bronchial asthma. It is recognized clinically with signs of cough, wheezing, exercise intolerance, and respiratory distress attributable to airway obstruction caused by bronchial inflammation.

Etiology

Feline asthma is thought to be an allergic disorder based on the associated tissue pathology and the response to glucocorticoid drugs, although it might be difficult to distinguish the condition from other types of chronic airway disease.

Pathophysiology

Clinical signs are related to reversible airway inflammation and obstruction linked to hyper-reactivity and smooth muscle hypertrophy, excessive mucus production (mucous gland hypertrophy) and accumulation, and bronchial wall edema. These changes are often reversible. However, chronic inflammation can lead to severe lower airway obstruction, which causes lung hyperinflation and air trapping. Lung hyperinflation may lead to permanent pathology, evidenced by progressive airway remodeling, including bronchiectasis, fibrosis, or emphysema. Sometimes reversible atelectasis can occur.

Clinical Presentation

Young to middle-aged cats are most commonly affected. The clinical signs are cough and increased breathing effort, which can vary in severity. The signs are often chronic or slowly progressive. Mildly affected cases may only have occasional and brief episodes of cough separated by long periods without symptoms, while in moderately or severely affected cases, cough occurs daily, and cats may have a decreased quality of life with breathing discomfort. Cats with severe exacerbations (also called "asthmatic crisis") may present acutely with open-mouth breathing, dyspnea, and cyanosis. Exacerbation may occur in association with exposure to potential allergens or irritants or after stress or exercise.

Differential Diagnosis

Includes any disease that can affect the feline airway. Pulmonary parasitic diseases, including infection with *Aelurostrongylus abstrusus* and *Dirofilaria immitis* (in endemic regions), will result in similar clinical findings including eosinophilic airway inflammation.

Diagnosis

Physical examination in the asymptomatic cat can be normal at rest, but those with active disease will show a prolonged expiratory phase of breathing with auscultable wheezes or crackles. The classic radiographic pattern with established disease includes signs of bronchial wall thickening (doughnuts or railroad tracks) and air trapping (increased lucency and flattening of the diaphragm). Some cats will have a right middle or some other lung lobe atelectasis.

The hemogram can range from normal to having an eosinophilia. Other abnormalities include a stress leukogram, a secondary polycythemia, or hyperglobulinemia. Fecal and blood smear examinations are recommended as part of the diagnostic workup in order to exclude a parasitic origin for the eosinophilic infiltration (*Aelurostrongylus* and *Dirofilaria*, respectively).

Cytologic examination of airway samples obtained by BAL or endotracheal wash generally provides evidence of airway inflammation, with increased numbers of eosinophils and/or neutrophils. Although a preponderance of eosinophils may be found in fluids from healthy cats, the number of eosinophils and neutrophils in BAL fluid has been shown to correlate with disease severity, both in cats with spontaneous disease and in those with experimentally induced bronchial disease. Feline asthmatic disease is primarily characterized by a predominance (as high as 17%) of eosinophils identified in the BAL fluid. Culture of BAL fluid and PCR for *Mycoplasma* detection can be useful, but its presence does not necessarily signify it being the cause of the airway disease. Feces examination (fecal floatation and Baermann) and heartworm antibody/antigen testing can help detect heartworm disease or *Toxocara cati* and *Aelurostrongylus abstrusus*.

Pulmonary function testing is not commonly used in the diagnostic assessment of cats with bronchial disease.

Management

Stress should be minimized, and an oxygen-enriched environment provided when managing any cat with acute respiratory distress. Parenteral therapy with beta-agonist bronchodilators such as terbutaline (0.01 mg/kg IV, IM, or SC) and a rapidly acting corticosteroid (e.g., dexamethasone, 0.25 mg/kg IV or IM) should be administered. Inhaled bronchodilator medication can be used as well.

Most retrospective studies involving cats with lower airway disease have documented a beneficial response to oral or parenteral glucocorticoids and/or bronchodilators. An initial dose of prednisone or prednisolone beginning at 1–2 mg/kg q.24h. over a 2-week period followed by a gradual tapering dose over another 2-week period has been shown to be a consistent, reliable, and effective treatment. Bronchodilators, such as inhaled salbutamol and albuterol, are very useful to alleviate acute clinical signs, but as they fail to control airway inflammation, they should not be used without glucocorticoid drugs.



FIGURE 6.24 Inhaled steroid therapy for a dog with a chronic cough using a spacer and face mask. (Aerokat, Trudell Medical International, Ontario, Canada.)

The use of inhaled medication using a face mask and spacing chamber (Figure 6.24) is popular. Medications given via inhalation offer the advantage of providing high drug concentrations within the airways while attenuating systemic side effects. Long-term treatment with inhaled corticosteroids (e.g., fluticasone propionate) and bronchodilators (e.g., albuterol) is the preferred medication.

RECOMMENDED FURTHER READINGS

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CHAPTER

7

Diseases of the Pleural Space

J. Brad Case

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PNEUMOTHORAX

Definition/Overview

Pneumothorax is a common disease among dogs and cats and is characterized by an accumulation of air in the pleural space and subsequent restriction to pulmonary inflation. The result is hypoxemia, which can be severe in many cases and eventually cause death of the animal.

Etiology

Two broad etiologic categories are recognized in dogs and cats: Traumatic and spontaneous pneumothorax. Traumatic pneumothorax (closed or open chest) is seen most commonly after blunt automobile trauma but is also observed following thoracic penetrating trauma (e.g., bite, gunshot, porcupine quill wounds). In contrast, spontaneous pneumothorax is not associated with thoracic wall trauma or any observed inciting cause. Subpleural blebs (Figure 7.1) and pulmonary bullae (Figure 7.8a, b) are the most common causes of spontaneous pneumothorax, but parasitic, infectious, and neoplastic diseases have also been documented. Disease-specific etiologies are summarized in Table 7.1.

Pathophysiology

Pulmonary expansion and effective gas exchange at the blood–pulmonary interface is dependent on a negative intrapleural pressure gradient. With significant pneumothorax, this pressure gradient is lost, and the lungs do not expand with air. This in turn limits the transfer of oxygen and other gases to and from the systemic arterial circulation, ultimately resulting in hypoxemia.

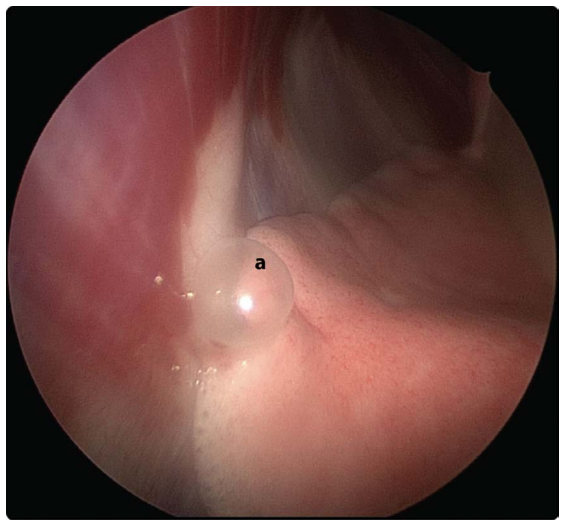


FIGURE 7.1 Thoracoscopic image of a subpleural bleb (a) in a dog with spontaneous pneumothorax.

Clinical Presentation

Dogs and cats with pneumothorax typically present with varying degrees of dyspnea, tachypnea, and restlessness. Dyspnea in animals with acute trauma should raise the index of suspicion for pneumothorax, and prompt support, therapy, and diagnostics should be performed. In most cases of closed traumatic pneumothorax, an obvious thoracic wound or communication with the pleural space will not be present. Furthermore, up to 50% of dogs with traumatic pneumothorax will also have significant concurrent musculoskeletal injuries. Animals with spontaneous pneumothorax often present with mild-to-moderate dyspnea and tachypnea with no other concurrent clinical signs.

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TABLE 7.1 Causes of pleural space diseases

Pneumothorax
- Traumatic closed chest (blunt trauma)
- Open chest (penetrating projectiles, bites, automobile)
- Spontaneous (bullae, blebs, foreign bodies, bronchoesophageal fistula, abscess, bronchiectasis, pneumonia)

Pyothorax
- Pneumonia
- Bronchiectasis
- Foreign body
- Esophageal perforation
- Trauma
- Surgical
- Chest drain
- Feline infectious peritonitis/feline leukemia virus
- Abscess (common causative agents: *Actinomyces* spp., *Nocardia* spp., *Filifactor* spp.)

Chylothorax
- Idiopathic
- Lung lobe torsion
- Neoplasia
- Traumatic cardiomyopathy
- Pericardial disease
- Heartworm disease

Lung lobe torsion
- Spontaneous
- Neoplasia
- Pneumonia
- Pleural effusion
- Surgery

Diaphragmatic herniation
- Traumatic
- Congenital

Thoracic neoplasia
- Hemangiosarcoma
- Lymphosarcoma
- Osteosarcoma
- Chondrosarcoma
- Carcinoma
- Mesothelioma
- Lymphoma and others

Differential Diagnosis

See Tables 7.2 and 7.3.

Diagnosis

Diagnosis of pneumothorax is made either by visualization of a full-thickness thoracic wall lesion, thoracic radiography, or thoracocentesis. However, it is important that the examining clinician prioritize stabilization of the patient prior to thoracic radiography, as sudden stress can exacerbate the condition and lead to rapid deterioration of the patient. Typical survey radiographic findings include regions of radiolucency in the pleural cavity, which abut retracted lung lobes, and dorsal elevation of the cardiac silhouette off the sternum on the lateral projection (Figures 7.2–7.4). CT (Figure 7.5) is useful for identifying accompanying orthopedic injuries, bronchiectasis, neoplasia, and, in some cases, pulmonary foreign bodies. However, in most instances of spontaneous pneumothorax, it is associated with a low sensitivity and negative predictive value.

TABLE 7.2 Differential diagnosis of pleural versus pulmonary parenchymal and vascular diseases

Reduction of thoracic capacity
- Pleural effusions
  - Hydrothorax
  - Hemothorax
  - Chylothorax
  - Pyothorax
  - Neoplastic
  - Inflammatory
- Pneumothorax
- Diaphragmatic rupture/hernia
- Cardiac enlargement
- Intrathoracic masses
- Abdominal masses/fluid

Loss of pulmonary exchange capacity
- Bronchopneumonia
- Pulmonary edema
- Pulmonary hemorrhage/contusion
- Metastatic neoplasia
- Pulmonary emphysema
- Idiopathic pulmonary fibrosis
- Pulmonary thromboembolism
- Paraquat poisoning

Management

Initial stabilization of the patient is essential regardless of the ultimate management strategy (medical or surgical). Oxygen supplementation is administered and therapeutic thoracocentesis performed. The patient is then monitored for signs of worsening dyspnea. If dyspnea is progressive, a thoracostomy tube is placed. In the case of

TABLE 7.3 Types and causes of pleural effusion

Transudate
- Hypoproteinemia (gut or urine loss, severe liver disease)

Modified (protein-rich) transudate
- Congestive cardiac failure, particularly in cats
- Neoplasia (particularly cranial mediastinum, thoracic wall)
- Lung lobe torsion
- Diaphragmatic rupture and incarceration of liver

Hemothorax
- Trauma
- Coagulopathies
- Neoplasia
- Anticoagulant rodenticide

Chylothorax
- Trauma
- Neoplasia
- Congestive heart failure, especially in cats
- Heartworm disease
- Infections
- Lung lobe torsion
- Idiopathic

Pyothorax
- *Nocardia* spp.
- *Bacteroides* spp.
- Tuberculosis
- *Actinomyces* spp.

Inflammatory
- Feline infectious peritonitis
- Acute pancreatitis
- Feline pansteatitis

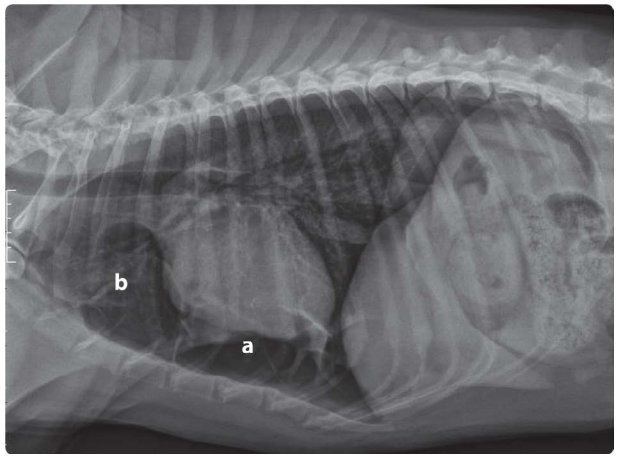


FIGURE 7.2 Lateral thoracic radiograph of a dog with a moderate pneumothorax showing cardiac elevation (a) and cranial lobe retraction (b).

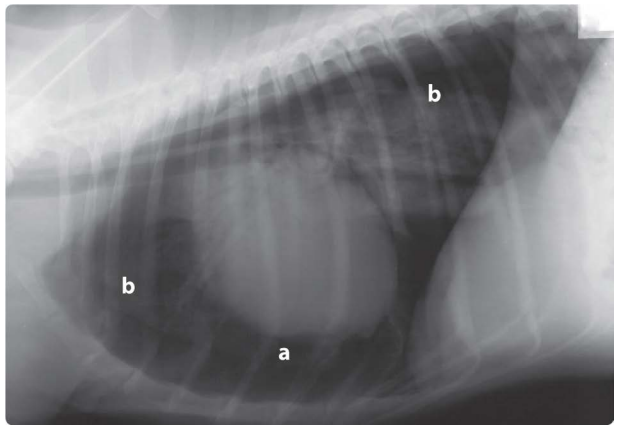


FIGURE 7.4 Lateral thoracic radiograph of a dog with a severe pneumothorax showing cardiac elevation (a) and minimal aeration of the pulmonary parenchyma (b).

flail or open chest pneumothorax, the wound is débrided and repaired to allow stabilization of the patient. In most instances of closed traumatic pneumothorax, intermittent needle thoracocentesis is effective in resolving the pneumothorax. If frequent, repetitive aspiration

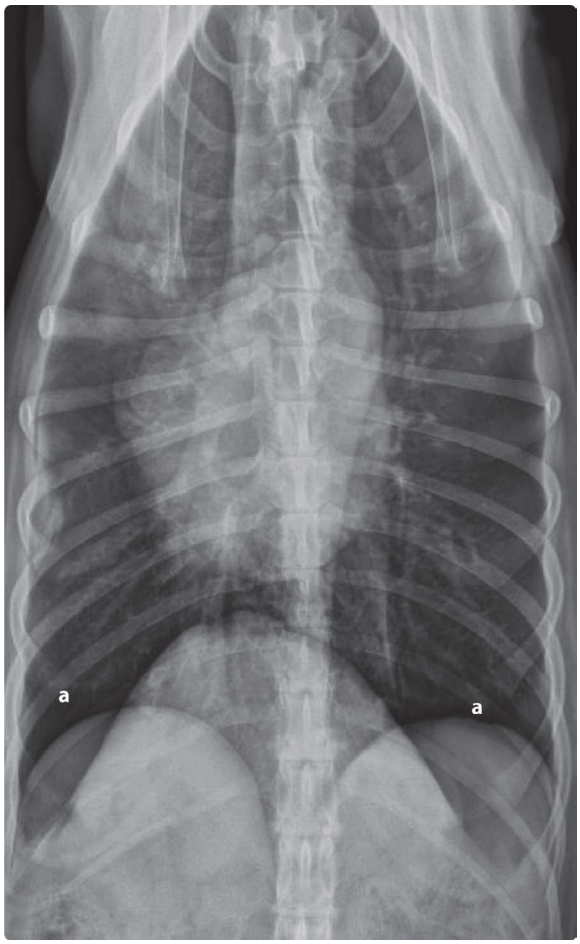


FIGURE 7.3 Ventrodorsal thoracic radiograph of a dog with pneumothorax demonstrating caudal lung lobe retraction (a).

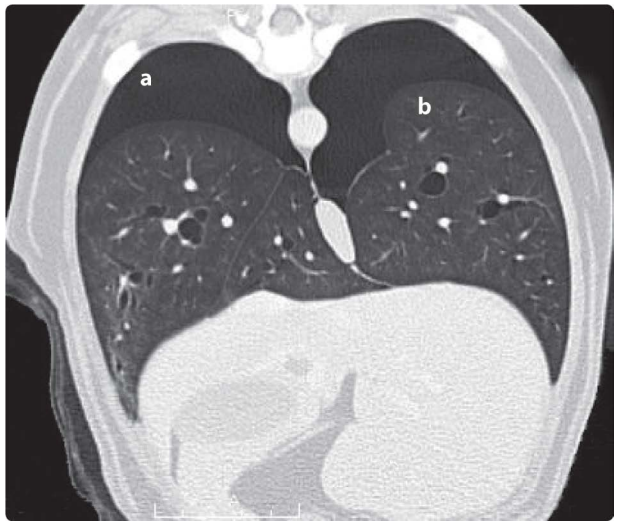
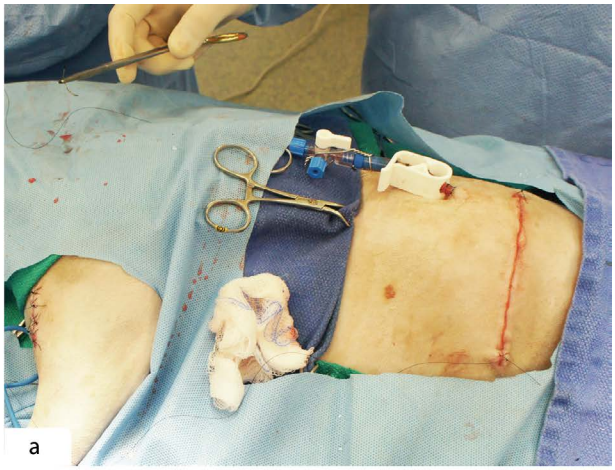


FIGURE 7.5 Transverse computed tomography scan of a dog with pneumothorax. Note the free gas in the pleural space (a) and retraction of the lungs (b).

of air from the pleural cavity is required, a chest tube should be placed (**Figure 7.6a, b**). Thoracostomy tubes can be aspirated intermittently or continuously depending on the production of air. The author prefers a continuous negative pressure approach if repeat aspiration is required more frequently than every 2 hours. A negative pressure between 2 and 4 cm H_2O is effective in most cases. If pneumothorax is continuous and persists longer than 2–3 days, surgical exploration and complete or partial lung lobectomy (**Figures 7.7–7.9**) of the pathologic lung lobe is indicated.

Dogs with spontaneous pneumothorax present a significant challenge and most often require surgical lung lobectomy for definitive resolution of the pneumothorax. Although many cases of spontaneous pneumothorax can resolve temporarily with medical treatment, recurrence is very common. Surgical exploration of the thoracic cavity is performed via a median sternotomy or exploratory thoracoscopy. Intercostal



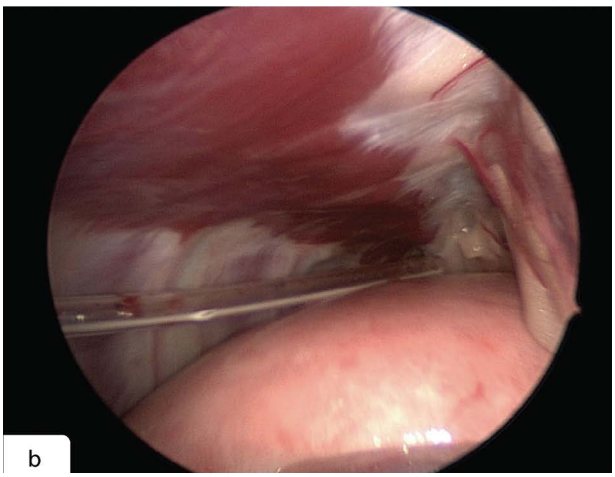


FIGURE 7.6 Extrathoracic **(a)** and intrathoracic **(b)** views of appropriate chest tube placement.

thoracotomy does not allow evaluation of both hemithoraces, which is necessary in most spontaneous pneumothorax cases.

Prognosis

Short-term prognosis for pneumothorax in dogs and cats is generally good provided that emergent and effective treatment is instituted. Long-term prognosis is dependent on the specific pathologic condition causing the pneumothorax. Spontaneous pneumothorax treated surgically is associated with a 10% mortality and 3% recurrence rate, whereas medically treated dogs have a 50% mortality and recurrence rate.

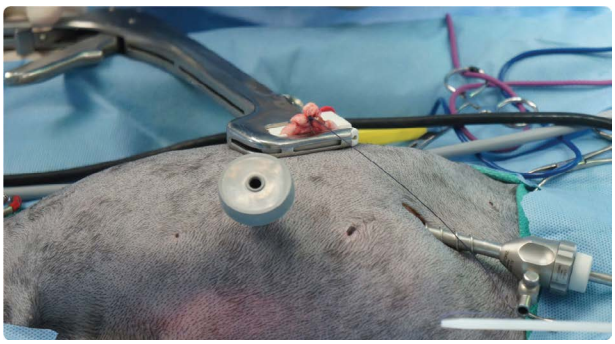
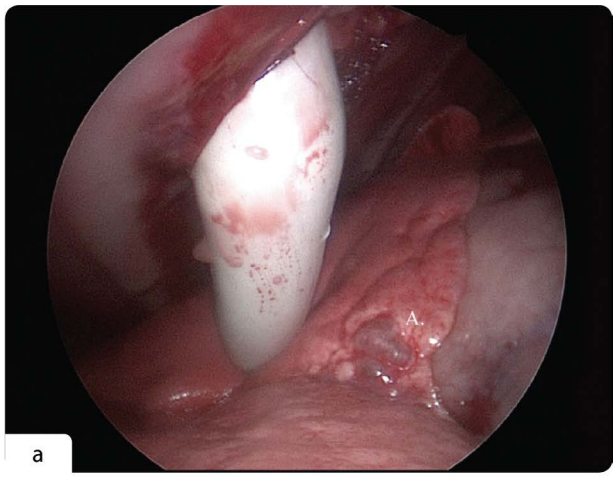


FIGURE 7.7 Video-assisted partial lung lobectomy from the dog in **Figure 7.1**.



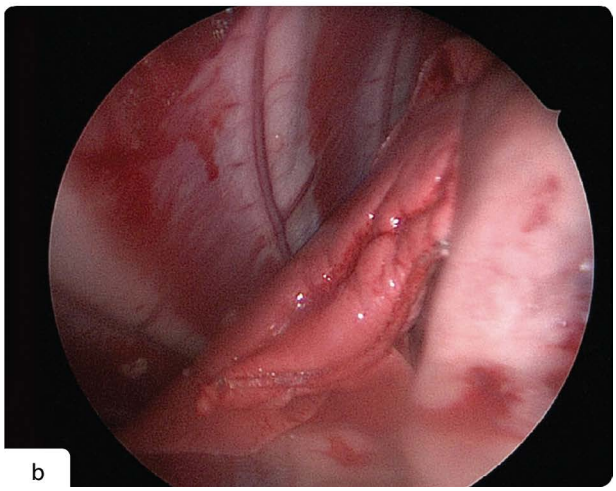


FIGURE 7.8 Thoracoscopic image of a pulmonary bulla before **(a)** and after **(b)** a stapled partial lung lobectomy.

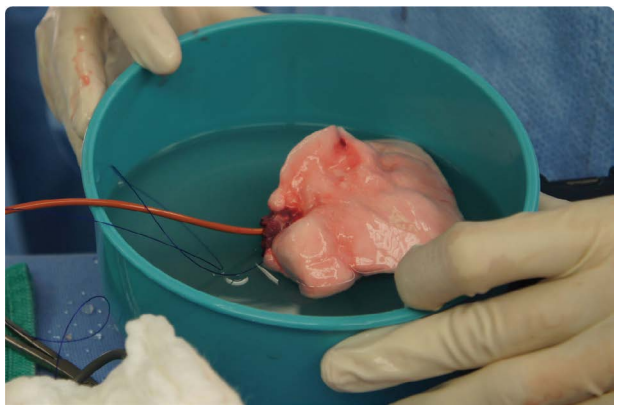


FIGURE 7.9 Intraoperative leak test to confirm the presence of a leaking lobe.

PYOTHORAX

Definition/Overview

Pyothorax, taken from the Greek words "py," meaning pus, and "thorac," pertaining to the chest, is a serious and life-threatening disease. The disease is characterized by accumulation of septic exudate within the thoracic cavity. Most cases of pyothorax are bacterial in origin; however, fungal pyothorax also occurs. Pyothorax is typically seen in young field dogs such as the German Shorthaired Pointer and is consistently more common in males. Pyothorax is commonly diagnosed in cats, and it can also be seen associated with a variety of diseases such as feline infectious peritonitis.

Etiology

Aerobic and anaerobic microbes are causative in most cases of pyothorax, and many infections are polymicrobial. *Actinomyces* and actinomyces-like bacteria (e.g., *Nocardia* spp. And *Filifactor* spp.) are also responsible for infections and can be associated with migrating grass awns. Migrating grass foreign bodies are thought to migrate through the respiratory system after inhalation, ultimately penetrating the pulmonary parenchyma. Other mechanisms of infection include esophageal perforation, hematogenous seeding, extension from a pneumonic infection, penetrating trauma, chest tube stoma, and surgical site infections. Often, the exact mechanism of infection is not identified. Disease-specific etiologies are summarized in Table 7.1.

Pathophysiology

In addition to restrictive pulmonary function due to fluid buildup within the pleural space, bacterial pathogens release endotoxins that act as pyrogens. This can lead to a myriad of untoward systemic sequelae, including systemic inflammatory response syndrome and multiple organ dysfunction/failure. Furthermore, inoculated foreign material within the thoracic cavity presents a significant challenge for clearance of infection. Specifically, foreign bodies can wall themselves off, thus preventing penetration and clearance by the immune system. The persistence of foreign material within the chest cavity is a common cause of long-term failure and recurrence.

Clinical Presentation

Most dogs and cats with pyothorax are dull, lethargic, hyporexic, often febrile, and have differing degrees of restrictive dyspnea. In severe cases, open-mouthed breathing, abducted elbows, and cyanosis may be observed. Clinical examination reveals variable findings, including elevated rectal temperature, diminished lung and heart sounds, and potentially penetrating thoracic wounds (e.g., dog bite).

Differential Diagnosis

See Tables 7.2 and 7.3.

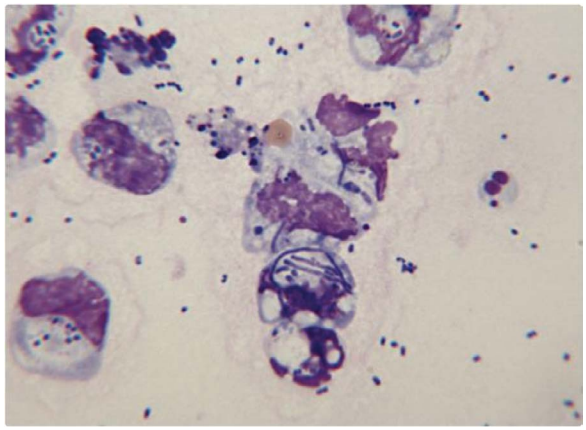


FIGURE 7.10 Cytologic example of a septic exudate from a dog with pyothorax. (*Courtesy of H. Wamsley.*)

Diagnosis

The definitive diagnosis of pyothorax is made by thoracocentesis and identification of a septic suppurative exudate on cytologic examination (Figure 7.10). *Actinomyces* is Gram positive and nonacid-fast, while *Nocardia* is Gram positive and partially acid-fast. Culture and susceptibility testing are necessary for species identification and for evaluation of appropriate antimicrobial therapy. Other important clinical diagnostics include complete blood count (CBC), serum biochemistry, urinalysis, and 2-view thoracic radiography. Thoracic radiographs demonstrate increased radiopacity in the pleural space, with concomitant dorsal elevation and scalloping of lung lobes on the lateral view. Pleural fissure lines are easily seen, and the cardiac silhouette is typically obscured (Figure 7.11a, b). Positive

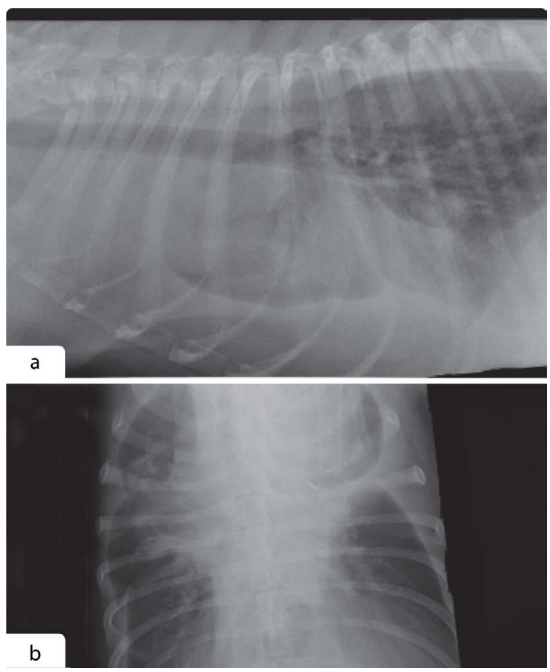


FIGURE 7.11 Lateral **(a)** and dorsoventral **(b)** thoracic radiographs of a dog with pyothorax.

contrast computed tomography (CT) is also recommended when available. This is helpful in cases where radiopaque foreign bodies may be present, as associated regions of tissue inflammation will typically demonstrate enhancement.

Management

Antimicrobial therapy is the cornerstone of treatment of pyothorax in dogs and cats. Broad-spectrum, empirical antibiotic therapy is indicated early and for an extended period of time (usually 6–8 weeks) in most cases. Popular and effective combinations of antibiotics include (1) a potentiated penicillin or (2) cephalosporin in conjunction with clindamycin or metronidazole. *Actinomyces* is most sensitive to penicillins, while *Nocardia* is often sensitive to sulfonamides. Other antibiotics can also be used effectively, as most infections are not particularly resistant. Antibiotic susceptibility testing should be utilized to guide therapy once results are available.

In addition to antimicrobial therapy, removal of septic fluid and any foreign or necrotic material is important, as treatment failure and recurrence may result if this is not performed. Thoracostomy drain placement either unilaterally or bilaterally is necessary in the initial treatment of pyothorax. Thoracostomy drains are used to drain and lavage the pleural space, which facilitates clearance of debris and septic material. Failure to place a thoracostomy drain is associated with an unacceptable level of treatment failure. Pleural lavage is performed using sterile physiologic 0.9% saline at 10–20 mL/kg up to 4 times daily. The addition of heparin to the lavage fluid at 5–10 U/mL has been recommended and theoretically may result in diminished adhesion formation.

Surgical intervention may be important in dogs with masses or cases where a foreign body is present or highly suspected (e.g., *Actinomyces* infection). Median sternotomy is indicated for exploration of both hemithoraces in cases of bilateral pyothorax when a cause is not identified or if medical treatment failure occurs. If a mass lesion is seen or if pus is limited to a single hemithorax, an intercostal thoracotomy may be an appropriate alternative to median sternotomy. Thoracic surgery regardless of the approach is challenging and marred with potential complications and should be performed only by experienced surgeons.

The author prefers exploratory thoracoscopy (Figures 7.12–7.14) as a diagnostic and therapeutic procedure in most cases of pyothorax. Exploratory thoracoscopy utilizes two to three 5.5-mm portals to explore, débride, and biopsy pleural and mediastinal tissues and is used to perform thorough lavage of both hemithoraces followed by video-assisted thoracostomy drain placement. A single thoracostomy drain is used after exploratory thoracoscopy as the mediastinal tissues are well débrided and, therefore, do not isolate one side of the thorax from the other. The efficacy of this treatment has recently been reported in the veterinary literature. All dogs resolved with thoracoscopic treatment, but two were converted to thoracotomy, and one dog developed

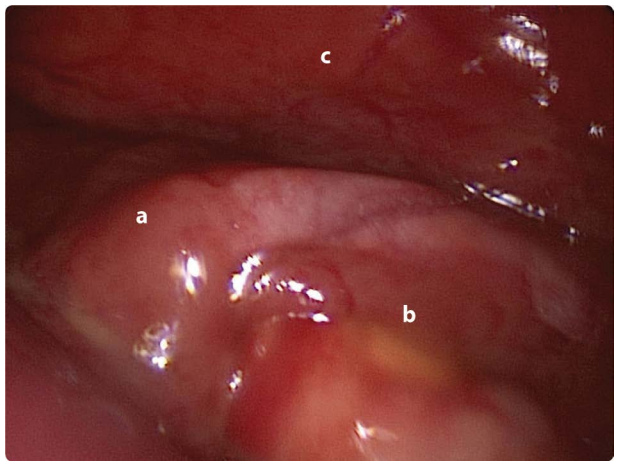


FIGURE 7.12 Dog undergoing thoracoscopic treatment for pyothorax. Purulent fluid (a) and fibrin (b) in the cranial thorax. The pulmonary pleura is inflamed (c).

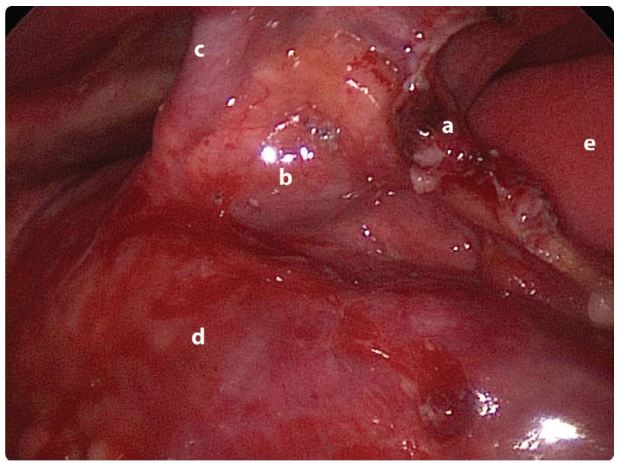


FIGURE 7.13 Thoracoscopic view of the cranial mediastinum after mediastinal débridement (a) and sternal lymph node (b) biopsy. The right internal thoracic artery (c), inflamed dorsal mediastinum (d), and left cranial lung lobe (e) are also visible.

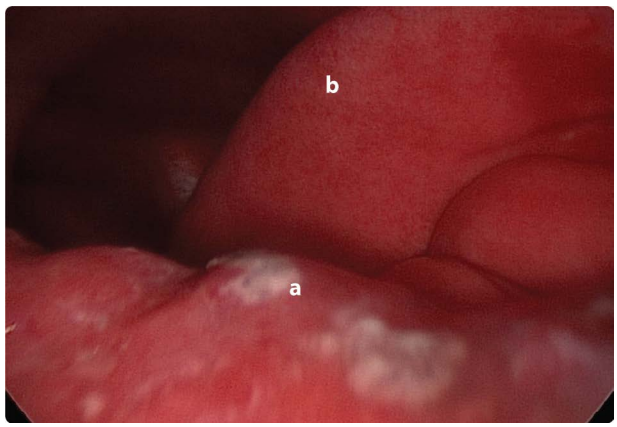


FIGURE 7.14 Thoracoscopic view of the cranial mediastinum. Note the fibrinous plaques (a) and left cranial lung lobe erythema (b).

recurrent disease in the long term (Scott J, et al., 2017—see Recommended Further Readings).

Prognosis

Overall prognosis for pyothorax in dogs and cats is good as long as appropriate and prudent medical treatment is instituted. The long-term success rate for dogs managed medically ranges from 30% to 70%, while dogs managed surgically experience a more consistent long-term success rate between 70% and 90%.

CHYLOTHORAX

Definition/Overview

Chylothorax is defined as a pathologic accumulation of chyle within the thoracic cavity. It is a relatively rare disease in dogs and cats but is associated with an untoward outcome in many cases despite treatment.

Etiology

There are a number of potential causes of chylothorax, including traumatic thoracic duct rupture, neoplasia, cardiomyopathy, heartworm disease, restrictive pericarditis, and lung lobe torsion. However, most cases in dogs are idiopathic. Because the exact cause is often unidentified despite appropriate diagnostic testing, target-based treatment can be challenging. Disease-specific etiologies are summarized in Table 7.1.

Pathophysiology

Direct injury to the thoracic duct can occur secondary to trauma or neoplastic disease. Disease processes that increase right-sided cardiac pressure, such as cardiomyopathy or restrictive pericarditis, also can induce chylothorax by causing extravasation of lymph from the lymphatic system. Similarly, lymphaticovenous obstructive diseases such as mediastinal lymphoma can cause chylothorax. Chylothorax induces significant inflammation within the pleural cavity, ultimately resulting in restrictive pleural fibrosis. Consequently, early and effective treatment is indicated to minimize the risk and severity of pleural fibrosis.

Clinical Presentation

Clinical signs typical of pleural effusion are seen in dogs and cats with chylothorax. Specifically, restrictive dyspnea, tachycardia, lethargy, and hyporexia are commonly reported. Reduced or absent bronchovesicular sounds on thoracic auscultation is a common finding. In chronic cases, poor body condition and cough may be observed. Among dogs, Afghan Hounds, Shetland Sheepdogs, and Shiba Inus are overrepresented.

Differential Diagnosis

See Tables 7.2 and 7.3.

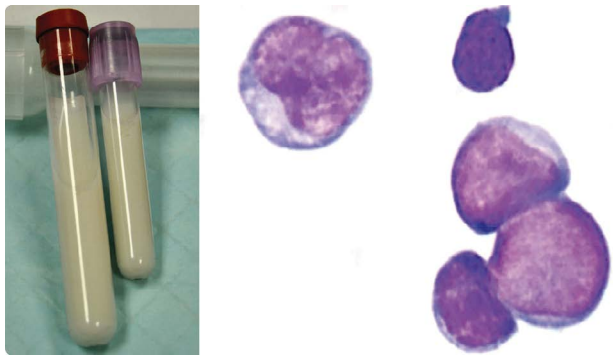


FIGURE 7.15 Pleural fluid. Gross appearance and cytology in a dog with chylothorax secondary to lymphangiosarcoma. Note the neoplastic characteristics of the cells: High nuclear to cytoplasmic ratio, multiple nucleoli, and anisokaryosis. (*Courtesy of H. Wamsley*.)

Diagnosis

Chylous fluid has a milky, white-to-pink, gross appearance (Figure 7.15) and is characterized as a modified transudate. The definitive diagnosis of chylothorax is based on pleural fluid analysis. Distinguishing between chyle and pseudochyle is typically done by measuring fluid triglyceride levels and then comparing those with serum triglyceride levels. Dogs and cats with a pseudochylous effusion will have equivalent fluid and serum triglyceride values, whereas patients with true chylous effusion will have fluid triglyceride levels significantly higher than serum levels. Other benchtop tests that can be performed to help differentiate a chylous effusion from a pseudochylous effusion include a positive ether clearance test and positive Sudan black uptake by chylomicrons. Cytology of pleural fluid is important to rule out other potential diseases such as neoplasia (Figure 7.15).

Thoracic radiographs demonstrate increased radiopacity in the pleural space with concomitant dorsal elevation and scalloping of lung lobes on the lateral view (Figure 7.16). Pleural fissure lines are easily seen, and the cardiac silhouette is typically obscured.

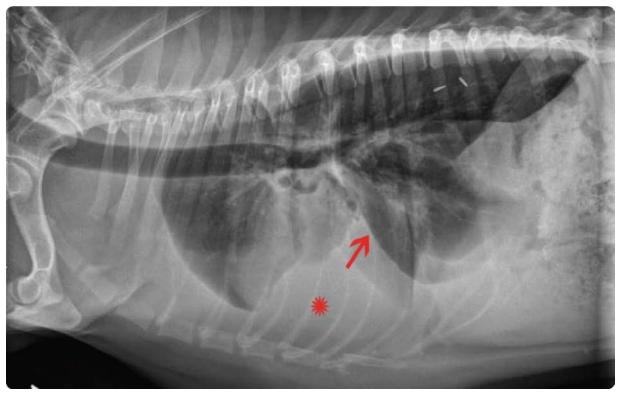


FIGURE 7.16 Lateral thoracic radiograph of a dog with recurrent pleural effusion 8 months after thoracic duct ligation and pericardectomy. This dog was eventually diagnosed with lymphangiosarcoma. Note the retracted lung lobes (arrow) and pleural fluid (asterisk).

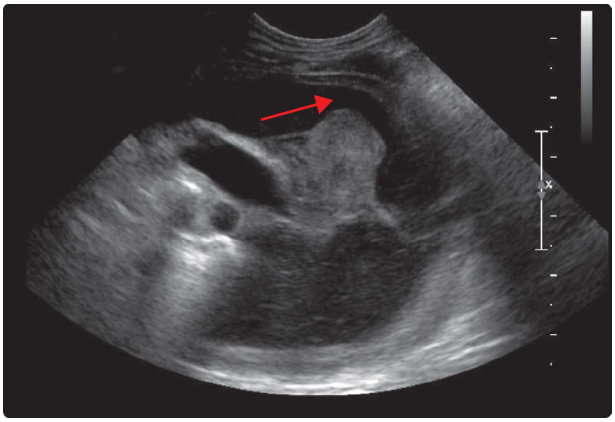


FIGURE 7.17 Thoracic ultrasonogram of a dog with pleural effusion. Note the hypoechoic shadow and linear hyperechoic fibrin strands indicative of pleural fluid. (*Courtesy of M. Winter.*)

Thoracic ultrasonography (Figure 7.17) can also be used to diagnose the presence of free pleural fluid and may be preferred in emergent cases, as it can be performed without significant restraint in most cases. Ultrasonography also allows for diagnostic and therapeutic image-guided thoracocentesis, which can be rapidly performed in emergency situations. Pleural fluid is identified as a hypoechoic to anechoic signal on ultrasound. Small volumes of fluid may not be easily visible using ultrasound. Presence of a thin hyperechoic pleural fissure line immediately adjacent to the body wall with associated gas shadow is consistent with significant pleural effusion.

CT lymphangiography is the procedure of choice for imaging of the thoracic duct (Figure 7.18) and cisterna chyli (Figure 7.19). While it is not necessary to perform CT lymphangiography to make the diagnosis of chylothorax, it is an important diagnostic test in the presurgical evaluation of patients with chylothorax.

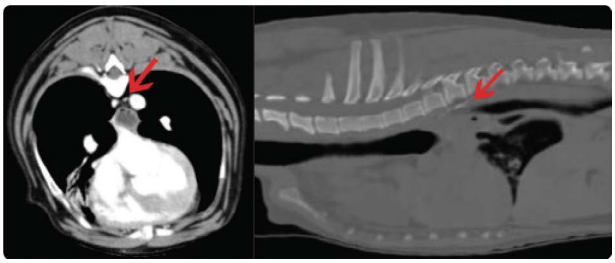


FIGURE 7.18 Transverse and sagittal computed tomography lymphangiography has been performed. Note the thoracic duct medial and dorsal to the descending aorta (arrows).

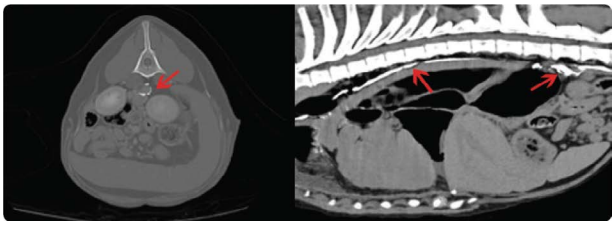


FIGURE 7.19 Transverse and sagittal computed tomography lymphangiography has been performed. Note the thoracic duct (sagittal view, left arrow) and cisterna chyli (both projections, right arrow on sagittal view).

Management

Conservative management of dogs and cats with chylothorax is rarely rewarding and is associated with a high degree of treatment failure. Medical options include feeding a low-fat/high-fiber diet to minimize the absorption and flow of chyle within the lymphatics. Nutraceuticals, such as bioflavonoids (e.g., Rutin, 20–50 mg/kg q.8h.), can also be supplemented to enhance macrophage activity. Other medications such as somatostatin and octreotide have also been used. Serial thoracocentesis is frequently required in medically managed dogs and cats with chylothorax. Because prolonged exposure of the visceral pleura to chylous fluid can result in pleural fibrosis, medical management should be attempted with caution. Owners should be counseled about the risks of pleural fibrosis at the time of diagnosis.

Surgical management is recommended in dogs and cats with idiopathic chylothorax, as it is associated with the best chance of treatment success. A number of surgical treatments have been recommended, but the most commonly performed are thoracic duct ligation (Figure 7.20), in combination with cisterna chyli ablation (Figures 7.21 and 7.22) and/or pericardectomy and thoracic cavity omentalization. Thoracoscopic thoracic duct ligation in combination with lymphatic embolization has recently been reported as well (Figures 7.23 and 7.24).

Prognosis

Prognosis with medical management alone is successful in less than 25% of cases. Surgical success varies among treatments but in recent reports ranges from 85% to 90% in the short and medium term. Long-term resolution of chylothorax is expected in about 80%–85% of dogs treated surgically.

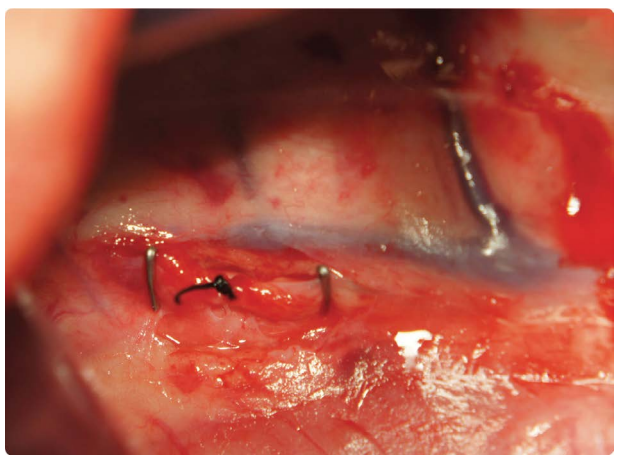


FIGURE 7.20 Intraoperative image of the thoracic duct subsequent to ligation. Note the azygous vein just dorsal to the ligated thoracic duct.

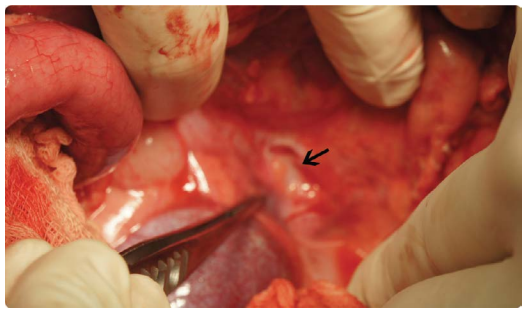


FIGURE 7.21 Intraoperative image of the cisterna chyli during ablation surgery. Note the dilated milky white appearance of the cisterna (arrow). This dog was fed cream prior to surgery to enhance visualization during the procedure.

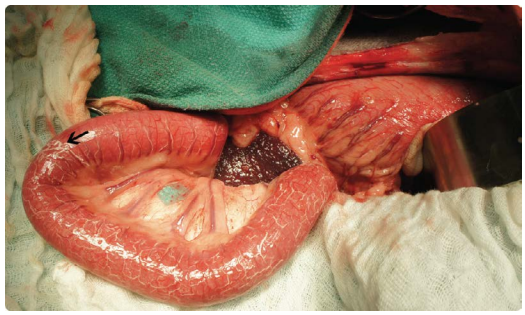


FIGURE 7.22 Dilated intestinal lymphatics (arrow) following oral cream administration in the dog in **Figure 7.21**.

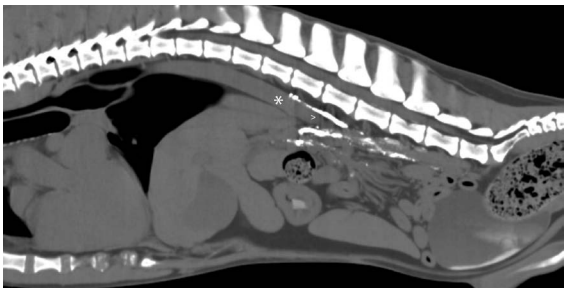


FIGURE 7.23 Postoperative CT demonstrating thoracic duct ligation (asterisk) and embolization of the caudal thoracic duct and cisterna chyli.

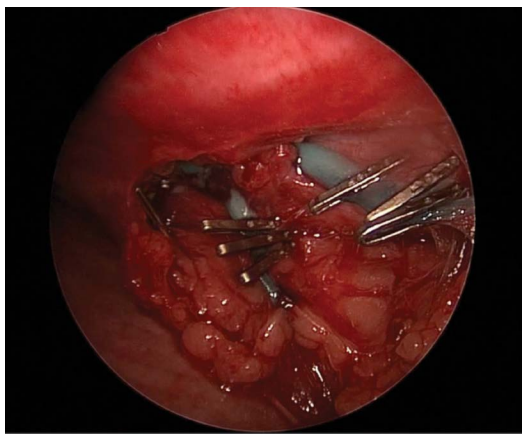


FIGURE 7.24 Intraoperative thoracoscopic image of ligation of multiple branches of the thoracic duct in a dog with chylothorax.

LUNG LOBE TORSION

Definition/Overview

Lung lobe torsion occurs when a lung lobe becomes twisted about its longitudinal axis so as to obstruct the pulmonary vasculature and the bronchus. In most cases, the pulmonary artery is patent. Lung lobe torsion is a relatively uncommon disease. Male dogs and those with a narrow and deep chest appear to be predisposed to lung lobe torsion. Afghan Hounds and Pug dogs appear to be overrepresented. Lung lobe torsion does occur in the cat, but it is rare.

Etiology

The precise etiology of lung lobe torsion in many cases is unknown, and it is, therefore, referred to simply as spontaneous. In some dogs, the condition may be seen in conjunction with other pathology, including pulmonary neoplasia and chylothorax. Any disease process that results in collapse of the airway and which increases mobility of a particular lobe may predispose that lobe to torsion. Examples of associated diseases include bronchomalacia and bronchial collapse, pulmonary neoplasia, chylothorax, and alteration of normal anatomy due to previous thoracic surgery (e.g., lung lobectomy). Disease-specific etiologies are summarized in **Table 7.1**.

Pathophysiology

When a lung lobe undergoes torsion, the venous and lymphatic outflow becomes obstructed, resulting in fluid congestion and distension of the affected lobe. With time, the fluid accumulation becomes severe, eventually resulting in necrosis and pleural effusion formation. A low ventilation/perfusion mismatch results but may not be clinically apparent if the remaining lung lobes are healthy.

Clinical Presentation

Clinical signs include coughing, respiratory difficulty, tachypnea, lethargy, and hyporexia. Respiratory signs can be severe, especially if significant pleural effusion exists. In some cases, a history of previous thoracic surgery may be known, but in many instances, no significant medical history exists.

Differential Diagnosis

See **Tables 7.2** and **7.3**.

Diagnosis

Diagnosis is typically made via thoracic radiography (**Figures 7.25** and **7.26**) or CT (**Figures 7.27** and **7.28**). Survey radiographic findings may vary depending on the presence of pleural fluid and chronicity of the disease. In early cases without significant pleural effusion

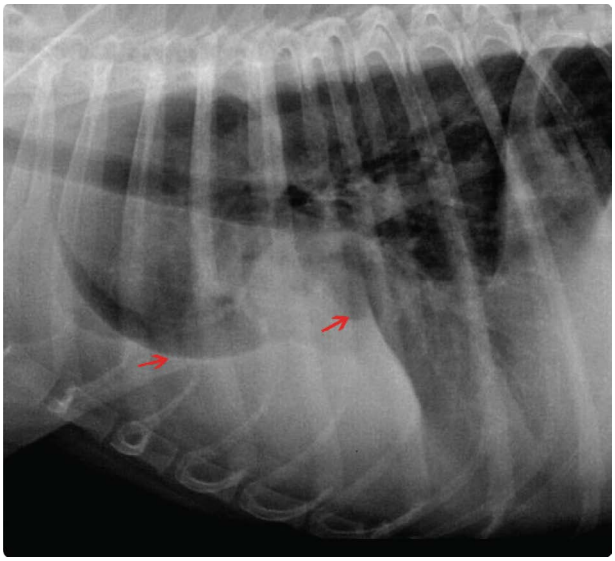


FIGURE 7.25 Dog with lung lobe torsion. Lateral thoracic radiograph. Note the pleural effusion (left arrow) and blunt-ended bronchus (right arrow).

or following thoracocentesis, consolidation with or without the presence of air bronchograms may be evident. In more chronic cases, complete consolidation of the lung lobe with blunting of the pulmonary bronchus may occur. CT is useful in identifying obstructed or narrowed bronchi and is more sensitive than survey radiography for detection of lung lobe torsion.

Pleural fluid analysis typically reveals a modified transudate, which may be chylous.

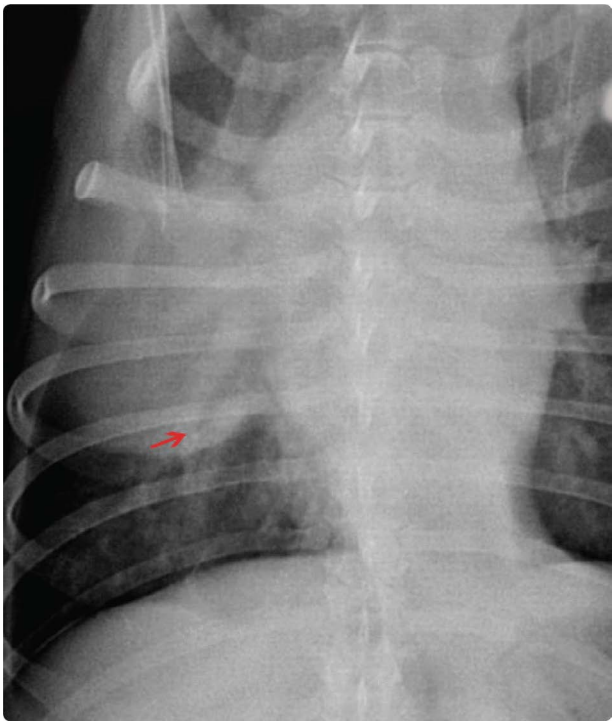


FIGURE 7.26 Ventrodorsal thoracic radiograph. Note the consolidated right middle lung lobe with blunted bronchus (arrow).

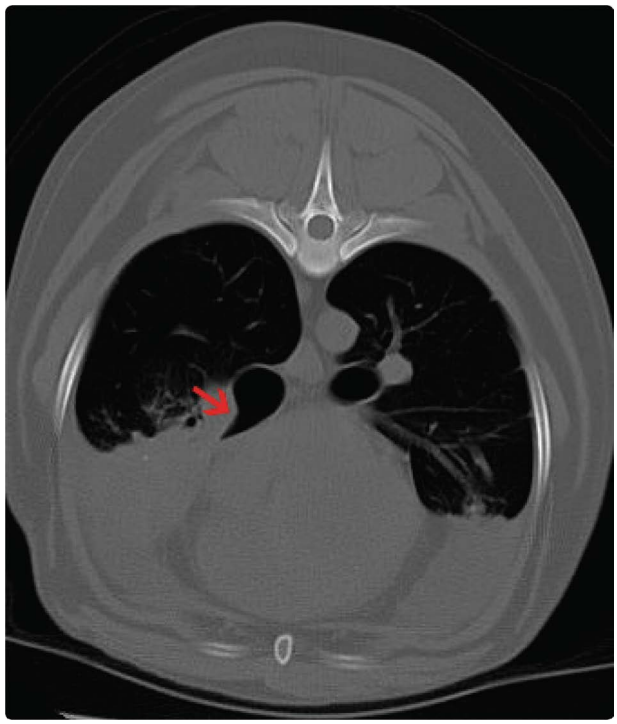


FIGURE 7.27 Transverse computed tomography view. The occluded bronchus and consolidated lung lobe are easily visualized (arrow).

Management

Surgical ligation and excision of the affected lung lobe is the recommended treatment. Dogs and cats with lung lobe torsion are stabilized prior to surgical lung lobectomy. Stabilization usually requires therapeutic thoracocentesis and IV fluid replacement. Any electrolyte or acid–base disruptions should be corrected prior to anesthesia and surgery. Dogs and cats undergoing thoracotomy should have a preoperative hematocrit of at least 30% (0.3 L/L), as hemoglobin is the most significant contributor to blood oxygen content, and hypoxemia and blood loss can be significant with thoracic surgery.

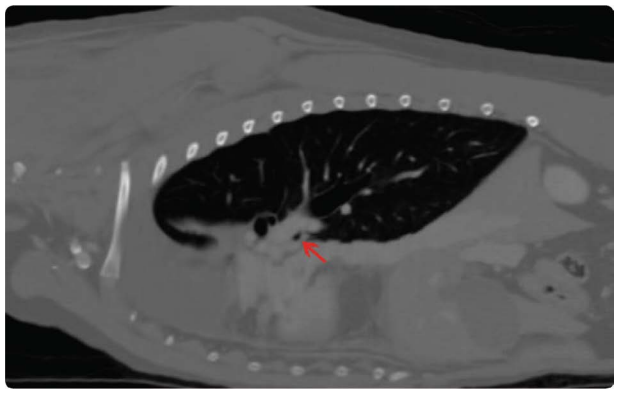


FIGURE 7.28 Sagittal computed tomography view. The occluded bronchus is demonstrated (arrow).

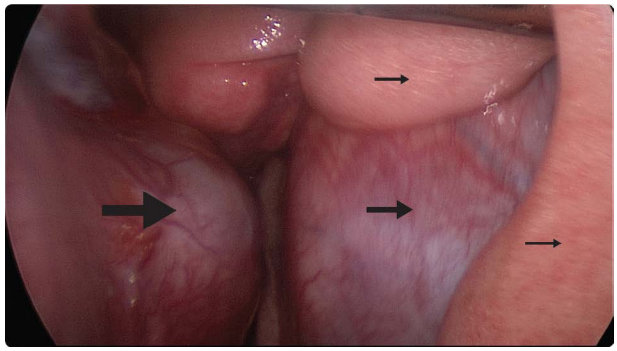


FIGURE 7.29 Same dog as in Figures 7.25–7.28. Video-assisted thoracic surgical view of the consolidated right middle lung lobe (thickest arrow), which was adhered to the chest wall. The heart (middle-thickness arrow) and lungs (thinnest arrows) are retracted to the right of the image.

Lung lobectomy can be performed via a video-assisted thoracic approach (Figure 7.29), median sternotomy, or video-assisted or intercostal thoracotomy (Figure 7.30). Video-assisted thoracic surgery is the author's preferred approach when feasible as exploration of the pulmonary parenchyma is possible, and the procedure can be performed with minimal tissue injury and postoperative pain. Regardless of the surgical approach, ligation of the vascular pedicle (without derotation of the lung lobe) using a triple-row surgical stapler or suture ligation is performed (Figure 7.31). Patients are monitored and supported in a critical care facility postoperatively.

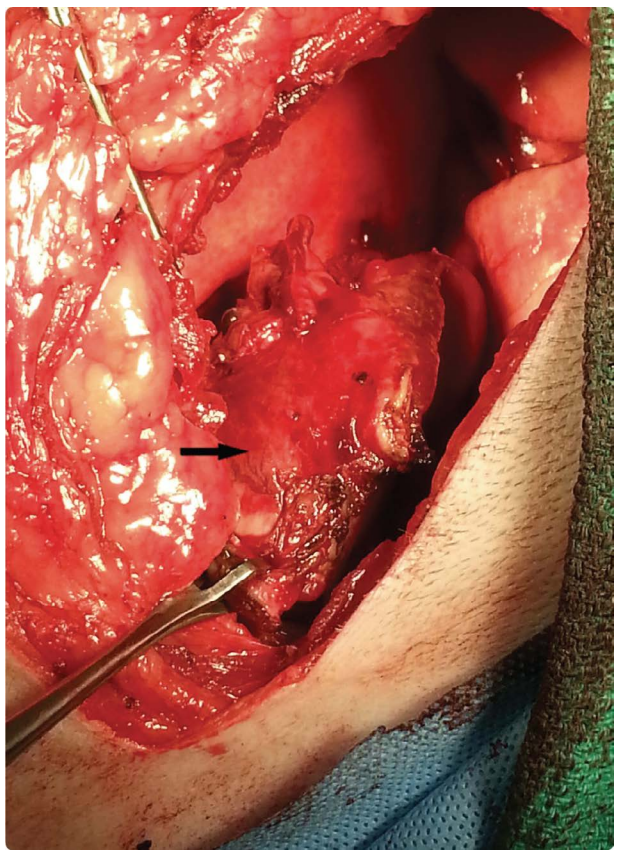


FIGURE 7.30 Intraoperative view of the torsed lung lobe (arrow) during intercostal thoracotomy just prior to lung lobectomy.

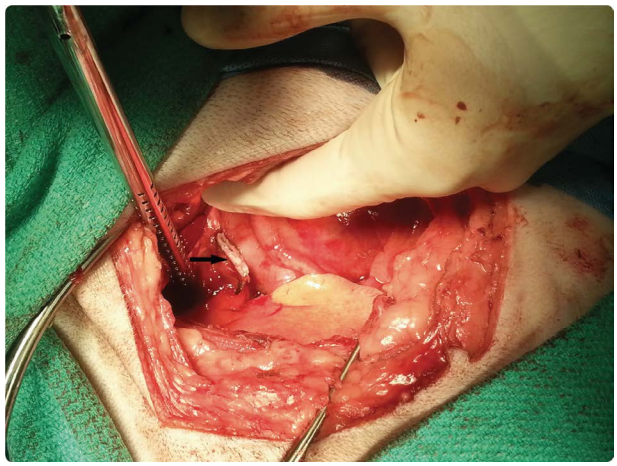


FIGURE 7.31 Intraoperative view of the ligated bronchus (arrow) following lung lobectomy.

Prognosis

Prognosis is dependent on the underlying disease process and the experience and ability of the anesthesia and surgery services. Mortality rates have been reported as high as 40%, but Pug dogs appear to have a much higher survival rate.

DIAPHRAGMATIC HERNIATION

Definition/Overview

Pleural–peritoneal diaphragmatic herniation results when the diaphragm is ruptured or when an abnormal communication of the peritoneal and pleural cavities exists. The diaphragm is composed of a large central tendon, which originates from the sternal, costal, and lumbar musculature. In health, the diaphragm maintains three normal ostia: The aortic, vena cava, and esophageal hiatus. Peritoneal–pericardial diaphragmatic hernias are not true pleural–peritoneal hernias as the communication exists only between the peritoneum and pericardial spaces.

Etiology

Diaphragmatic hernias are broadly classified as congenital or acquired, with acquired being most common. Congenital diaphragmatic hernias are rare and typically result from failure of the lumbar musculature to fuse. These hernias are typically located in the dorsolateral region of the diaphragm. Acquired diaphragmatic hernias are seen commonly following blunt trauma such as automobile-associated injury. Traumatic diaphragmatic herniation can develop in any part of the diaphragm. Tears can be multiple or single, large or small, and

radial or longitudinal. Disease-specific etiologies are summarized in Table 7.1.

Pathophysiology

The pathophysiologic effects of diaphragmatic herniation depend on the severity of the hernia, chronicity, and presence of concurrent injuries. The diaphragm plays an integral role in ventilation and oxygenation by altering intrapleural pressure and volume during respiration. Injury to the diaphragm impairs this function. Furthermore, with herniation of viscera (liver most commonly), compression of the pulmonary pleura and pleural vasculature results in compressive atelectasis and venous impairment. The end result is hypoxemia and reduced cardiac output. Concurrent rib fractures cause pain, which further reduces ventilatory capacity and exacerbates hypoxemia. Herniation of intestine into the pleural space can result in intestinal obstruction and intestinal ischemia.

Clinical Presentation

The clinical presentation for dogs and cats with diaphragmatic herniation is variable and can range from minimal or no clinical signs to severe dyspnea and hypovolemic shock. It is important to remember that small diaphragmatic tears may not elicit significant clinical signs and may go undetected until herniation of abdominal viscera occurs. This may take years in some cases. Thus, diaphragmatic injury should be considered even in dogs and cats without respiratory signs following significant thoracic trauma. Dogs with herniated gastrointestinal (GI) organs may be obstructed and will often present with vomiting and anorexia.

Physical examination may reveal concurrent soft tissue and orthopedic injuries, reduced abdominal organ content, or minimal-to-absent bronchovesicular and heart sounds.

Differential Diagnosis

See Tables 7.2 and 7.3.

Diagnosis

Survey thoracic radiography is the most commonly performed diagnostic procedure and is very sensitive for diagnosing herniation of peritoneal contents in the pleural space (Figures 7.32 and 7.33). Typical radiographic findings include retracted pulmonary parenchyma, presence of increased soft tissue opacity in the pleural cavity, loss of normal cardiac silhouette, presence of gas-filled viscera in the pleural cavity, loss of a normal hepatic shadow, and cranial gastric axis shift. Contrast abdominal radiography can be performed to help identify intestinal herniation and obstruction (Figures 7.34 and 7.35).

CT is also useful and is more sensitive at detection of small diaphragmatic hernias with minimal or no herniation of GI viscera (Figures 7.36 and 7.37).

Arterial blood gas analysis and calculation of the alveolar–arterial oxygen gradient is helpful in diagnosing hypoxemia.

Management

Hypoxemic and hypovolemic patients should be resuscitated and stabilized on an emergency basis. Replacement IV fluid therapy and increased inspired oxygen content can be started immediately. Most dogs and cats will respond well to fluid therapy, but response to increased inspired oxygen may be poor due to the ventilation–perfusion mismatch that frequently exists. Reduction of herniated organs and repair of the diaphragm are required before significant improvement in oxygenation will occur.

Diaphragmatic herniorrhaphy by laparotomy (Figures 7.38–7.40) or laparoscopy (Figures 7.41 and 7.42) in stable dogs only, following reduction of herniated viscera is the definitive treatment for pleural–peritoneal diaphragmatic herniation. Adjunctive surgical procedures such as resection and anastomosis of devitalized bowel or liver lobectomy for refractory hemorrhage may also be indicated.

Prognosis

Prognosis for dogs and cats with traumatic diaphragmatic herniation is good to excellent, with overall survival around 90%. Dogs and cats with traumatic diaphragmatic hernias undergoing surgery without effective resuscitation and support have a higher mortality.

THORACIC NEOPLASIA

Definition/Overview

Thoracic neoplasia is common in aged dogs and cats. The result in most cases is production of malignant pleural effusion and respiratory difficulty. Space-occupying masses can also impair normal respiratory effort and function. Thoracic neoplasia is almost exclusively malignant, but effective treatment can be accomplished in many cases depending on the owner's expectations and the biology of the particular disease.

Etiology

Thoracic neoplasia is most commonly mesenchymal or epithelial and can originate from the ribs, pleura, lungs, mediastinum, thymus, lymph nodes, pericardium, heart, trachea, and esophagus. Mediastinal lymphoma and lymphangiosarcoma are also commonly diagnosed. Disease-specific etiologies are summarized in Table 7.1.

Pathophysiology

Thoracic neoplasia commonly results in malignant pleural effusion, while pericardial and cardiac neoplasms

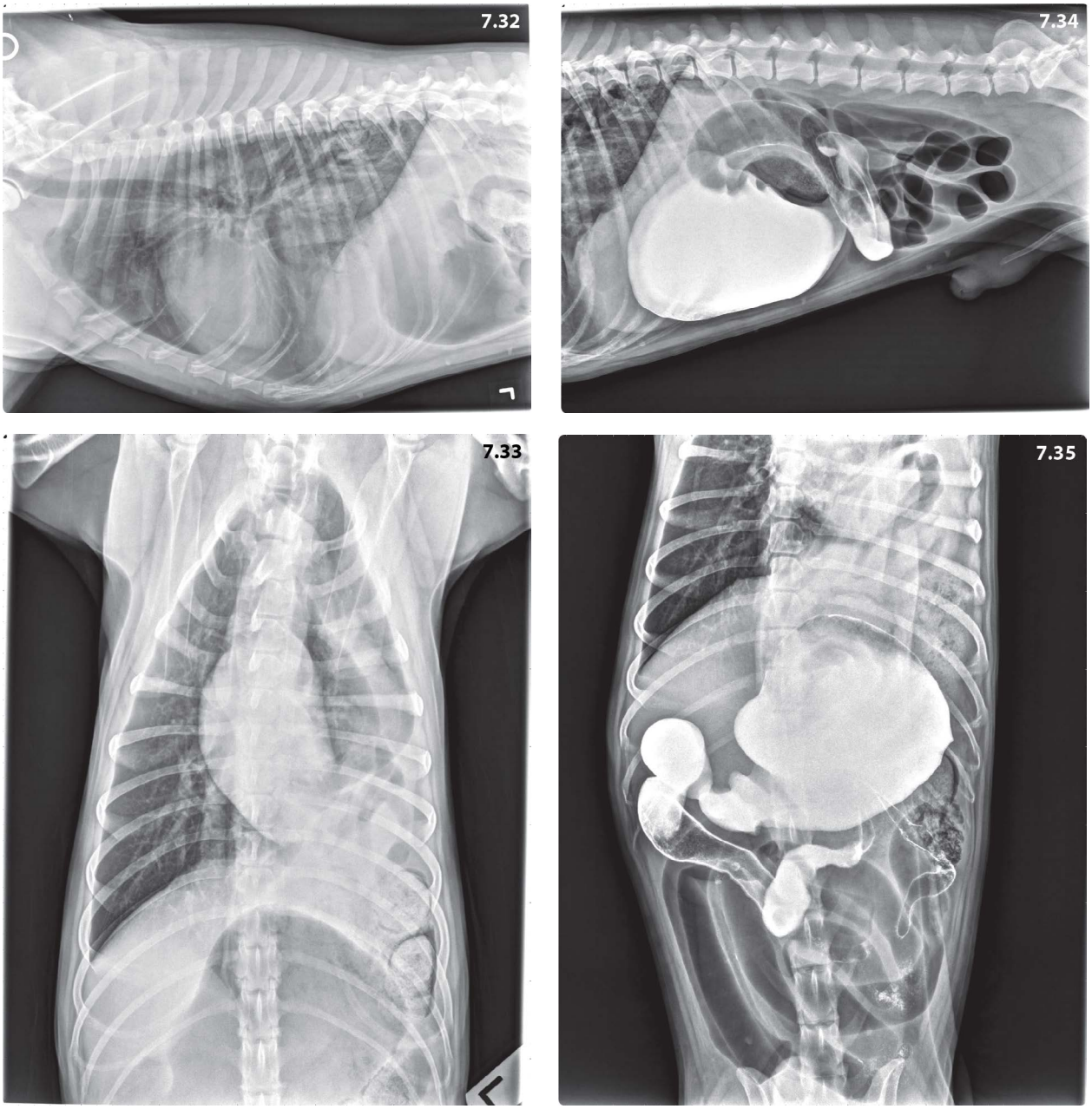


FIGURE 7.32 Dog with a diaphragmatic hernia. Lateral thoracic radiograph. Note the cranial displacement of the gastric axis and gas-filled viscus in the pleural cavity.

FIGURE 7.33 Ventrodorsal thoracic radiograph. Note the loss of liver shadow and the gas-filled viscus in the pleural cavity.

FIGURES 7.34, 7.35 Contrast lateral **(Figure 7.34)** and ventrodorsal **(Figure 7.35)** abdominal radiographs. This dog had persistent emesis, which was thought to be secondary to intestinal obstruction. Contrast was retained in the duodenum due to herniation and occlusion of the orad jejunum. Note the absence of a splenic shadow.

frequently engender pericardial effusion with or without pleural effusion. Consequently, respiratory and diastolic cardiac function are compromised in affected dogs and cats. Moderate-to-marked volumes of pleural space fluid cause restriction of the pulmonary parenchyma, which results in hypoxemia. Excessive pericardial effusion or mechanical compression of the right cardiac chambers by a mass results in tamponade and diastolic compromise.

Clinical Presentation

Dogs with thoracic neoplasms can present in significant distress depending on the location and size of the mass as well as the location and volume of malignant effusion. Common clinical signs include dyspnea, coughing, lethargy, and hyporexia. Cough is usually associated with a lesion that compresses a bronchus. In some cases, cyanosis and syncope may be reported. Dogs and cats

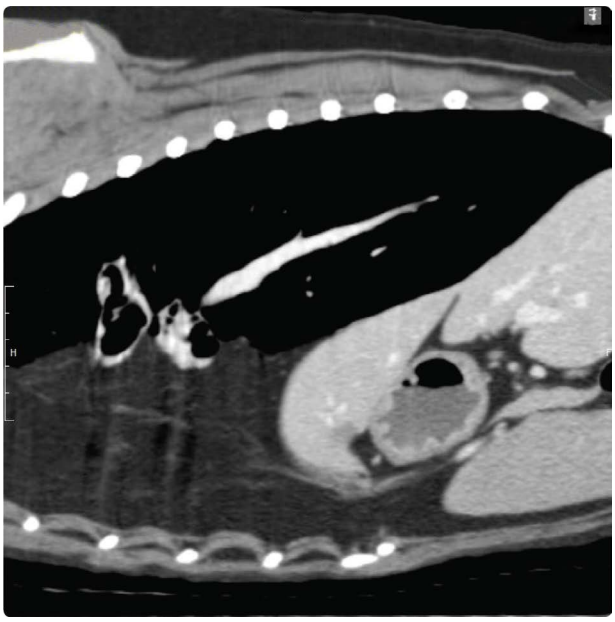


FIGURE 7.36 Dog with a traumatic ventral diaphragmatic rupture. Sagittal computed tomography scan. Note the diaphragmatic defect and omental fat streaking into the thoracic cavity.



FIGURE 7.37 Dog with a traumatic ventral diaphragmatic rupture. Coronal computed tomography scan. Note the diaphragmatic defect and omental fat streaking into the thoracic cavity.

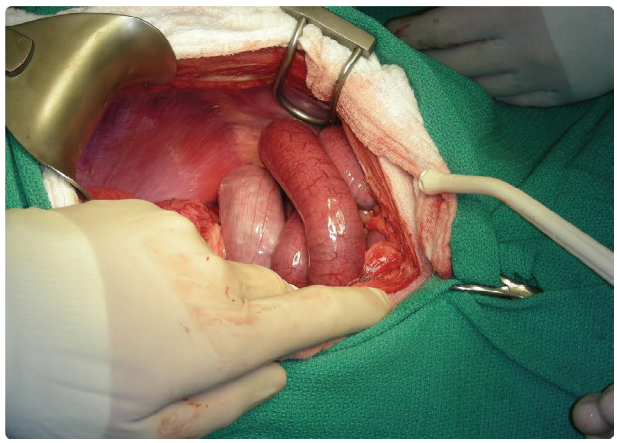


FIGURE 7.38 Intraoperative view of the dog in **Figures 7.32–7.35**. Note the herniated colon and obstructed erythematous jejunum.

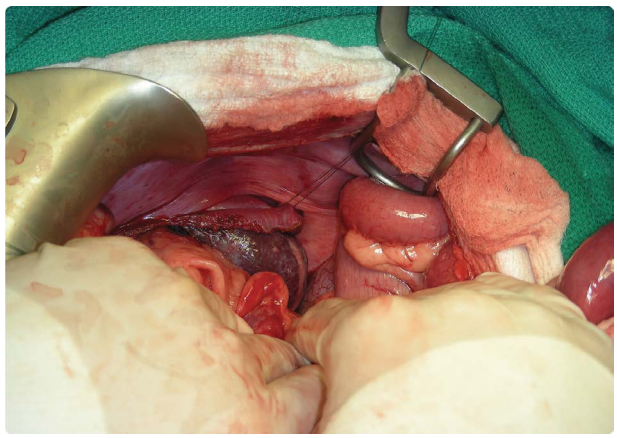


FIGURE 7.39 Intraoperative view of the dog in **Figures 7.32–7.35**. Note that the bowel has been reduced, and the herniated spleen is now visible.

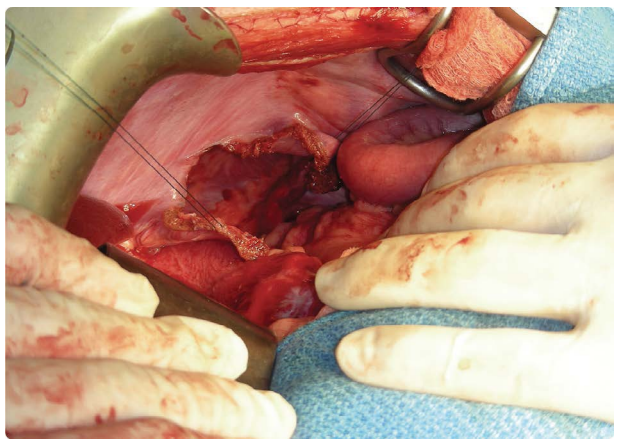


FIGURE 7.40 Intraoperative view of the dog in **Figures 7.32–7.35**. Note that all of the abdominal viscera has been reduced.

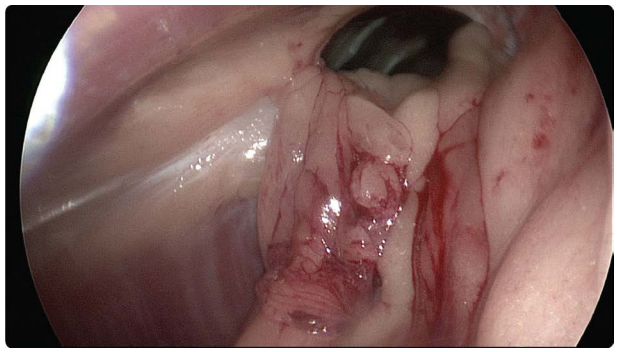


FIGURE 7.41 Laparoscopic view of the dog in Figures 7.32–7.35. The greater omentum is herniated into the pleural space.

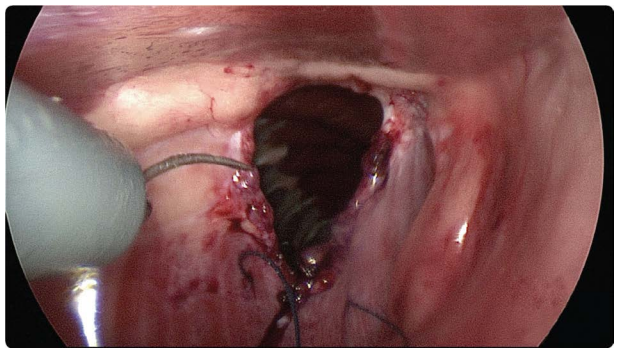


FIGURE 7.42 Laparoscopic view of the dog in Figures 7.32–7.35. An intracorporeal knotless herniorrhaphy is being performed.

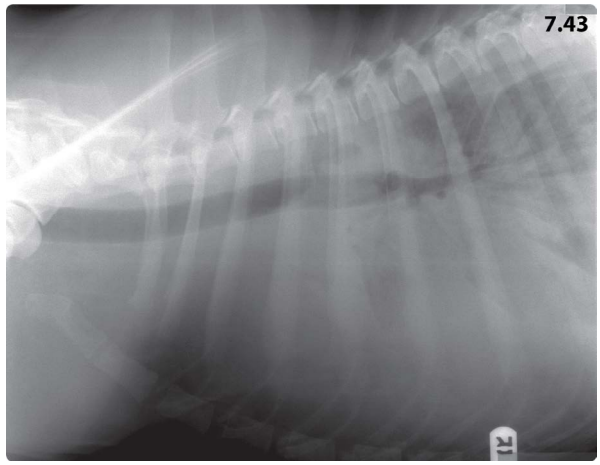
with thoracic wall tumors may have a visible or palpable mass present on physical examination. Cardiothoracic auscultation may reveal diminished or absent bronchovesicular or cardiac sounds.

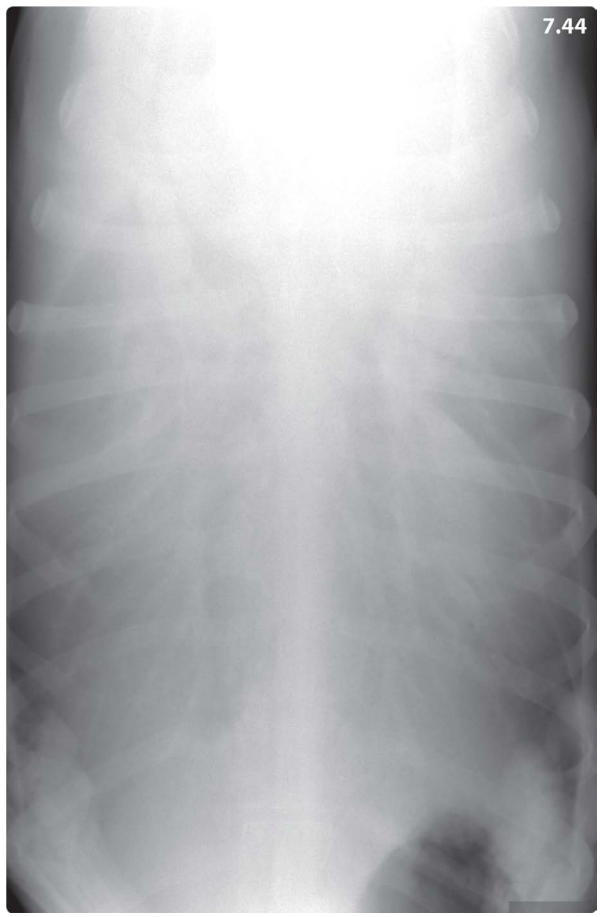
Differential Diagnosis

See Tables 7.2 and 7.3.

Diagnosis

Cytologic analysis of malignant effusions is often inconclusive either due to lack of representative cells in the sample or because of similarity of reactive mesothelial cells to malignant mesothelial cells. Routine blood work is typically nonspecific. Radiographic and echocardiographic imaging usually reveals the presence of pleural and/or pericardial effusion. Mediastinal, pulmonary, and thoracic wall masses can be identified with thoracic radiography (Figures 7.43–7.46), but masses within the pericardial space typically are only seen via echocardiography. Three-dimensional imaging with CT or MRI is ideal for imaging the thoracic cavity (Figure 7.47). Cytology obtained from ultrasound-guided fine-needle aspirates may be useful, but tissue biopsy and histopathology are often essential for a definitive diagnosis (Figures 7.48–7.50).

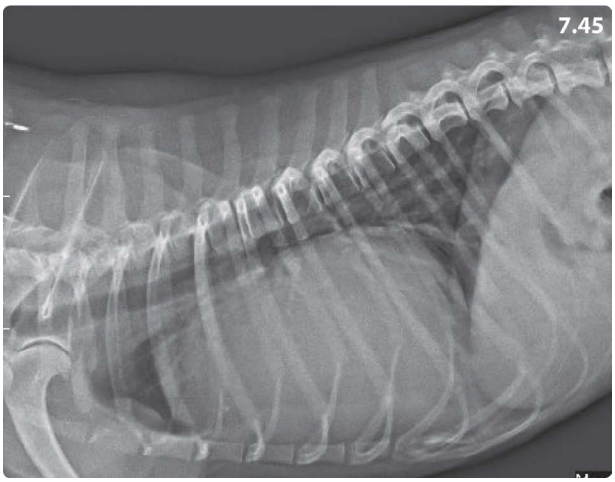


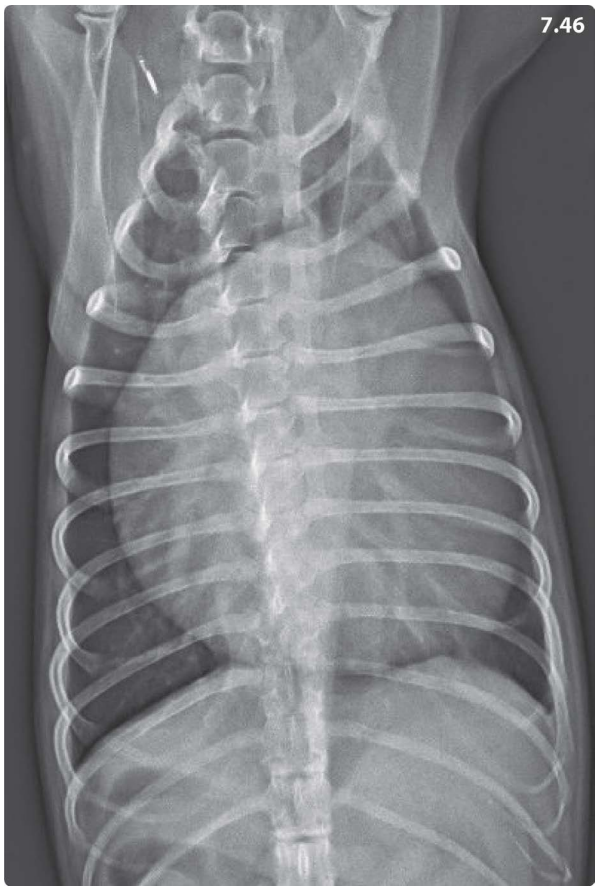


FIGURES 7.43, 7.44 Dog with severe malignant pleural effusion. Lateral (Figure 7.43) and ventrodorsal (Figure 7.44) thoracic radiographs. This dog was diagnosed with pleural mesothelioma.

Management

Initial medical treatment may include thoracocentesis, pericardiocentesis, IV fluid resuscitation, and oxygen supplementation. Tissue diagnosis and staging is recommended (although sometimes not possible) before prescribing a treatment plan. Surgery is often indicated for a variety of neoplastic processes, and chemotherapy



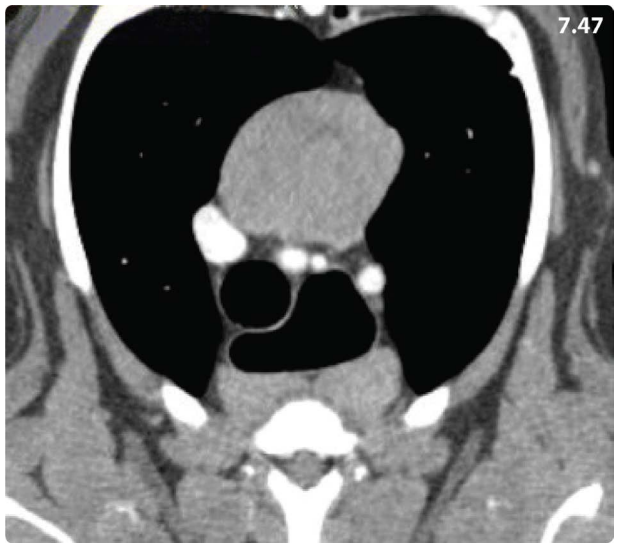


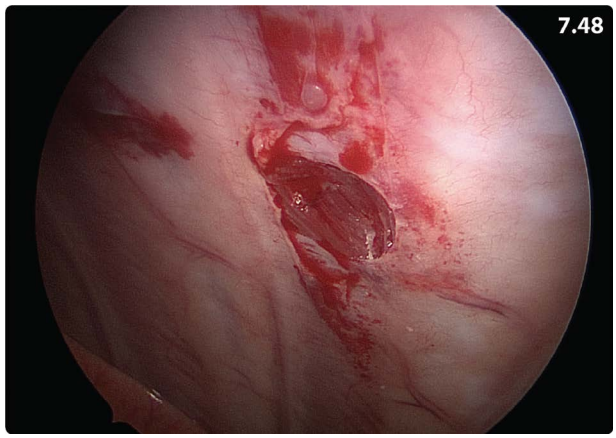
FIGURES 7.45, 7.46 Dog with severe malignant pericardial effusion. Lateral (**Figure 7.45**) and ventrodorsal (**Figure 7.46**) thoracic radiographs. This dog was diagnosed with a right auricular hemangiosarcoma.

may also be indicated depending on the biologic behavior of the cancer.

Prognosis

Prognosis is dependent on the clinical health of the subject, the specific neoplasm, and the treatment elected. In general, thoracic neoplasms have a poor long-term prognosis, but disease-free intervals and survival times





FIGURES 7.47, 7.48 Dog with a noninvasive thymoma. Transverse computed tomographic view. Note the thymoma (center of image), left subclavian artery, left internal thoracic artery, brachiocephalic artery, and cranial vena cava (**Figure 7.47**). Thoracoscopic pleural biopsy has been performed. Note the pleural nodule above the biopsy site (**Figure 7.48**).

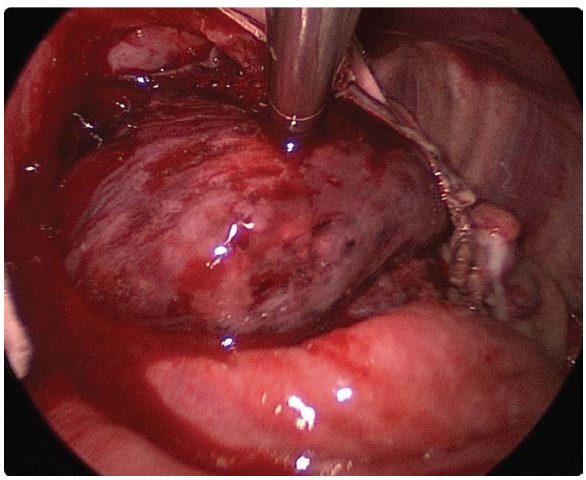


FIGURE 7.49 Pericardioscopic view of a massive right atrial appendage hemangiosarcoma that is compressing the right atrium.

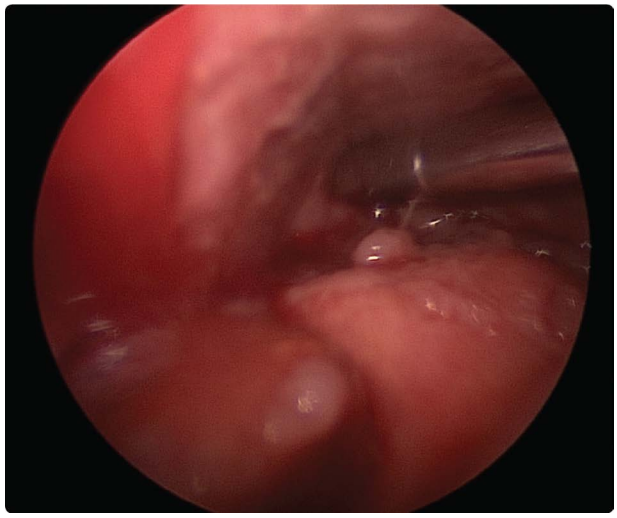


FIGURE 7.50 Pericardioscopic view of a dog with multiple small heart base nodules. These nodules were not seen on echocardiography or preoperative computed tomography. The diagnosis was pericardial and pleural mesothelioma.

up to years can be achieved in some cases. Prognosis should be based on histopathology, if possible, as some diseases (e.g., idiopathic pleural effusion) can mimic malignant thoracic neoplasms.

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CHAPTER

8

Cardiovascular Disorders

Romain Pariaut and Carley Saelinger

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HISTORY AND PHYSICAL EXAMINATION

Introduction

Cardiovascular disease is common in dogs and cats, and a thorough history and physical examination are crucial steps in making the diagnosis of heart disease. They not only can assist in differentiating respiratory from cardiac disease but also help determine the severity of the disease and response to therapy.

Signalment

Age, breed, and sex are useful information to establish a short list of differential diagnoses. Young animals tend to present with congenital defects, while acquired diseases should be suspected in older animals. There are known breed predispositions, and males are more susceptible to certain diseases. However, there are exceptions in all of these cases, and care should be taken not to exclude diseases simply from signalment. Signalment in combination with heart murmur characteristics and pulse quality are particularly useful to shorten differential lists in puppies with congenital heart disease.

History

A thorough history should include questions about onset, duration, and progression of presenting signs; current medications and the response to those medications; travel history and possible infectious disease exposure; a complete diet history; and concurrent medical problems.

Presenting Complaints

Common presenting signs of cardiac disease include tachypnea, dyspnea, cough, exercise intolerance, syncope, abdominal swelling, decreased appetite, weight loss, cyanosis, paresis/paralysis, and poor growth.

Tachypnea/Dyspnea

Tachypnea is an overly rapid respiratory rate. Owners of pets with cardiac disease should be instructed to keep a resting respiratory rate log at home, and this should be reviewed as part of the history. If the resting respiratory rate is steadily increasing, or is > 40 bpm, cardiogenic pulmonary edema should be suspected in animals previously diagnosed with cardiac disease. Dyspnea is labored breathing and can be caused by primary respiratory disease or decompensated cardiac disease. Caution should be taken with dyspneic animals, as they may quickly become unstable if placed in a stressful environment.

Cough

Cats rarely cough with cardiac disease, although it is reported with heartworm infection. However, cough is the most common complaint in dogs with cardiac disease. It is important to differentiate cough due to cardiac disease from that due to respiratory causes. A high-pitched or honking cough is more commonly associated with

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TABLE 8.1 Causes of syncope in dogs and cats

Arrhythmia
- *Bradyarrhythmia*
  - High-grade second-degree atrioventricular block, third-degree atrioventricular block, sick sinus syndrome
- *Tachyarrhythmia*
  - Sustained supraventricular tachycardia, ventricular tachycardia
  - Severe pulmonary hypertension
  - Vasovagal syncope associated with coughing, urination, defecation
- *Systemic hypotension*
  - May be induced by vasodilatory therapy
  - Severe decrease in cardiac output (dilated cardiomyopathy [DCM], obstructive cardiomyopathy)
  - Cardiac tamponade

tracheobronchial collapse, whereas dogs with heart disease will tend to have an intermittent, harsh, low-pitched cough. Cough can be more specific for congestive heart failure (CHF) in large breed dogs than in small breeds.

Syncope

Syncope is a loss of consciousness associated with decreased cerebral blood flow. It is important to differentiate syncope from seizures. Syncopal episodes are generally brief, and the animal is normal immediately preceding and following the episode. Syncope has a variety of causes (Table 8.1).

Abdominal Distension

Abdominal swelling from cardiac disease is due to ascites, which can be caused by right-sided heart disease, pericardial effusion, constrictive pericardial disease, severe pulmonary hypertension (PH), and obstructions to venous return. Ascites develops secondary to congestion in the liver and spleen. It can lead to dyspnea and tachypnea because of increased pressure on the diaphragm, as well as decreased appetite due to abdominal discomfort. Increased intra-abdominal pressure impairs renal blood flow and intestinal absorption of nutrients and drugs. Ascites can be differentiated from other causes of abdominal swelling (organomegaly) by the presence of a palpable fluid wave.

Weight Loss/Cachexia

Cardiac cachexia is a generalized loss of muscle, bone, and adipose tissue mass secondary to CHF. It is due to a catabolic/anabolic imbalance and carries a poor prognosis. High-calorie diets and more frequent feeding are often required to limit the effects of cardiac cachexia. Patients with ascites usually develop more profound and rapid cardiac cachexia.

Cyanosis

Cyanosis is associated with decreased oxygenation of blood and leads to blue-tinged mucous membranes (Figure 8.1). Cyanosis is most commonly seen secondary to cardiac defects leading to right-to-left blood shunting, although it can also be due to severe left heart failure or respiratory disease. There will often be a concurrent polycythemia.



FIGURE 8.1 Cyanosis in a dog with a right-to-left intracardiac shunt.

Paresis

Paresis is most commonly seen in cats with arterial thromboembolic disease. The limb affected depends on the location of the thromboembolus, with the hind limbs being most frequently affected.

Physical Examination

The physical examination should begin with inspection from a distance to collect information on respiratory status and mentation.

Examination of the Mucous Membranes

Mucous membrane color and perfusion should be examined. Cyanosis is due to poor ventilation or alveolar diffusion. Pallor can indicate anemia, hypoxemia, or poor perfusion, and hyperemia may indicate polycythemia or sepsis. The color of the oral mucous membranes should be compared with caudal membranes to assess for differential cyanosis, which is characteristic of a right-to-left patent ductus arteriosus (PDA). Capillary refill time (CRT) is a poor indicator of tissue perfusion.

Palpation of the Pulses

The femoral pulse should be evaluated in every patient. The palpated pulse pressure is determined by the difference between systolic and diastolic pressures and the rate at which pressure reaches its peak systolic value. For example, a large difference between diastolic and systolic pressures or a rapid rise of pressure results in a "bounding" or "hyperdynamic" pulse. Pulse quality

TABLE 8.2 Description of pulses and their causes

Pulse type	Description	Cause
Bounding / hyperkinetic	"Water hammer" forceful pulse	Aortic insufficiency, PDA, thyrotoxicosis, anemia
Pulsus bisferiens (bifid)	Double pulse for each beat	Hypertrophic cardiomyopathy (HOCM), subvalvular aortic stenosis (SAS), aortic insufficiency
Pulsus alternans	Alternating pulse strength with each beat	Severe myocardial disease
Pulsus paradoxus	Inspiration is associated with weakened or absent pulse	Pericardial effusion and tamponade
Pulsus parvus et tardus	Delayed onset of pulse and weak pulse	SAS
Pulsus bigeminus	Pulses come in pairs with pause between each pair and the second pulse weaker than the first	Bigeminal arrhythmias
Pulse deficits	Auscultated heart beats do not have coinciding pulse	Arrhythmias
Hypokinetic pulses	Weak and difficult to palpate	Hypotension, hypovolemia, SAS, congestive heart failure
Absent pulses	No pulse palpated	Thromboembolism

HOCM, hypertrophic obstructive cardiomyopathy; PDA, patent ductus arteriosus; SAS, subaortic stenosis.

cannot be used to estimate actual arterial blood pressure values. Both femoral pulses should be evaluated and the pulse rate compared with the auscultated heart rate. The detection of changes in pulse quality and pattern can help establish a list of differential diagnoses (Table 8.2).

Examination of the Jugular Veins

The jugular veins should be examined while the animal is standing with its head in a neutral position. Any pulse extending above the lower third of the neck is considered abnormal and may be due to right-sided CHF, pulmonic stenosis (PS), severe pulmonary hypertension (PHT), pericardial disease, heartworm disease, or arrhythmias. In addition to abnormal pulses, generalized jugular distension may be noted. This finding indicates increased systemic venous pressures secondary to right heart failure, pericardial disease, or cranial vena cava obstruction that can occur with mediastinal or heart base masses. The hepatojugular reflux sign, which corresponds to a distension of the jugular veins when pressure is applied to the cranial abdomen, can be seen with right-sided heart disease and occurs due to the inability of the diseased heart to compensate for the increased return of blood occurring during abdominal compression (Figure 8.2).



FIGURE 8.2 Hepatojugular reflux sign. There is marked distension of the jugular veins (right) when pressure is applied to the cranial abdomen, compared with baseline (left).

Palpation

The apex beat should be felt most strongly on the left side of the thorax between the 4th and 6th intercostal spaces. The apex beat may be shifted due to cardiac enlargement, intrathoracic masses, collapsed lung lobes, diaphragmatic hernias, or sternal abnormalities. A decreased intensity of the apex beat may be secondary to pericardial effusion, pleural effusion, pneumothorax, diaphragmatic hernia, thoracic masses, or obesity. A precordial thrill, a localized vibration of the chest caused by turbulent blood flow, can be felt when a severe murmur is present.

Auscultation

Auscultation should be performed in a quiet room with both the bell (for low-frequency sounds) and diaphragm (for high-frequency sounds) of the stethoscope. Auscultation should be performed in a systematic manner, evaluating all areas of the thorax and each valve region (Table 8.3). The animal should be in a standing position for auscultation. The heart and lungs should be auscultated separately to avoid confusing or overlooking abnormal sounds. Heart rate and rhythm should be noted, as well as the presence or absence of heart sounds and abnormalities. The normal heart sounds

TABLE 8.3 Areas of auscultation in dogs

Mitral area	Left hemithorax	5th intercostal space at costochondral junction
Aortic area	Left hemithorax	4th intercostal space just above costochondral junction
Pulmonic area	Left hemithorax	2nd–4th intercostal space just above sternal border
Tricuspid area	Right hemithorax	3rd–5th intercostal space near costochondral junction

are S1, associated with closure of the atrioventricular (AV) valves, and S2, associated with closure of semilunar valves. S1 is normally longer and louder than S2. A split S1 may be auscultated and indicates asynchronous closure of the AV valves. S2 is shorter and higher pitched than S1 and is loudest over the pulmonic and aortic areas. Splitting of S2 indicates asynchronous closure of the aortic and pulmonic valves (Table 8.4).

Abnormal heart sounds in small animals include S3, due to rapid ventricular filling, and S4, due to atrial contraction into overly distended or noncompliant ventricle. Both S3 and S4 are quiet, low pitched, and occur in diastole. An audible S3 is indicative of dilated ventricles, and S4 indicates a thickened or noncompliant ventricle or atrial contraction against an already closed AV valve. When S3 or S4 is audible, it is called a gallop rhythm and normally indicates advanced cardiac disease. A midsystolic click is a transient sound that may mimic a gallop rhythm. It is caused by the prolapse of the AV valves, typically in the early stage of degenerative mitral valve disease in dogs.

TABLE 8.4 Abnormal heart sounds and their causes

Abnormal heart sound	Causes
Split S1	– Normal in some large breed dogs – Right bundle branch block – APCs – VPCs – Mitral valve / tricuspid valve stenosis – Cardiac pacing
Split S2	– Normal during inspiration in some animals – Pulmonary hypertension – Right bundle branch block – VPCs – Pulmonic stenosis – Left bundle branch block – SAS – Heartworm disease – Atrial septal defect – Severe hypertension – Aortic insufficiency
S3	– DCM – Decompensated AV valve disease – PDA with left ventricular dilation
S4	– HCM – Third-degree AV block
Midsystolic click	– Mitral valve prolapse

APC, atrial premature complex; AV, atrioventricular; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; PDA, patent ductus arteriosus; SAS, subaortic stenosis; VPC, ventricular premature complex.

TABLE 8.5 Causes of functional murmurs in dogs and cats

Physiologic
- Anemia
- Fever
- Hypoproteinemia
- Hypertension
- Pregnancy
- Hyperthyroidism

Innocent
- No known cause or underlying cardiac disease

Cardiac murmurs are abnormal sounds caused by turbulent blood flow. Murmurs may be functional or pathologic. Functional murmurs are further divided into physiologic and innocent. Physiologic murmurs have a known cause unrelated to primary cardiac disease and are associated with increased cardiac output or altered blood viscosity. Innocent murmurs occur in young animals and have no known cause or associated cardiac disease. They should be no louder than a grade 3 and should disappear by 5 months of age (Table 8.5). Pathologic murmurs are caused by an underlying cardiac disease (Table 8.6).

Murmurs should be described by their timing, duration, grade, and point of maximal intensity (PMI). Additional information includes quality and pitch of the murmur. The timing of the murmur is either systolic, diastolic, continuous, or to-and-fro. Systolic murmurs are the most common and can be further classified into early, mid-, or late systolic; holosystolic (murmur extends throughout systole, but heart sounds remain audible); or pansystolic (murmur extends through systole, but S2 is obscured). Diastolic murmurs are often quiet and are much less common. Continuous murmurs can be

TABLE 8.6 Causes (and location) of pathologic murmurs in dogs and cats

Systolic murmurs
- AV valve regurgitation (left or right apical)
- Right ventricular outflow tract obstruction; pulmonic stenosis or dynamic right ventricular outflow tract obstruction (right basilar)
- Left ventricular outflow tract obstruction; subaortic stenosis or dynamic left ventricular outflow tract obstruction (left basilar)
- Ventricular septal defect (right apical, sternal, left basilar)
- Valvular endocarditis (left apical)

Diastolic murmurs
- Aortic insufficiency (left basilar)
- Mitral valve stenosis (left apical)
- Valvular endocarditis (left basilar)

Continuous murmurs
- Patent ductus arteriosus

TABLE 8.7 Murmur intensity grading system

Murmur grade	Description
1	Can only be heard after several minutes of listening in a silent room
2	Soft and only heard in a focal region of the thorax
3	Heard throughout one side of the thorax but does not radiate to the opposite side; equal in volume to normal heart sounds
4	Loud murmur that radiates to the opposite side of the thorax, no precordial thrill
5	Palpable precordial thrill, very loud murmur
6	Audible with the stethoscope slightly off the thorax

heard during all phases of the cardiac cycle. To-and-fro murmurs occur when there is a distinct systolic and diastolic murmur. Murmurs are graded on a 1–6 scale (Table 8.7). Murmur grade does not necessarily correlate with the severity of the underlying disease.

The PMI is the location where the murmur is heard loudest. If possible, it should be localized to a single valve region. However, in small dogs and cats, the distinction of apical versus basilar is acceptable. Additionally, the locations of the radiation of the murmur should be described.

ELECTROCARDIOGRAPHY AND HOLTER MONITORING

Definition

The electrocardiogram (ECG) records the electrical activity of the heart from electrodes positioned at the surface of the body. A normal ECG displays three distinct events: P wave during atrial depolarization; followed by QRS complex during ventricular depolarization; and finally, T wave, which corresponds to ventricular repolarization (Figure 8.3). The atrial repolarization is usually not detected. The duration and the amplitude of the waves can be measured from the ECG. The duration (or width) of a wave depends on the time it takes for the electrical impulse to propagate within the cardiac chambers. The amplitude, or height, of a wave usually changes with the size of the cardiac chambers. All measurements should be made in lead II. The amplitude of the waves can decrease when fluid, air, fat, or a large mass interferes with the propagation of the electrical signals to the surface of the body. The PR interval reflects the conduction time through the AV node (Figure 8.3 and Table 8.8).

Ambulatory electrocardiography devices, known as Holter systems, allow clinicians to record a 24- to 72-hour ECG recording while the animal has a normal activity level in a familiar environment (Figure 8.4). Implantable

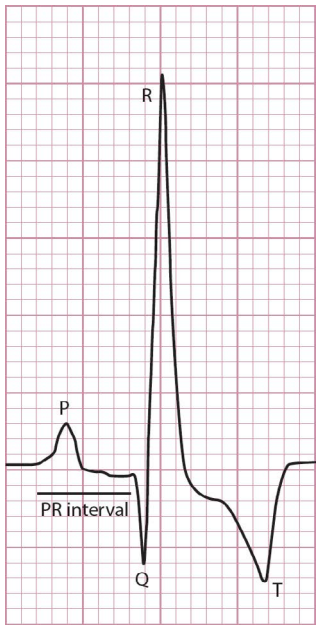


FIGURE 8.3 P-QRS-T illustrating the sequence of activation of the heart. Note that on this ECG there is no clearly defined S wave.



FIGURE 8.4 A 24-hour Holter recording on a dog.

devices are now available to collect ECG data. These devices are event recorders that can be manually triggered to save an ECG whenever clinical signs are observed by the owner of a pet. They are indicated in animals that only present with rare episodes of weakness or syncope.

Indications

The ECG is used to measure heart rate and evaluate cardiac rhythm. It is less reliable for gathering information about structural cardiac changes, such as hypertrophy. Therefore, it should be performed when an arrhythmia is detected on physical examination and when the presenting complaint may be explained by an arrhythmia.

The main indications for Holter recordings are the detection of an arrhythmia as the cause for unexplained syncope, the quantification of arrhythmias, and monitoring of the response to antiarrhythmic therapies. This

TABLE 8.8 ECG features of the normal dog and cat

	Dog	Cat
Heart rate	– 60–170 bpm for adult dogs – 60–140 bpm for giant breeds – Up to 180 bpm for toy breeds – Up to 220 bpm for puppies	– Range 140–220 bpm – Mean 197 bpm
Rhythm	– Normal sinus rhythm – Sinus arrhythmia – Wandering SA pacemaker	– Normal sinus rhythm
P wave	– Duration: Maximum 0.04 sec; 0.05 s in giant breeds – Amplitude: Maximum 0.4 mV – Mean electrical axis: –18 to +90 degrees	– Duration: Maximum 0.04 sec – Amplitude: Maximum 0.2 mV
PR interval	– Duration: 0.06–0.13 sec	– Duration: 0.05–0.09 sec
QRS complex	– Duration: Maximum 0.07 sec – R-wave amplitude: Maximum 2.5 mV in small breeds, 3 mV in large breeds – Mean electrical axis: +40 to +100 degrees	– Duration: Maximum 0.04 sec – R-wave amplitude: Maximum 0.9mV – Mean electrical axis: 0 to +160 degrees
ST segment	– No depression: Not more than 0.2 mV – No elevation: Not more than 0.15 mV	– No marked depression or elevation
T wave	– Positive, negative, or biphasic – Not greater than one-fourth amplitude of R wave	– Positive, negative, or biphasic – Most often positive – Maximum amplitude 0.3 mV
QT interval	– Duration: 0.15–0.24 s at normal HR, varies with HR	– Duration: 0.16–0.22 s at normal HR, varies with HR

Adapted from Santilli R, Moïse NS, Pariaut R, Perego M (2018). *Electrocardiography of the Dog and Cat*, 2nd ed. Edra, Milano. All measurements made in lead II.

technique is also used to screen predisposed breeds for signs of specific cardiac diseases, in particular arrhythmogenic right ventricular cardiomyopathy (ARVC) in Boxers.

Method

Recording artifacts caused by poor contact between the skin and the electrodes, breathing, shivering, or electrical interference frequently interfere with the interpretation of ECG recordings. It is, therefore, critical to dedicate enough time and personnel to obtain a good quality ECG. First, the animal should be restrained in right lateral recumbency. Although ECGs can be recorded in a standing position or in sternal recumbency in patients in respiratory distress or that are uncooperative, it may change the appearance of the ECG tracing. The electrodes should be secured at the level of the elbows and knees or as distal as possible on the four limbs to reduce artifacts secondary to the motion of the chest during breathing (Figure 8.5). Alcohol or a specifically formulated conducting gel is applied to improve contact between the skin and the electrodes. The recording sensitivity is usually selected at 10 mm/mV but should be increased or decreased according to the amplitude of the waves on the ECG. A recording speed of 50 mm/s is usually preferred. Some filters can be applied to the recording to reduce artifacts.

The placement of four electrodes on the surface of the body allows recording of six leads: I, II, III, aVR, aVL, and aVF. These six leads display simultaneously the ECG from six different directions. If a wave is mostly above the baseline, it indicates that the electrical signal travels toward the recording electrode. The wave is below the baseline if the signal moves away from the recording electrode.

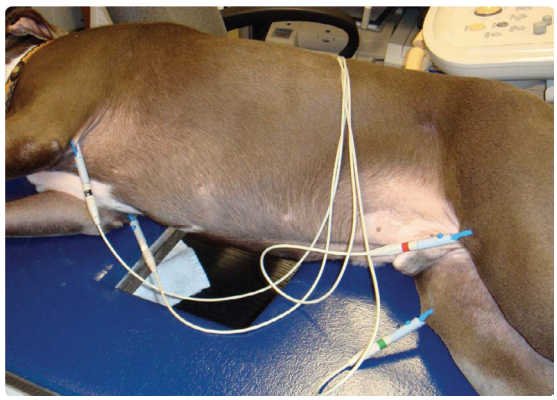


FIGURE 8.5 Electrode placement for good-quality ECG recording.

Tracing Interpretation

First, the heart rate (in beats per minute [bpm]) should be calculated manually because the number displayed by some electronic ECG systems may be inaccurate. Usually, an average heart rate calculated over a few seconds is sufficient. For example, the number of QRS complexes can be calculated for 3 seconds (which corresponds to 15 cm, or the length of a regular pen, when the recording speed is set at 50 mm/sec), and the number obtained is multiplied by 20 to obtain the heart rate per minute. Second, the waves should be identified on the tracing, and their duration and amplitude measured (Table 8.8).

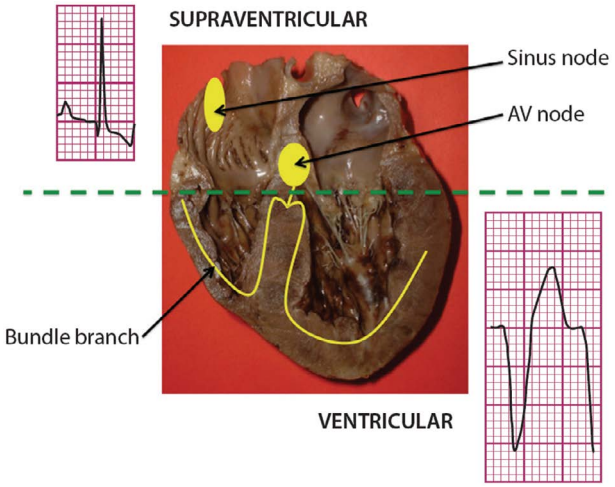


FIGURE 8.6 QRS complex morphology based on the origin of the electrical impulse. Electrical impulses originating at or above the atrioventricular node, that is the supraventricular area, conduct through the specialized conduction system (in yellow). Electrical impulses originating in the ventricles travel within nonspecialized tissue at a lower speed. Supraventricular QRS complexes are narrow; ventricular QRS complexes are wide.

The P waves can be absent in some arrhythmias, but the T waves are always present following QRS complexes. Next, the heart rhythm is analyzed in order to evaluate if it is regular or irregular and if the rhythm is sinus (each P wave related to each QRS complex with a constant PR interval) or not. Analysis of the morphology of the QRS complexes provides information on the origin (e.g., supraventricular or ventricular) of the rhythm. QRS complexes of normal duration indicate that the electrical impulse travels through the specialized conduction system within the ventricle and, therefore, that the rhythm originated in the atrium or the AV node. Conversely, wide QRS complexes usually indicate that the electrical impulses originate within the ventricles (Figure 8.6). Alternatively, it may indicate a bundle branch block, which is a lesion of part of the specialized conduction system requiring the electrical depolarization to travel slowly between cardiomyocytes. Left and right ventricular hypertrophy and intraventricular conduction disturbances can change the amplitude, duration, and/or the direction of the QRS complexes during sinus rhythm. The direction of the QRS complexes is determined by calculation of the mean electrical axis. In dogs, the QRS complex in lead I should always be positive (larger amplitude R wave), indicating that the mean electrical axis of the QRS complexes is oriented toward the left. A negative QRS complex (larger amplitude S wave) in lead I indicates a right-axis shift. In cats, the QRS complex in lead aVF should always be positive, indicating that the mean electrical axis is oriented caudally. When the QRS complex is negative in lead aVF and positive in lead I, it indicates a left-axis shift. When it is negative in lead aVF and lead I, it indicates a right-axis shift (Figures 8.7–8.12).

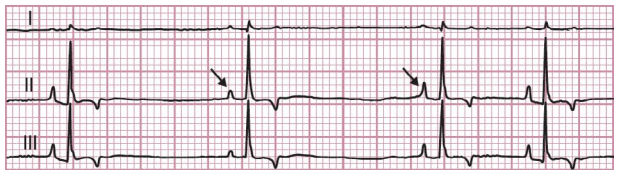


FIGURE 8.7 ECG showing respiratory sinus arrhythmia with wandering pacemaker (arrows) in a dog. Both result from variation of vagal tone with breathing in a healthy dog. Wandering pacemaker is a variation in the amplitude of the P waves with breathing caused by a shift of the origin of the electrical impulses within the sinus node (amplitude 10 mm/mV, speed 50 mm/s).



FIGURE 8.8 ECG showing sinus rhythm with a tall and wide P wave suggesting atrial enlargement (most likely left atrium) (amplitude 10 mm/mV, speed 50 mm/s).

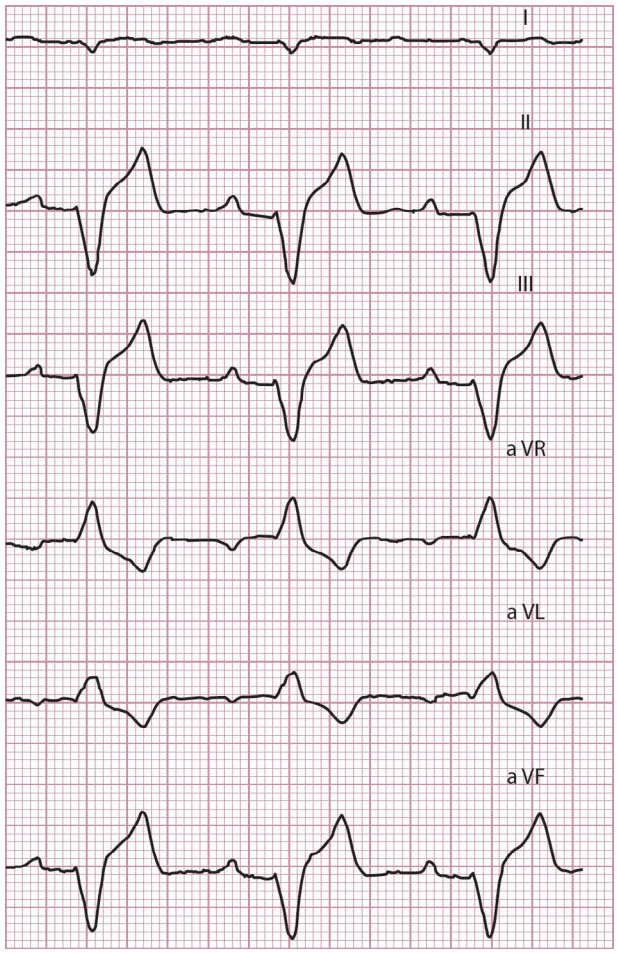


FIGURE 8.9 ECG showing sinus rhythm with a right-axis shift (negative QRS in lead I, II, III, and aVF) and wide QRS complexes, consistent with a right bundle branch block (amplitude 10 mm/mV, speed 50 mm/s).

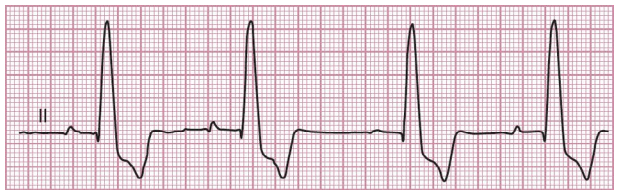


FIGURE 8.10 ECG showing sinus rhythm with positive and wide QRS in lead II, consistent with a left bundle branch block (amplitude 10 mm/mV, speed 50 mm/s).

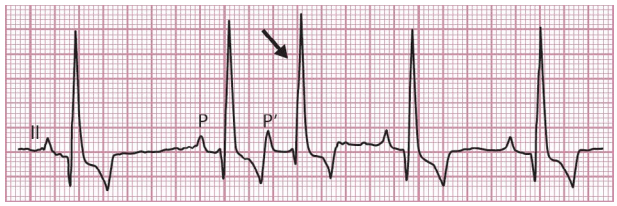


FIGURE 8.11 ECG showing sinus rhythm with one atrial premature contraction (APC) (arrow). The morphology of the QRS complex of APCs is similar to the QRS of sinus beats, as the electrical impulse uses the specialized conduction pathways in the ventricles. A P wave is visible just after the T wave, and its morphology slightly differs from the P wave of sinus beats (amplitude 10 mm/mV, speed 50 mm/s).

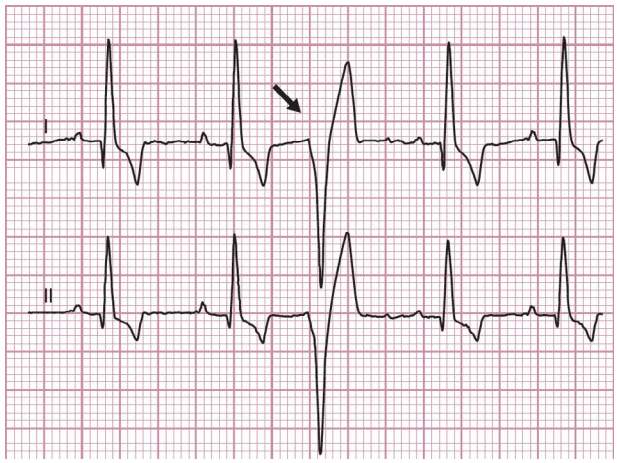


FIGURE 8.12 ECG showing sinus rhythm with one ventricular premature contraction (VPC) (arrow). The morphology of the QRS is "wide and bizarre" and very different from the QRS complexes of sinus beats. It indicates the slow conduction of the electrical impulse in the ventricles.

ECHOCARDIOGRAPHY

Indications

Echocardiography is a noninvasive method of evaluating cardiac anatomy and function. Thoracic radiography and echocardiography are complementary in the evaluation of an animal with cardiac disease. Presence or absence of CHF and size of the pulmonary vessels can only be evaluated from chest radiographs, while information about chamber size, valve motion, and ventricular function can only be obtained via echocardiography. A comprehensive echocardiographic examination requires the use of various modalities, including 2D, M-mode, and Doppler echocardiography (Figure 8.13a–d).

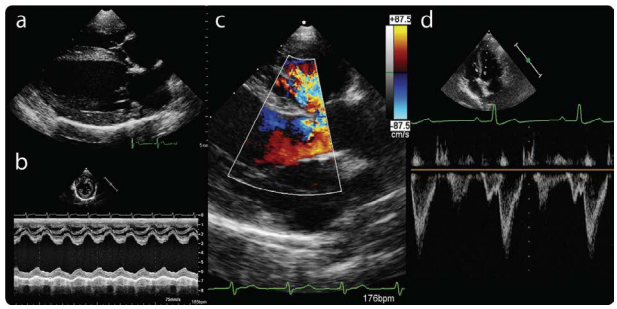


FIGURE 8.13 Echocardiographic modalities: Two-dimensional **(a)**, M-mode **(b)**, color Doppler **(c)**, spectral Doppler **(d)**.

At the end of an echocardiogram, the clinician should have identified the primary lesion and its severity, the presence of coexisting abnormalities, and the size and function of all four cardiac chambers. Finally, the initial echocardiographic examination provides baseline information for assessing the progression of the disease and monitoring the response to treatment of individual patients on follow-up examinations.

Imaging Techniques

Echocardiographic Windows

Transthoracic images of the heart can be obtained where lung tissue is not interposed between the heart and the chest wall. A parasternal window is present on the right side of the thorax between the sternal border and the costochondral junction from the 3rd to the 6th intercostal spaces. On the left side, it is close to the sternal border between the 5th and 7th intercostal spaces (caudal or apical views) and between the sternum and the costochondral junction at the 3rd or 4th intercostal space (cranial views) (Figure 8.14a–f).

Animal Positioning

Echocardiograms are usually obtained with the patient in lateral recumbency on a "cutout" table that allows transducer manipulation from beneath the animal. One or two assistants help restrain the patient in left and right lateral recumbency. ECG cables should be attached to the animal's limbs, and an ECG tracing should be continuously displayed on the monitor. Sedation is usually not needed. Dogs and cats can also be examined in standing position.

Transducer Selection

Transducers with a small contact surface are preferred. The optimal transducer frequency is, therefore, determined by the size of the animal: 8–10 MHz for cats and small breed dogs, 5–8 MHz for medium-size dogs, and 2–5 MHz for large breed dogs.

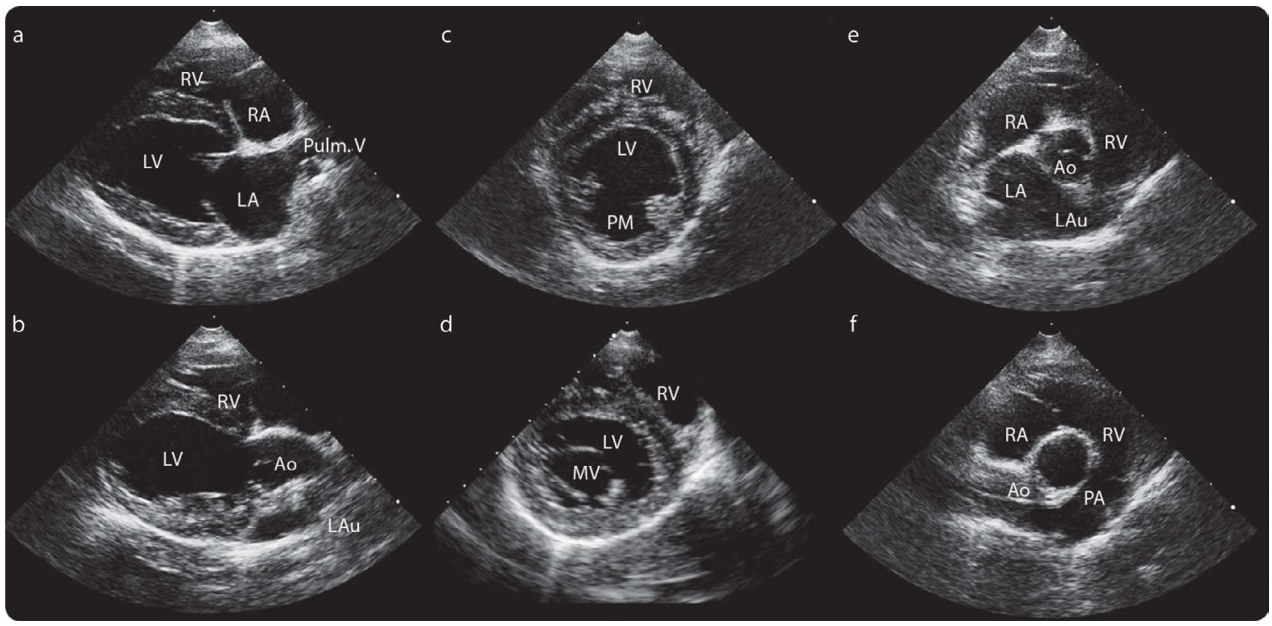


FIGURE 8.14 Standard 2D echocardiographic views. **(a)** Right parasternal long-axis four-chamber view allows visualization of all four cardiac chambers. **(b)** Right parasternal long-axis outflow view. **(c)** Right parasternal short-axis view at the level of the left ventricular papillary muscles. This view is used to measure wall thicknesses and the diameter of the left ventricle in diastole and systole. **(d)** Right parasternal short-axis view at the level of the mitral valve; also called "fish-mouth" view. **(e)** Right parasternal short-axis view at the left atrium/aorta level. This view is used to measure the diameter of the left atrium. **(f)** Right parasternal short-axis view at the pulmonary artery level. The pulmonic valve and the diameter of the pulmonary artery and its main branches can be evaluated from this view.

Echocardiographic Evaluation of Cardiac Chamber Size and Function

Every clinician should be able to evaluate left atrial size, left ventricular size and function, and the size of the right-sided cardiac chambers (Box 8.1).

Left Ventricle

The left ventricle is the largest cardiac chamber. It is conical in shape and forms the apex of the heart. The cavity of the left ventricle is divided into an inflow and an outflow region. The inflow region is directly below the mitral valve and is best assessed from the right parasternal long-axis four-chamber view and the left apical four-chamber view. The interventricular septum limits the outflow tract medially, and the septal leaflet of the mitral valve forms an intermittent lateral boundary at the base of the heart. There is no anatomic partition of the outflow tract in the apical and midventricular regions. The outflow tract is best imaged from the right parasternal long-axis outflow view and the left apical five-chamber view. The interventricular septum separates the left ventricle from the right ventricle and is best imaged from a right parasternal long-axis view. It is thick and muscular for most of its length but has a thin membranous part at the origin of the aorta.

Standard measurements include the interventricular septum thickness, the left ventricular internal diameter, and the left ventricular posterior wall thickness in end-diastole and end-systole. End-diastole is measured at the onset of the QRS complex on ECG, which also corresponds to the frame following mitral valve closure. End-systole occurs at the end of the T wave. In the absence of an ECG, end-systole coincides with the frame preceding mitral valve opening or the frame in which the left ventricular internal diameter is the smallest. Measurements are made on the right parasternal short-axis view at the chordae tendineae level, either directly with calipers on a 2D still frame or on an M-mode display (Figure 8.15).

Qualitative assessment of left ventricular function should be complemented with quantitative measurements. In dogs and cats, left ventricular systolic function is usually determined by measuring the left ventricular internal diameter at end-systole (LVIDs). Measuring

Box 8.1 Qualitative echocardiographic evaluation of cardiac structure and function in the dog

- Left and right atrium are approximately the same size
- The diameter of the left atrium is less than 1.5 times the diameter of the aortic valve annulus
- The right ventricular internal diameter is approximately one-third of the left ventricular internal diameter
- The thickness of the right ventricular wall is approximately one-third of the thickness of the left ventricular free wall
- The interventricular septum is approximately the same thickness as the left ventricular free wall
- The left ventricular internal diameter should decrease by 30%–40% in systole compared with diastole
- The diameter of the main pulmonary artery is the same as the aortic root diameter

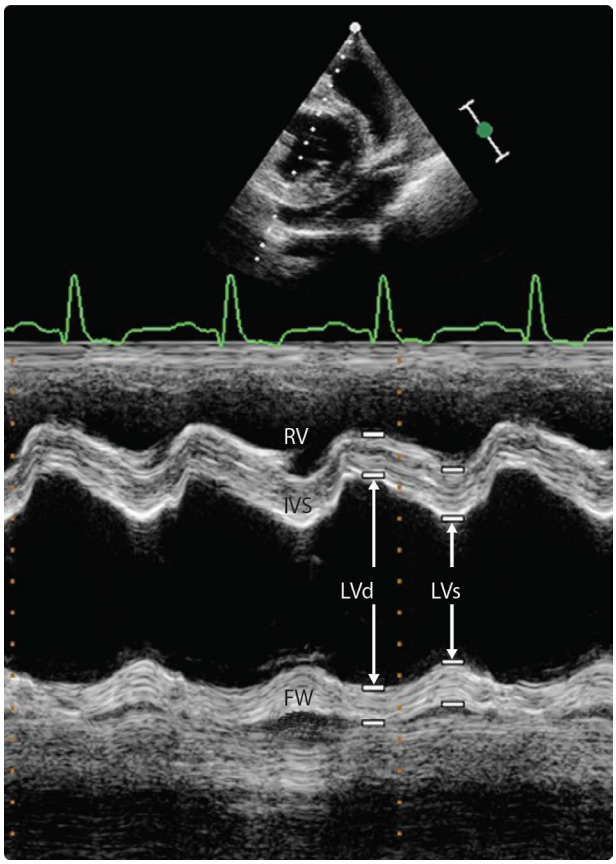


FIGURE 8.15 M-mode view of the left ventricle at the chordae tendineae level. The M-mode cursor is placed perpendicular to the interventricular septum and bisects the left ventricular free wall between the two papillary muscles. FW, left ventricular free wall; IVS, interventricular septum; LVd (LVIDd), left ventricular internal diameter in diastole; LVs (LVIDs), left ventricular internal diameter in systole; RV, right ventricle.

the left ventricular internal diameter at end-diastole (LVIDd) in either 2D or M-mode determines whether chamber dilation (eccentric hypertrophy) is present. In dogs, an allometric equation normalizing chamber dimension to body weight is used (LVIDDN). Left ventricular dilation is present when the normalized left ventricular internal dimension at end-diastole is equal to or greater than 1.7.

$$\text{LVIDDN} = \frac{\text{left ventricular internal diameter indiastole (cm)}}{(\text{body weight [kg]})^{0.294}}$$

Right Ventricle

The right ventricle has a complex geometry, described as crescent shaped or pyramid shaped. This, in addition to its smaller size and thinner walls, makes the echocardiographic assessment of the right ventricle difficult. Qualitatively, the right ventricular internal diameter is approximately one-third of the left ventricle, and the right ventricular free wall is equal to one-third or one-half the thickness of the left ventricular free wall.

The right ventricle chamber is divided into an inflow and an outflow region by a ridge of muscular tissue known as crista supraventricularis. Both regions cannot be fully examined on the same echocardiographic view. The inflow region is directly beneath the tricuspid valve. It is best assessed from the right parasternal long-axis four-chamber view and the left apical four-chamber view. The outflow region is best imaged from the right parasternal short-axis view at the aorta level and the left cranial short-axis views.

Left Atrium

The left atrium is an oval-shaped chamber positioned caudal to the aorta and above the left ventricle. It is divided into the body of the atrium and the auricle. The auricle is heavily trabeculated. The left atrium is best imaged from a right parasternal short-axis view at the aortic valve level. Contraction of the left atrium delivers 15%–30% of left ventricular filling at the end of diastole. The left atrium receives blood from five to eight (usually seven) pulmonary veins, which enter the craniodorsal and caudodorsal part of the chamber. They are usually not clearly visible on the echocardiogram, but pulmonary venous inflow can be identified and studied by pulsed-wave Doppler. The interatrial septum separates the left atrium and the right atrium. The flap of the foramen ovale may be seen from a right parasternal long-axis four-chamber view on the left atrial side in animals with a patent foramen ovale.

Linear measurements of the left atrium are used to calculate the left atrium-to-aortic ratio (LA:Ao). LA:Ao ratio is independent of body weight. In healthy dogs and cats, the LA:Ao ratio is between 1.3 and 1.5 (Figure 8.16). It is usually not > 1.6.

Right Atrium

The right atrium is an ovoid structure divided into a main chamber and the right auricle. In clinical practice, qualitative assessment of the right atrium is made by

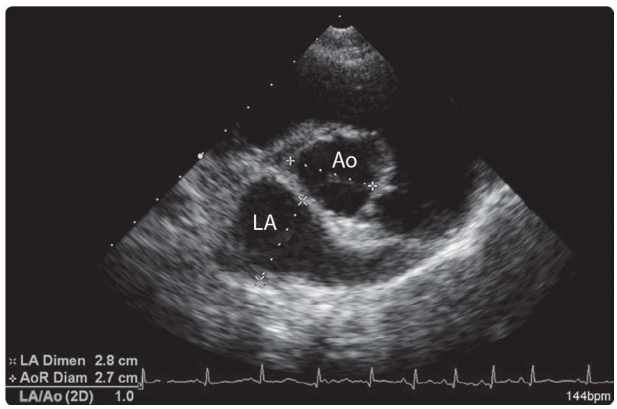


FIGURE 8.16 Measurement of the left atrium and aortic valve annulus from a 2D right parasternal short-axis view. The LA:Ao ratio should be less than 1.6 in healthy animals. Ao, aorta; LA, left atrium.

comparing its size with the left atrium. In healthy animals, left and right atrium are of comparable size.

Doppler Echocardiography

Doppler echocardiography provides information on blood flow direction and velocity. Color-flow Doppler is used to map blood flow on a 2D view of the heart. Blood flow velocity across valves, septal defects, and at the level of extracardiac vascular shunts is measured via pulsed-wave and continuous-wave Doppler. Pressure gradients between cardiac chambers can be calculated from blood flow velocity using the simplified Bernoulli equation (pressure gradient = 4 × peak velocity^2), which makes Doppler echocardiography a practical and noninvasive technique for estimating intracardiac chamber pressures.

CARDIAC BIOMARKERS

Cardiac biomarkers are biological molecules found in the blood that inform about the presence of cardiac disease.

Natriuretic Peptide

Natriuretic peptides are released by the atria and ventricles in response to stretch caused by excessive volume or pressure. A nonbiologically active fragment of the B-type natriuretic peptide (NT-proBNP) has been extensively studied. It has been suggested that NT-proBNP might be useful in identifying a cardiac cause for dyspnea, detecting occult cardiac disease (dilated cardiomyopathy [DCM], hypertrophic cardiomyopathy [HCM]), and predicting mortality in dogs with heart disease. Studies have shown that NT-proBNP has limited value as a stand-alone test but can be used to orientate a decision to pursue more advanced tests (chest radiographs, echocardiogram, Holter recording). Typically, NT-proBNP level is elevated in dogs with heart failure and increases as the heart enlarges. In cats with HCM, NT-proBNP concentration is increased. High NT-proBNP levels in a cat with pleural effusion strongly suggest a cardiac cause for the effusion. However, increased NT-proBNP concentration is also detected with hyperthyroidism, systemic hypertension, PH, and renal failure because it is renally excreted. Noncardiac disease should be suspected in a dyspneic cat with normal NT-proBNP levels.

Cardiac Troponin I

Cardiac troponin I (cTnI) is one of the proteins involved in contraction of cardiomyocytes. Disruption of the membrane of some cardiomyocytes leads to leakage of cTnI into the circulation. Moderate-to-large elevations in cTnI concentration can be detected with current assays. Moderate elevations (approximately ten-fold increase compared with healthy animals) are common in the presence of CHF, third-degree AV block, or subaortic stenosis (SAS). Large elevations (approximately 50- to 200-fold increase compared with healthy animals) are thought to indicate myocarditis if this diagnosis is supported by the history and clinical presentation. Important elevations of cTnI concentration also occur with myocardial infarction, which is rare in dogs and cats.

HEART FAILURE

Definition/Overview

Heart failure occurs when there is inadequate delivery of oxygen to the tissues of the body from impaired cardiac function and maldistribution of blood despite adequate venous return to the heart. CHF occurs with impaired cardiac function and a concurrent increase in venous and capillary pressures, which result in fluid accumulation in tissues and organs of the body.

Pathophysiology

Biochemical, mechanical, and functional alterations occur in the failing heart. Biochemical changes are dominated by a decrease in the rate of adenosine triphosphate (ATP) hydrolysis. Cardiac contraction depends on the interaction between actin and myosin proteins, particularly the heavy meromyosin heads that repeatedly bind to actin. Decreased ATP hydrolysis leads to less interaction of heavy meromyosin heads with actin. The primary mechanical derangement in the failing heart is a reduction of the maximal velocity at which the heavy meromyosin heads can cycle, resulting in a decrease in myocardial fiber shortening. Overall, this is a decrease in contractility or pump function that is observed with heart failure. In a healthy heart, increased ventricular filling (or preload) results in a more forceful contraction. The failing heart, however, generates a lower force of contraction (systolic function) than expected despite an increased preload present prior to contraction. Hence, for any given preload, the systolic function is less than anticipated when compared with normal.

A small decrease in cardiac output is detected by high-pressure baroreceptors in the aorta and triggers an activation of the adrenergic system. Alpha and beta-adrenergic stimulation results in an increase in heart rate and cardiac contractility, as well as peripheral vasoconstriction. In addition to the stimulation of the sympathetic nervous system, renin is released from the kidneys secondary to decreased renal blood flow. Angiotensinogen is cleaved via renin to angiotensin I in the liver. Angiotensin I is then cleaved by the angiotensin-converting enzyme (ACE) to angiotensin II in the vasculature. Angiotensin II activation results in vasoconstriction; antidiuretic hormone (ADH) release from the posterior pituitary gland, which further constricts small arteries, arterioles, and veins and decreases urine production; and aldosterone release from the adrenal medulla, which results in sodium and water retention in the distal collecting duct. Moreover, over

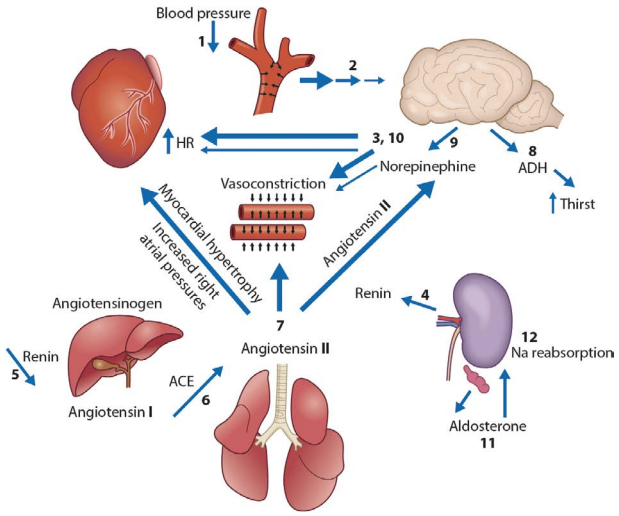


FIGURE 8.17 Sequence of compensatory mechanisms during heart failure. Numbers indicate the sequence of events. Vascular under filling (1) detected by the arterial baroreceptors activates the sympathetic nervous system (2), resulting in vasoconstriction and tachycardia (3), and renin release (4). Activation of the renin angiotensin system (5–7) contributes to activation of the sympathetic system (9) and vasoconstriction (10). Release of ADH (8) causes thirst, and aldosterone (11) is responsible for sodium and water retention (12).

time, angiotensin II stimulates myocardial hypertrophy, fibrosis, and vascular smooth muscle growth, leading to arteriolar narrowing (Figure 8.17).

Pulmonary edema from left-sided CHF occurs typically when left atrial pressure is above 18–22 mmHg (normally 7 mmHg), and a large volume of serum begins to weep from the pulmonary capillaries into the lung inter stitium and alveolar space at a rate above the capacity of the pulmonary lymphatics to drain it in accordance with the principles of Frank-Starling law.

Clinical Presentation

Animals with left-sided CHF (pulmonary edema) typically present with tachypnea and dyspnea depending on the chronicity and amount of edema accumulation. Thoracic auscultation most commonly reveals tachycardia; however, some cats and, rarely, dogs are bradycardic. Cardiac auscultation may also reveal the presence of heart murmurs, gallop sounds, and arrhythmias. Respiratory sounds are usually increased, and crackles may or may not be present. Tachycardia with increased respiratory rate and effort in a dog is a more reliable indicator of pulmonary edema than the presence of crackles alone. Cough may be present but can commonly occur with airway disease in small breed dogs with concurrent mitral valve degeneration and tracheal collapse. Cough in a large breed dog is a more reliable indicator of pulmonary edema. Syncope may also be reported in dogs with mild pulmonary edema. More severe clinical signs include coughing up pink-tinged sputum; these animals require immediate emergency attention and exceptional measures such as intubation and mechanical ventilation (Figure 8.18).



FIGURE 8.18 Dog with severe pulmonary edema coughing up pink, blood-tinged sputum.

Left-sided CHF in cats may differ from dogs in terms of clinical signs and fluid accumulation. Cats more frequently develop bradycardia, hypotension, and hypothermia. Additionally, left-sided CHF can also lead to pleural effusion and/or small amounts of pericardial effusion. Dual venous drainage of the pleural surfaces in cats can allow pleural effusion with left- and/or right-sided CHF. It is hypothesized that in cats with left-sided CHF the visceral lung drainage via the pulmonary veins is impaired and pleural effusion results. Conversely, pleural effusion in cats with right-sided CHF would result from impaired drainage of the parietal lung via the systemic veins.

Right-sided CHF in dogs typically causes ascites. Pleural effusion, pericardial effusion, and subcutaneous edema can also be seen but tend to occur at a later stage of the disease than ascites. Pleural effusion alone is unusual but can be seen with tricuspid valve dysplasia (TVD)/stenosis, pericardial disease, cranial caval obstruction, and supraventricular tachyarrhythmias. Signs of right-sided CHF include abdominal distension, jugular pulsation and distension, positive hepatojugular reflex, and possibly swollen subcutaneous tissue. Limb edema is most commonly seen with advanced disease, and focal facial and neck swelling may suggest cranial caval obstruction or pericardial disease. Auscultation most commonly reveals tachycardia. Murmurs, gallop sounds, split S2 heart sounds, and arrhythmias may also be noted. Lung sounds and heart sounds may be decreased in the presence of a large volume of pleural effusion.

In cats, right-sided CHF is rare, and ascites alone in a cat is usually not cardiac related. Pleural effusion is the most common presentation for right-sided CHF in cats.

Differential Diagnosis

Conditions that mimic left-sided CHF include pulmonary thromboembolism (PTE), noncardiogenic pulmonary edema (airway obstruction, electrocution, strangulation, near-drowning, neurogenic), hemorrhage, neoplasia, systemic inflammatory response syndrome, and acute respiratory distress syndrome. Differential diagnoses for ascites and pleural effusion should include right-sided CHF, hypoalbuminemia, hepatic disease, vasculitis, hemorrhage, infection, and neoplasia.

Diagnosis

Diagnosis of left-sided CHF can be made readily from thoracic radiographs (see Chapter 6). Pulmonary edema can be noted in canine patients, and pulmonary edema and/or pleural effusion may be noted in cats. In dogs, pulmonary infiltrates are most commonly seen in the caudodorsal lung lobes and typically in the right caudal lung lobe first. Left-sided cardiomegaly will often be present, as well as pulmonary venous distension unless the patient is already being administered furosemide (Figure 8.19). In cats, pulmonary edema has a more diffuse distribution, and cardiomegaly may be more difficult to recognize than in dogs. Ultrasonography is a useful tool to detect pleural effusion.

Diagnosis of right-sided CHF can be made from physical examination, radiographs, and/or ultrasound. Thoracic radiographs may show pleural effusion and suggest ascites as a loss of detail in the cranial abdomen. Abdominal ultrasound shows abdominal effusion and hepatic venous congestion.

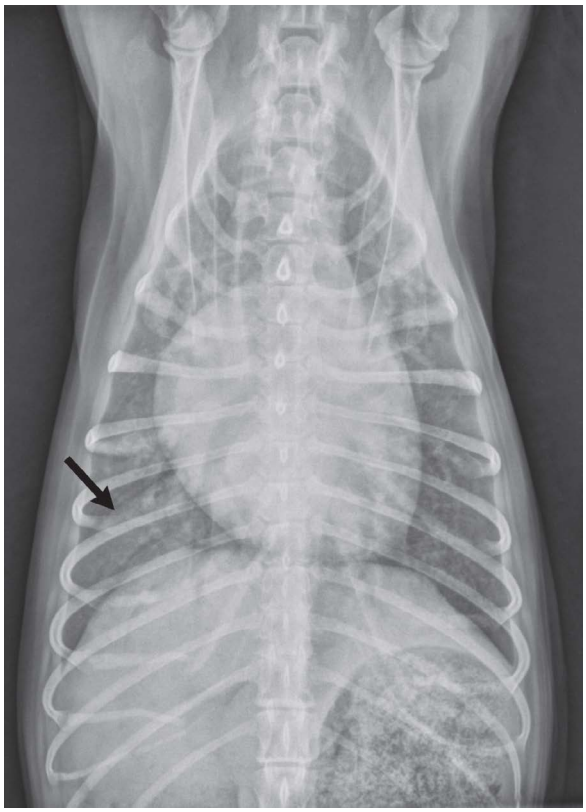


FIGURE 8.19 Radiograph from a dog with cardiogenic pulmonary edema. Note that the alveolar pattern is predominantly right-sided (arrow).

Management

Treatment recommendations are made according to a classification of the consecutive stages of heart failure (Table 8.9). Drugs indicated for the treatment of heart failure include diuretics, inodilators (pimobendan), ACE inhibitors, aldosterone antagonists, vasodilators,

TABLE 8.9 Classification of heart disease stages (based on American College of Veterinary Internal Medicine [ACVIM] consensus statement)

Stage of heart disease	Description
A	Animals at high risk for developing heart disease but currently have no identifiable structural disorder of the heart
B	Animals with structural heart disease (e.g., the typical murmur of mitral valve regurgitation is present) but have never developed clinical signs caused by heart failure – *Stage B1:* Asymptomatic animals that have no radiographic or echocardiographic evidence of cardiac remodeling in response to CVHD MMVD as well as those in which remodeling changes are present but not severe enough to initiate medical therapy (pimobendan) – *Stage B2:* Asymptomatic animals that have hemodynamically significant valve regurgitation, as evidenced by radiographic or echocardiographic findings of left-sided heart enlargement and for whom medical therapy is warranted (pimobendan)
C	Animals with past or current clinical signs of heart failure associated with structural heart disease May or may not require hospitalization and aggressive therapy
D	Animals with end-stage disease with clinical signs of heart failure caused by MMVD that are refractory to standard therapy Such patients require advanced or specialized treatment strategies in order to remain clinically comfortable with their disease As with stage C, some animals in stage D will require acute, hospital-based therapy, and others can be managed as outpatients

CVHD, chronic valvular heart disease; MMVD, myxomatous mitral valve disease.

TABLE 8.10 Drugs commonly used in treatment of congestive heart failure*

Diuretics	– Furosemide 0.5–4 mg/kg p.o., IM or IV q.8–12h.; usually 0.3–0.5 mg/kg/h CRI (up to 1 mg/kg/h in refractory cases) – Spironolactone 0.5–2 mg/kg p.o. q.12–24h. – Hydrochlorothiazide 0.5–1 mg/kg p.o. q.12–48h. – Torsemide—total daily furosemide dose divided by 10–20 and split into p.o. q.12–24h. dosing (author currently uses total daily furosemide dose divided by 10 and split into q.12h. dosing)
ACE inhibitors	– Benazepril 0.25–0.5 mg/kg p.o. q.24h. – Enalapril 0.25–0.5 mg/kg p.o. q.12–24h.
Positive inotropes	– Pimobendan 0.2–0.4 mg/kg p.o. q.12h. – Digoxin 0.005 mg/kg p.o. q.12h. – Dobutamine 3–10 μg/kg/min IV CRI
Calcium channel blockers	– Amlodipine 0.1–0.5 mg/kg p.o. q.24h. – Diltiazem 0.5–2 mg/kg p.o. q.8–12h. – Diltiazem extended release 2–5 mg/kg p.o. q.12h.
Beta-adrenergic receptor blockers	– Atenolol 0.5–2 mg/kg p.o. q.12–24h. – Propranolol (beta 1 & 2) 0.25–2 mg/kg p.o. q.8h.
Vasodilators	– Nitroprusside 2–5 μg/kg/min CRI – Hydralazine 0.5–3 mg/kg p.o. q.12h.
Nitrates	– Nitroglycerin small dogs: 1/4–1/2 inch topically; medium dogs: 1/2–1 inch; large dogs 1–2 inches q.6–12h. for 24–48 hours (wear gloves) – Isosorbide dinitrate 0.2–2 mg/kg p.o. q.12h.
PDE-5 inhibitor	– Sildenafil 1–3 mg/kg p.o. q.8–12h.

* All doses are for canines unless otherwise indicated. CRI, continuous rate infusion; PDE-5, phosphodiesterase-5.

positive inotropes, and modulators of the autonomic tone (Table 8.10).

In dogs with valvular disease or dilated cardiomyopathy, pimobendan should be initiated once radiographic and echocardiographic evidence of heart enlargement are present (stage B2). The initiation of ACE inhibitors in dogs with severe cardiac disease but no evidence of decompensation (stage B2) is controversial. Dogs with stage B1 and B2 heart disease should be rechecked every 6–12 months to monitor progression of the disease, and owners should be educated to recognize the signs of CHF. Whenever the risk of CHF is high, the pet owner should monitor the animal's resting respiratory rate on a daily basis. A resting respiratory rate above 40 bpm is a sensitive indicator of CHF and should trigger evaluation by a veterinarian.

Treatment of left-sided CHF in dogs always involves administration of furosemide. IV, SC, or IM furosemide and oxygen therapy should be considered in patients with moderate-to-severe pulmonary edema and clinical signs. IV furosemide is beneficial in these patients to rapidly clear edema and cause release of prostaglandins, which increase renal blood flow. Administration of furosemide as a constant rate infusion (CRI) is a good alternative to repeated boluses every few hours; however, a bolus of furosemide should always be given when the CRI is started. In hospitalized patients, IV dobutamine administration for positive inotropic support via direct beta-adrenergic stimulation can be considered, especially in patients with DCM or advanced mitral valve disease. Pimobendan should be administered during hospitalization as part of the management of acute heart failure. Afterload reduction with IV nitroprusside through direct vasodilatory properties can be considered, especially in cases that are refractory to standard diuretic therapy. Mild edema may be treated on an outpatient basis with possible single-dose administration of furosemide (IV, SC, or IM) and continued therapy at home with oral furosemide. Pimobendan should always be initiated at the time of diagnosis if the dog is not already taking it, as long as there are no known contraindications to its use (left ventricular outflow tract obstruction). An ACE inhibitor should always be instituted for the long-term management of all cardiac patients with left-sided CHF as long as renal values and clinical signs related to renal disease are reasonable and the patient is eating well at home. ACE inhibitors are imperative for blunting the neurohormonal activation of the renin–angiotensin–aldosterone (RAAS) system, which is stimulated by the continuous administration of furosemide. Further RAAS blockade can be considered with spironolactone administration, an aldosterone blocker and weak potassium-sparing diuretic. Arrhythmias that are present may also require treatment. Chronic, refractory left-sided CHF can be managed by multinephron blockade with additional diuretics that work at different levels of the kidney (spironolactone, hydrochlorothiazide). Hydrochlorothiazide must be used very cautiously in patients with concurrent kidney disease, low sodium, and refractory CHF, as this diuretic will interfere with the ability of the patient to dilute urine and excrete solute free water. Torsemide, a diuretic 10 to potentially 20 times more potent than furosemide can be used to replace furosemide in chronic cases. Finally, sildenafil administration for treatment of severe PH can be considered with caution, as treatment may worsen left-sided CHF.

Treatment of right-sided CHF in canine patients is similar to that for left-sided CHF. Typically, treatment



FIGURE 8.20 Abdominocentesis in a dog using a 16-gauge catheter.

is not as urgent, but initiation of injectable furosemide may be beneficial in cases with ascites where abdominal organs surrounded by fluid may not readily absorb oral furosemide. Body cavity fluid removal is as imperative as furosemide administration, and as much fluid as possible should be removed from the abdominal and/or pleural spaces (Figure 8.20). Oral administration of the medications previously discussed is also recommended for right-sided CHF, with an emphasis on diagnosing and treating PH. Administering spironolactone is recommended by some, as normal aldosterone breakdown by the liver may be inhibited with a congested liver and right-sided CHF. Additionally, atrial tachyarrhythmias should also be investigated and treated, as loss of atrial contraction may worsen right-sided CHF more than left-sided CHF. Furosemide doses may also be more conservative in cases of severe PH where dramatic preload reduction may result in poor forward flow and systemic hypotension.

Treatment of cats with CHF will vary from dogs in five major ways: (1) Furosemide dosage will be lower and more conservative; (2) efforts should be made to correct hypothermia and hypotension; (3) pimobendan is only indicated if there is no evidence of a left ventricular outflow tract obstruction; (4) hypokalemia is a common side effect of furosemide therapy; therefore, potassium concentration should be monitored frequently and oral supplementation initiated before signs of hypokalemia occur; (5) diuretics other than furosemide and spironolactone must be used with extreme caution.

PH, cough from bronchi compression by an enlarged heart, and syncope are also complications of heart failure that may require specific therapies (Table 8.11).

TABLE 8.11 Treatment of clinical signs of heart failure in the absence of congestive heart failure

Clinical sign	Treatment
Syncope	Rule out CHF with radiographs and consider ruling out an arrhythmia via Holter monitor Start or adjust dosage of ACE inhibitor, spironolactone, or pimobendan or increase current dose of furosemide to alter loading of the heart
Pulmonary hypertension	Sildenafil 1–3 mg/kg p.o. q.8–12h.
Cough	Hydrocodone 0.25 mg/kg p.o. q.6–12h. or butorphanol 0.2–0.4 mg/kg p.o. q.6–12h.

Prognosis

The average survival time for a patient with CHF is approximately 6–14 months with aggressive medical management. Dogs with right-heart failure and recurrent ascites quickly develop cardiac cachexia, which significantly impairs their quality of life.

CONGENITAL HEART DISEASES

Congenital heart diseases (CHDs) are morphologic abnormalities of the heart and great vessels present at birth. CHDs are uncommon in dogs and rare in cats. The most common CHDs in the dog are SAS, PS, and PDA. The most common CHDs in the cat are atrial septal defects (ASDs), ventricular septal defects (VSDs), and valvular dysplasias. Although many CHDs have breed predispositions and some have been shown to be heritable traits, not all CHDs are inherited (Table 8.12). CHDs are often diagnosed based on auscultation of a significant or unusual murmur in a young patient, leading to further cardiac workup. Swift detection may allow for treatment at an earlier stage of disease, improving patient prognosis and quality of life.

SUBAORTIC STENOSIS

Definition/Overview

Aortic stenosis results from a narrowed left ventricular outflow tract in the region of the aortic valve, which can occur at a subvalvular, valvular, or supravalvular level. In dogs, the most common manifestation is subaortic stenosis (SAS).

Etiology

A genetic mutation responsible for SAS has been identified in Newfoundlands.

Pathophysiology

Stenosis occurs from anomalous development of a fibrous band or ring of tissue at the subvalvular level which interferes with blood flow. The induced pressure overload on the left ventricle causes left ventricular concentric hypertrophy and sometimes left atrial enlargement. The turbulence and increased velocity of flow through the stenotic outflow tract creates a left systolic basilar murmur. SAS predisposes to ventricular arrhythmias secondary to myocardial ischemia due to the increase in myocardial volume, diminished coronary blood flow, and subendocardial fibrosis. Less commonly, the increase in pressure in the left atrium can lead to left-sided CHF.

Clinical Presentation

Animals with moderate-to-severe SAS often present with signs of failure to thrive, exercise intolerance, and syncope. Tachypnea or dyspnea associated

TABLE 8.12 Breed predisposition for congenital heart diseases

Congenital defect	Breed predisposition	Known heritable mutation
Subaortic stenosis	Newfoundland, Rottweiler, Golden Retriever, Boxer, Great Dane, German Shorthair Pointer, German Shepherd Dog, Bouvier des Flandres, English Bulldog, Samoyed, Bull Terrier (valvular stenosis)	Newfoundland
Pulmonic stenosis	English Bulldog, French Bulldog, West Highland White Terrier, Beagle, Mastiff, Samoyed, Miniature Schnauzer, American Cocker Spaniel, Keeshond, Boxer, Chihuahua, Airedale Terrier	Beagle
Tricuspid valve dysplasia	Labrador Retriever, Golden Retriever, German Shepherd Dog	Labrador Retriever
Ventricular septal defect	Beagle, English Springer Spaniel, Keeshond, English Bulldog	Beagle, English Springer Spaniel
Atrial septal defect	Poodle, Dobermann, Boxer, Samoyed	Poodle
Mitral valve dysplasia	Bull Terrier, Rottweiler, Golden Retriever, Newfoundland, Mastiff, German Shepherd Dog	
Patent ductus arteriosus	Poodle, German Shepherd Dog, Pomeranian, Shetland Sheepdog, Collie, Maltese, Yorkshire Terrier, Chihuahua, Bichon Frise, Keeshond, American Cocker Spaniel, Rottweiler, English Springer Spaniel, Labrador Retriever, Newfoundland	Poodle
Tetralogy of Fallot	Keeshond, English Bulldog, Wire-haired Fox Terrier, Miniature Schnauzer, West Highland White Terrier	Keeshond
Persistent right aortic arch	German Shepherd Dog, Irish Setter, German Short-haired Pointer, Greyhound	German Short-haired Pointer

with the development of CHF occurs in older dogs. Animals that develop rapid and sustained ventricular tachyarrhythmias may die suddenly. Physical examination reveals a left basilar systolic murmur whose grade correlates with the degree of SAS, weak femoral pulses when the stenosis is severe, and, on occasion, arrhythmias.

Differential Diagnosis

PS, VSD, physiologic murmur.

Diagnosis

Thoracic radiographs may show a poststenotic dilation of the aortic root. Definitive diagnosis is accomplished via echocardiography, which allows visualization of the location of the stenosis and the fibrous anomaly itself, as well as the severity of secondary changes, including left ventricular concentric hypertrophy and atrial dilation (Figure 8.21a, b). Aortic insufficiency is often present. Color-flow echocardiography may show turbulent blood flow through the left ventricular outflow tract, and Doppler echocardiography is used to quantify the severity of the stenosis based on the peak systolic aortic blood flow velocity (Figure 8.22). A pressure gradient above 80 mmHg across the stenosis is consistent with severe SAS. Boxers and Golden Retrievers, which are predisposed to SAS, can also have mild forms of the disease that result in soft murmurs that can be difficult to differentiate from physiologic murmurs. In Boxers, a narrow left ventricular outflow tract compared with similar-sized dogs may explain the high prevalence of physiologic murmurs in this breed.

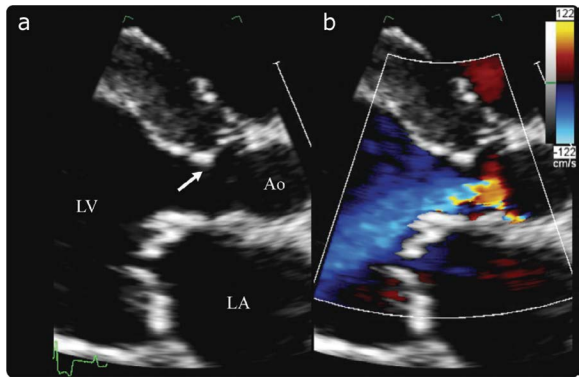


FIGURE 8.21 (a) Right parasternal long-axis echocardiographic view showing a subaortic ridge (arrow). **(b)** Color Doppler reveals turbulence in the aorta beyond the stenotic lesion.

Management

Moderate-to-severe SAS can be medically managed with beta-blockers (atenolol, 0.5–1 mg/kg p.o. q.12–24h.) to slow the heart rate, reduce myocardial oxygen demand, and for their antiarrhythmic properties. The goal of medical therapy is to decrease the frequency of syncopal episodes, improve exercise tolerance, and reduce the risk of sudden death. Interventional procedures to relieve the stenosis have had mixed results. Severe cases of SAS with a poor long-term prognosis may benefit from balloon valvuloplasty with a cutting and/or high-pressure balloon to relieve the pressure gradient across the stenosis, but this technique is as yet unproven in terms of improving quality of life and long-term survival. The less common cases of valvular stenosis may improve with a

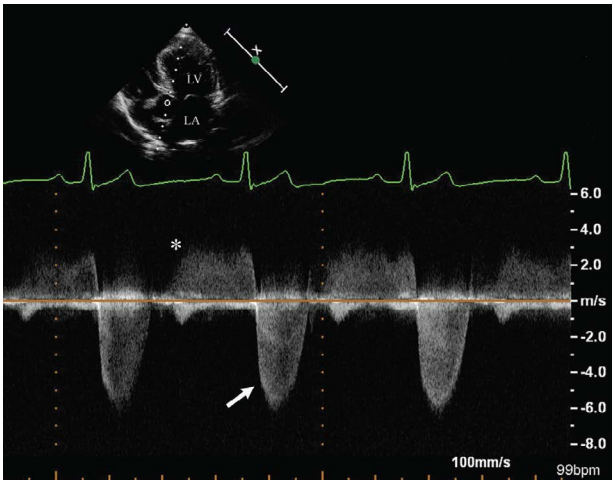


FIGURE 8.22 Continuous-wave Doppler recording of aortic flow in a dog with severe subaortic stenosis. The ultrasound beam has been oriented parallel to the blood flow from a left-sided apical four-chamber echocardiographic view. Peak velocity in systole is 6 m/s (pressure gradient of 164 mmHg) and consistent with severe subaortic stenosis (arrow). There is also aortic insufficiency in diastole (asterisk).

more traditional balloon valvuloplasty technique. CHF is managed as appropriate with diuretic and ancillary medications. Antibiotics are recommended during surgery and for dental prophylaxis procedures because of the mildly increased risk of infective endocarditis found in patients with SAS.

Prognosis

Mild SAS has a good prognosis, but cases of moderate SAS tend to develop CHF later in life. Dogs with severe SAS are at significant risk of sudden death before 3–5 years of age.

PULMONIC STENOSIS

Definition/Overview

Pulmonic stenosis (PS) results from a narrowed right ventricular outflow tract in the region of the pulmonic valve, which can occur at a subvalvular, valvular, or supravalvular level. The most common manifestation in dogs is valvular. PS is less common in cats. The lesion consists of thickening or fusion of the valve leaflets and may be accompanied by hypoplasia of the valve annulus. English Bulldogs and some Boxers may have an abnormal coronary vasculature, which consists of a single right coronary artery circling in front of the pulmonary artery to supply blood to the left ventricle (R2A anomaly) (Figure 8.23). This vessel might contribute to the stenosis and may rupture or be occluded during balloon valvuloplasty, resulting in the dog's death. Other coronary vasculature anomalies have been described, such as a single left coronary artery, but they do not always preclude from performing a valvuloplasty.

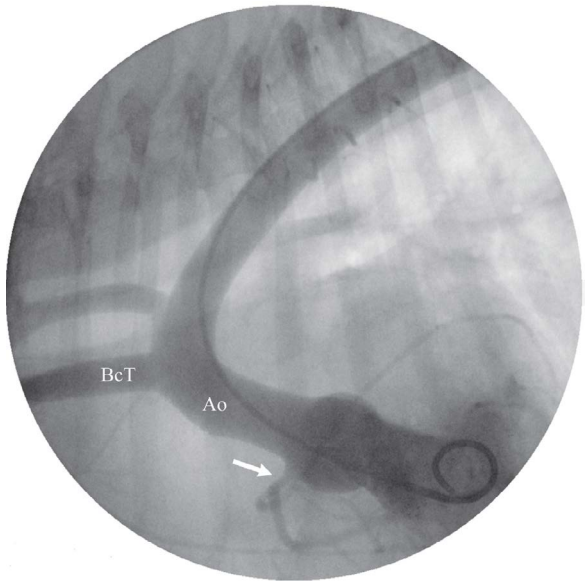


FIGURE 8.23 R2A anomaly in an English Bulldog. Aortogram using a pigtail catheter reveals a single coronary artery originating from the right coronary cusp (arrow). A branch crosses in front of the aorta and supplies blood to the left ventricle. Ao, aorta; BcT, brachiocephalic trunk.

Etiology

PS is heritable in Beagles.

Pathophysiology

The obstruction to flow results in an increased pressure within the right ventricle, causing concentric right ventricular hypertrophy and myocardial fibrosis with possible dilation of the right atrium. Turbulent blood flow and increased velocity through the stenotic valve result in a left basilar systolic murmur. Patients with severe PS develop right-sided diastolic dysfunction and ultimately are at risk of right-sided CHF from chronic pressure overload. Right ventricular myocardial failure may eventually result from severe PS. TVD is an occasional concurrent congenital defect and results in exacerbation of right heart dysfunction and more severe clinical signs.

Clinical Presentation

Most animals with PS will have no clinical signs to mild clinical signs. The approximately one-third of dogs with PS that do exhibit clinical signs often present with dyspnea, lethargy, exercise intolerance, or syncope. In later stages, signs associated with right-sided heart failure may be present. Physical examination reveals a left-sided systolic basilar murmur (with a concurrent right apical murmur if tricuspid regurgitation is present). Jugular distension is associated with an increase in right atrial pressure. If right-sided CHF is present, abdominal palpation may reveal the presence of ascites and hepatomegaly. The presence of a patent foramen ovale at the atrial level can be the site of right-to-left blood shunting, leading to cyanosis, hypoxemia, and polycythemia.

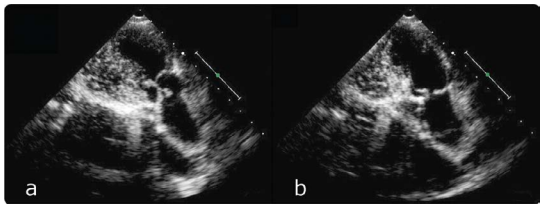


FIGURE 8.24 Right parasternal short-axis echocardiographic view from a dog with pulmonic valve stenosis. The valve is shown in diastole **(a)**. In systole, the valve takes a dome-like shape **(b)**.

Differential Diagnosis

SAS, physiologic murmur, tetralogy of Fallot (TOF), VSD.

Diagnosis

Thoracic radiographs often show the presence of post-stenotic dilation of the pulmonary trunk and right-sided cardiomegaly. Echocardiography is used to determine the structure of the pulmonic valve and the severity of ventricular concentric hypertrophy and to detect the presence of tricuspid insufficiency (Figure 8.24a, b). Doppler echocardiography is essential to determine the severity of the stenosis. Continuous-wave Doppler is used to determine the peak systolic pressure gradient across the stenosis. Good alignment of the Doppler beam with blood flow can usually be obtained from the right parasternal short-axis view at the level of the pulmonary artery or from a left cranial window along the sternum. The severity of the stenosis is based on peak systolic pressure gradient. It is mild when the peak gradient is between 20 and 49 mmHg (velocity of 2.25–3.5 m/s), moderate when peak gradient is between 50 and 80 mmHg (velocity of 3.5–4.5 m/s), and severe if the peak gradient is above 80 mmHg (velocity above 4.5 m/s).

Management

The goal of treatment is to reduce the systolic right ventricular pressure overload. This is accomplished in cases of moderate-to-severe PS via surgical procedures or balloon valvuloplasty. Balloon valvuloplasty works best in cases of valvular stenosis without hypoplasia of the valve annulus (Figure 8.25). Generally, a reduction of 40%–50% can be expected in the pressure gradient, and this reduction is maintained in the majority of cases. In cases of mild PS or those with mild clinical signs, beta-blockers can be used to reduce myocardial oxygen demand and for their antiarrhythmic properties.

Prognosis

Prognosis varies based on the severity of the stenosis.

PATENT DUCTUS ARTERIOSUS

Definition/Overview

The ductus arteriosus during fetal development serves to shunt oxygenated blood from maternal circulation away from the fetal lungs directly to the systemic circulation. When the lungs inflate at birth, reversal of the blood flow brings oxygenated blood from the aorta through the ductus and stimulates constriction of the ductus smooth muscle. Normally, the ductus closes by 7–10 days after birth. A patent ductus arteriosus (PDA) occurs when the ductus remains patent past this period, allowing blood to shunt according to the pressure gradient.

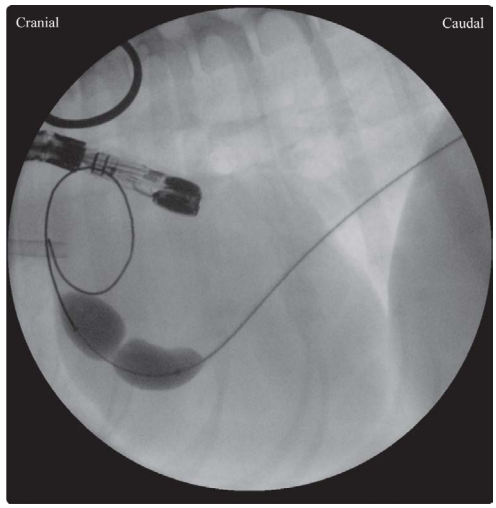


FIGURE 8.25 Fluoroscopic view during balloon valvuloplasty. The catheter is inserted from a femoral vein and positioned at the level of the pulmonic valve. During inflation, a waist is seen in the center of the balloon. Rapid expansion of the balloon usually results in a successful procedure.

Etiology

PDA is considered heritable in Poodles.

Pathophysiology

In most cases, a PDA results in blood shunting from the aorta to the pulmonary artery (left-to-right shunt) and left-sided volume overload. The blood shunting directly to the pulmonary circulation returns to the left side of the heart. As a result, the left ventricle and the left atrium become dilated. Large shunts increase the filling pressure in the left heart and pulmonary veins, with the end result being left-sided CHF. The severity of the shunt (mostly determined by the size of the patent vessel) and the presence of other defects result in varying progression of secondary changes. In rare cases with large shunts and severe PH, shunt reversal is observed. Blood thus flows from the pulmonary artery to the aorta—a right-to-left shunt—causing a differential cyanosis, hypoxemia, and eventually polycythemia (Eisenmenger physiology). Shunt reversal typically occurs in puppies that are a few days to a few weeks old. It is not the usual progression of a PDA in adult dogs.

Clinical Presentation

Clinical signs vary based on the size of the shunt, the direction of the shunt, and the presence of CHF. Signs

may include exercise intolerance, syncope, cough, dyspnea, and, in the case of a reverse shunt, hind limb weakness or seizures. On physical examination of animals with a left-to-right PDA, a pathognomonic continuous (machinery) murmur is heard cranially in the left axillary region. Bounding femoral pulses may be palpated due to diastolic runoff. In animals with a reverse PDA, there is no audible murmur, but careful inspection of the mucous membranes should reveal differential cyanosis, that is cyanosis limited to the caudal mucous membranes.

Differential Diagnosis

Aorto pulmonary window, which is a connection between the ascending aorta and the pulmonary trunk. A to-and-fro murmur from aortic stenosis and insufficiency could mimic the continuous murmur heard with a PDA.

Diagnosis

Thoracic radiographs may show left-sided cardiomegaly, pulmonary over circulation, signs of CHF, and a ductal aneurysm of the aorta at the insertion of the ductus. Electrocardiography frequently shows a tall R wave in lead II (indicative of left ventricular enlargement). Echocardiography is necessary to confirm the presence of the shunt, evaluate the severity of left heart chamber enlargement, and identify concurrent CHDs and the presence of mild-to-severe PH. Measurement of the shunt is performed to determine suitable procedures for shunt closure (Figure 8.26a, b).

Management

PDAs are best treated with early closure, either by surgical or cardiac catheterization procedures. Medical treatment for patients in CHF is indicated prior to closure. Surgery performed by experienced surgeons has a success rate of up to 95% (Figure 8.27), and there are comparable results for catheterization procedures, even in very small dogs. Current interventional procedures used to close shunts use catheterization to place coils (coil embolization) or other devices produced specifically to interrupt blood flow across the shunt (occluder, vascular plug) (Figure 8.28). Residual flow after intervention, if present, may decrease over time. The risk of infection of the implants is unknown. Antibiotics are recommended during surgery and for dental prophylaxis procedures for 1 year after the implant is placed. Closure of reverse PDAs is contraindicated.

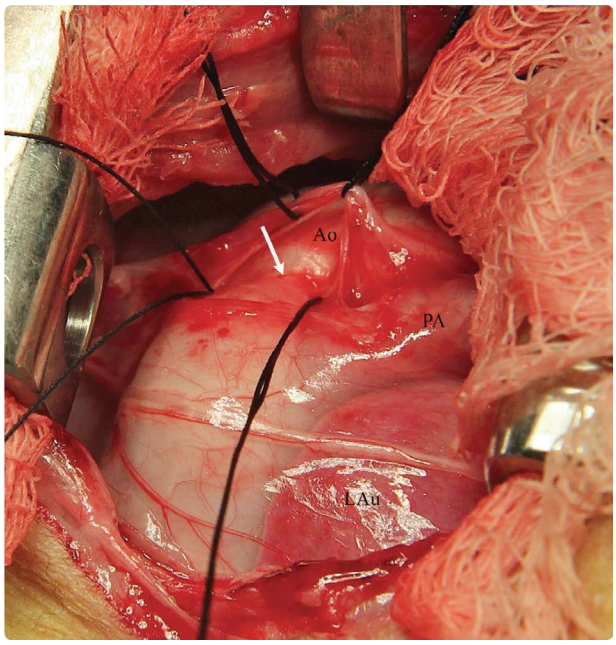


FIGURE 8.27 Surgical ligation for a patent ductus arteriosus (arrow) from a left thoracotomy. Ao, aorta; LAu, left auricle; PA, pulmonary artery.

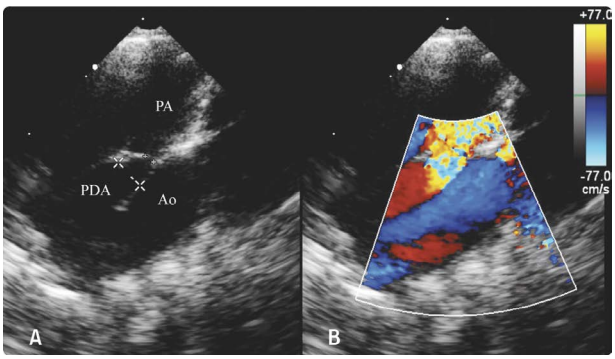


FIGURE 8.26 (a) Transthoracic echocardiographic view of a patent ductus arteriosus (PDA). Measurements of the PDA diameters are obtained. **(b)** Color Doppler reveals turbulence (mosaic of colors) in the pulmonary artery. Ao, aorta; PA, pulmonary artery; PDA, patent ductus arteriosus.

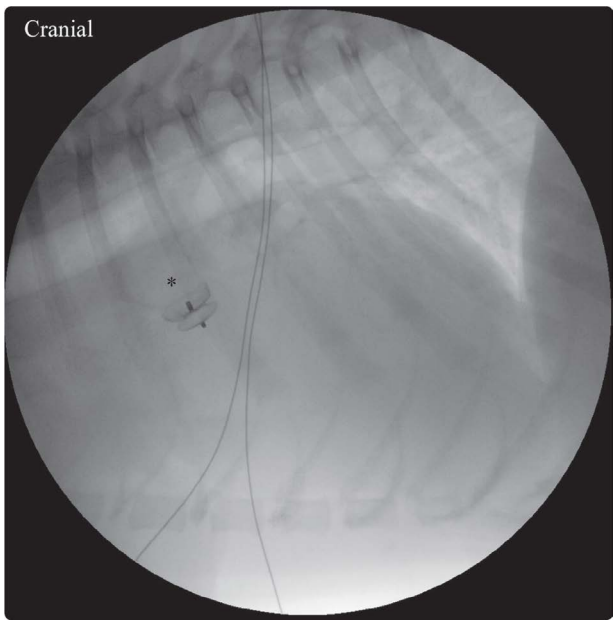


FIGURE 8.28 Lateral thoracic radiograph from a dog after patent ductus arteriosus occlusion with an Amplatzcanine duct occluder (asterisk). (*Distributor: Infiniti Medical, LLC.*)

Prognosis

Secondary changes can reverse with early and successful closure of the PDA, and in these cases, prognosis is excellent. Animals with a PDA that is not closed rarely live past 1 year of age, although rarely some can live well into adulthood with an uncorrected PDA.

VENTRICULAR SEPTAL DEFECTS

Definition/Overview

Ventricular septal defects (VSDs) are defects that allow communication between the left and right ventricles. The most common form is a defect in the membranous or upper portion of the septum. It is the most common congenital cardiac defect in cats.

Etiology

VSDs are heritable defects in Keeshonds and English Springer Spaniels.

Pathophysiology

Blood shunts from left to right during systole. Because of the location of VSDs in the upper portion of the outflow tract, the increased blood flow enters almost immediately into the pulmonary artery and returns to the left heart. Therefore, VSDs in dogs and cats typically result in volume overload of the left ventricle and atrium. The outcome of a VSD depends on the size of the defect and the pressure gradient between the systemic and the pulmonary circulation. Small VSDs that restrict blood flow have minimal hemodynamic consequences. Larger VSDs can result in left-sided volume overload and, subsequently, left-sided CHF. They also have the potential to cause significant pulmonary over circulation and lead to PH. In the presence of severe PH, right ventricular pressure may exceed left ventricular pressure during part of or the entire duration of the cardiac cycle, resulting in reversal of the shunt (right-to-left shunt) and cyanosis (Eisenmenger physiology).

Clinical Presentation

Physical examination findings associated with a VSD depend on the size of the shunt and the pressure gradient between the pulmonary and the systemic circulation. Left-to-right shunts result in a right-sided, sternal, or left basilar systolic murmur depending on the location of the septal defect on the interventricular septum. Smaller VSDs often result in a greater velocity of blood flow through the shunt and may have a louder murmur but are often associated with fewer secondary changes. Blood overflow through a VSD located in the basilar portion of the septum may damage the cusps of the aortic valve, leading to aortic insufficiency and a left basilar diastolic murmur on auscultation. A large VSD can allow pressures between the two ventricles to equalize and may cause a softer murmur or no audible murmur at all. Signs associated with CHF or hypoxemia may be present.

Differential Diagnosis

Mitral regurgitation, tricuspid regurgitation, SAS, PS.

Diagnosis

Diagnosis is made by visualization of the defect or the shunt with color-flow Doppler echocardiography. On echocardiography, the size of the VSD can be compared with the diameter of the aortic annulus. Small VSDs are less than 25%, moderate VSDs are between 25% and 75%, and large VSDs are more than 75% the aortic diameter. Various parameters are assessed to determine the clinical significance of VSDs. Color Doppler technique is used to scan the surface of the interventricular septum from different views and demonstrates a left-to-right turbulent, high velocity jet during systole (**Figure 8.29**). Blood flow velocity measurements recorded by continuous-wave Doppler are used to estimate the pressure gradient across the defect using the simplified Bernoulli equation. Assessment of left atrium and ventricle size and assessment of left ventricular function can be done with Doppler imaging. A right-to-left shunting VSD can be confirmed via contrast echocardiography.

The size of restrictive VSDs determines the risk of left ventricular volume overload and CHF. The clinical significance is better determined by measuring the size of the left-sided cardiac chambers. Follow-up examinations are usually necessary to determine the long-term hemodynamic consequences of a VSD.

Management

VSDs are treated based on the severity of secondary changes and clinical signs. Small VSDs may not require any intervention and carry a good prognosis.

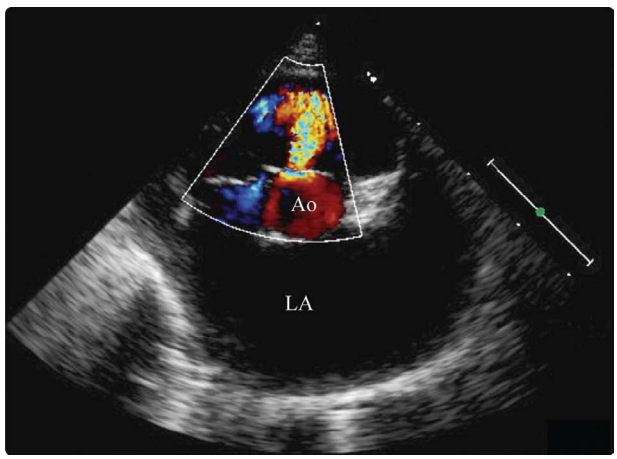


FIGURE 8.29 Right parasternal short-axis echocardiographic view confirming the presence of a ventricular septal defect with color-flow Doppler. Turbulent blood flow is seen entering the right ventricle from a defect located just below the aorta in the perimembranous portion of the interventricular septum. Ao, aorta; LA, left atrium.

Hemodynamically significant left-to-right VSDs are managed medically when signs of left-sided CHF occur. The cyanosis and polycythemia that result from right-to-left VSDs may improve with sildenafil, which targets PH.

Prognosis

Prognosis varies based on the size of the VSD.

ATRIAL SEPTAL DEFECTS

Definition/Overview

Atrial septal defects (ASDs) are defects that occur due to malformation of the septum primum and the septum secundum.

Pathophysiology

ASDs typically result in a left-to-right shunt of blood. This may cause dilation of the right heart, pulmonary over circulation, and right heart failure. Most shunts, however, are small and have minimal hemodynamic consequences. When right-sided heart disease results in elevated right atrial pressures, the direction of blood flow across the ASD may change.

Clinical Presentation

ASDs rarely cause a murmur because the low-volume and low-pressure gradient across the defect do not result in high-velocity turbulent blood flow. On occasion, a soft left basilar systolic murmur is auscultated. This is due to the increased volume of blood circulating within the right ventricular outflow tract, which becomes turbulent. Most ASDs remain asymptomatic. Large defects or those associated with another congenital defect may result in signs of right heart failure or shunt reversal with various degrees of cyanosis and hypoxemia.

Differential Diagnosis

Mild SAS, mild PS, physiologic murmur.

Diagnosis

Diagnosis is made by echocardiographic visualization of the defect.

Management

Most small ASDs do not require treatment. Large defects cause right heart failure if not treated surgically, which may be difficult due to limited access and expense. Right heart failure is managed medically if it develops.

Prognosis

Prognosis varies based on the size of the ASD. Most small ASDs have an excellent prognosis.

MITRAL VALVE DYSPLASIA

Definition/Overview

Mitral valve dysplasia (MVD) occurs from malformation of the mitral valve apparatus and can include the valve leaflets, chordae tendineae, or papillary muscles. Large breed dogs are predisposed.

Pathophysiology

Severe MVD causes significant mitral regurgitation and can cause secondary changes similar to degenerative valvular disease. In dogs, valvular insufficiency frequently occurs in combination with valve stenosis. Long-term complications include the development of left-sided CHF.

Clinical Presentation

Physical examination findings with MVD include a left apical systolic murmur whose intensity correlates with the severity of the regurgitation. Signs associated with arrhythmias or CHF may be present.

Differential Diagnosis

Mitral regurgitation from degenerative valve disease, DCM.

Diagnosis

Thoracic radiographs and echocardiography may show variable levels of left-sided heart enlargement. If CHF is present, signs of pulmonary edema in dogs or edema and/or pleural effusion in cats may be present. Echocardiography will reveal the abnormalities of the mitral valve apparatus.

Management

MVD is managed medically by treating CHF and arrhythmias.

Prognosis

Prognosis is poor due to the typical early onset of arrhythmias and/or CHF.

TRICUSPID VALVE DYSPLASIA

Definition/Overview

Tricuspid valve dysplasia (TVD) occurs from malformation of the tricuspid valve apparatus and can include the valve leaflets, chordae tendineae, or papillary muscles.

Etiology

TVD is the most common CHD in Labrador Retrievers and is heritable in that breed.

Pathophysiology

TVD causes significant tricuspid regurgitation and can cause elevations in right atrial pressures and development of right-sided CHF.

Clinical Presentation

Physical examinations findings with TVD include a right apical systolic murmur; however, mild TVD may not result in an auscultable murmur. Signs associated with arrhythmias or CHF may be present. A common arrhythmia in dogs with TVD is atrial fibrillation (AF).

Differential Diagnosis

Tricuspid regurgitation from degenerative valve disease, VSD, DCM.

Diagnosis

Radiographically, dogs with TVD often have dramatic right atrial enlargement, a dilated caudal vena cava, and hepatomegaly. Cats have an enlarged right atrium and a dilated, tortuous caudal vena cava. Right heart failure in dogs may cause signs of jugular venous distension, hepatomegaly, and ascites. Electrocardiography may show supraventricular arrhythmias, and splintered QRS complexes are a common finding in dogs (Figure 8.30). Echocardiography reveals structural abnormalities of the tricuspid valve apparatus (Figure 8.31).

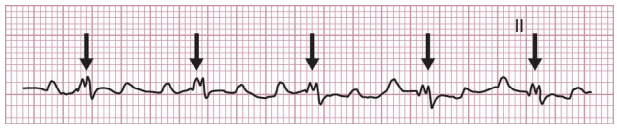


FIGURE 8.30 ECG from a dog with tricuspid dysplasia. There is a sinus rhythm with splintered QRS complexes (arrows) (amplitude 10 mm/mV, speed 50 mm/s).

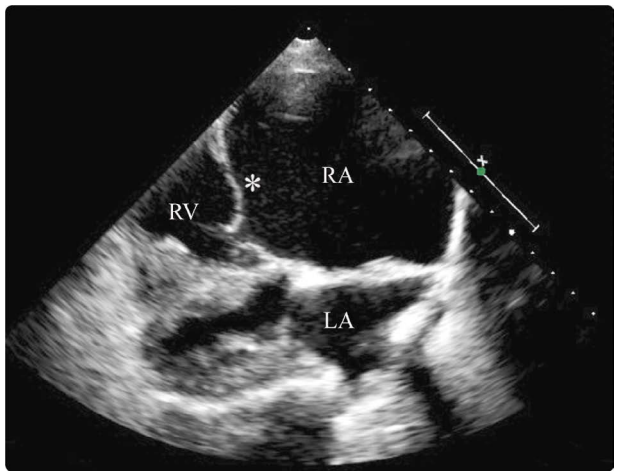


FIGURE 8.31 Right parasternal long-axis echocardiographic view from a dog with tricuspid dysplasia. The right atrium is markedly dilated, and the parietal leaflet of the tricuspid valve is elongated (asterisk). LA, left atrium; RA, right atrium; RV, right ventricle.

Management

TVD is treated medically by managing CHF and arrhythmias.

Prognosis

Prognosis is poor when tricuspid valve regurgitation is severe due to the early onset of arrhythmias and/or CHF. Dogs with mild TVD have a normal life expectancy.

TETRALOGY OF FALLOT

Definition/Overview

The four defects that form the tetralogy of Fallot (TOF) consist of a VSD, dextroposition of the aorta, PS, and the resulting right ventricular concentric hypertrophy.

Etiology

TOF is heritable in Keeshonds.

Pathophysiology

PS increases the right ventricular pressures and results in various degrees of right-to-left shunting across the VSD. The consequences include cyanosis, hypoxemia, and polycythemia. Concurrent CHD may be present.

Clinical Presentation

TOF is usually accompanied by a systolic murmur originating from the PS and/or the VSD. Animals with TOF may develop episodes of respiratory difficulties when the right-to-left shunting worsens, causing systemic hypoxemia.

Differential Diagnosis

PS, VSD.

Diagnosis

Thoracic radiographs show right heart enlargement and pulmonary under circulation. Echocardiography allows for visualization of the VSD, quantification of PS severity, the displacement of the aortic root toward the right side, and right ventricular hypertrophy. Color-flow Doppler is needed to visualize the shunt.

Management

Medical management is aimed at limiting right-to left shunting and hypoxemia by blunting the decrease in systemic vascular resistance in response to exercise with the administration of oral nonselective beta-blockers (propranolol). Phlebotomies are indicated when polycythemia is severe (usually PCV above 70%).

Prognosis

Prognosis varies based on the severity of the shunt and right ventricular pressure overload. Most dogs with TOF reach the age of 5 years.

VASCULAR RING ANOMALIES

Definition/Overview

Vascular ring anomalies occur from persistence of vessels that normally regress during development or abnormalities in vessel formation. The most common vascular ring is a persistent right aortic arch (PRAA).

Etiology

There is evidence that PRAA is heritable in German Shorthair Pointers and Greyhounds.

Pathophysiology

Normally, the right aortic arch develops into the brachiocephalic trunk and right subclavian artery, and the left aortic arch persists as the dorsal aorta. When the right aorta persists with a left ligamentum arteriosum, a vascular ring forms around the trachea and esophagus, with the heart base forming the last portion of the ring. A retroesophageal subclavian artery is the most common concurrent anomaly. PRAA alone does not result in cardiac abnormalities.

Clinical Presentation

PRAA is usually suspected based on the onset of regurgitation when a puppy is introduced to solid food. This occurs due to esophageal constriction by the vascular ring. Signs of aspiration pneumonia may be present.

Differential Diagnosis

Esophageal stricture, congenital megaesophagus, other gastrointestinal (GI) disorders.

Diagnosis

Diagnosis is often made based on clinical signs and thoracic radiographs. Thoracic radiographs show leftward deviation of the trachea cranial to the border of the heart in VD, and a barium esophagram can aid in diagnosis based on constriction of the esophagus at the heart base with cranial dilatation (see Figures 8.14–8.16). Definitive diagnosis may require advanced imaging or surgical exploration.

Management

Surgical ligation is the treatment of choice for PRAA and other vascular anomalies resulting in constricting vascular rings. Surgical procedures vary based on the type of vascular ring and the presence of concurrent anomalies. Early surgical treatment is recommended to prevent progressive esophageal dysfunction, although there have been reports of successful surgical treatment in adult dogs.

Prognosis

Prognosis is good with early intervention and dietary modification.

ACQUIRED VALVULAR DISEASES

DEGENERATIVE MITRAL VALVE DISEASE

Definition/Overview

Degenerative mitral valve disease is the most common form of acquired cardiovascular disease in dogs, representing approximately 75% of all cardiology cases seen in practice. It particularly affects small breed, middle-aged to older dogs and is approximately 1.5x more common in males. There are known breed predispositions, such as the Cavalier King Charles Spaniel and Dachshund; however, large breed dogs may also develop the disease. The mitral valve is affected alone in 60% of cases, the tricuspid valve alone in 10% of cases, and both valves are affected in 30% of cases. Rarely, involvement of the aortic and pulmonic valves is seen.

Etiology

The etiology is unknown, although there is a known genetic component. It has been suggested that there are predisposing abnormalities/disruptions in the collagen and extracellular matrix components, with accumulation of proteoglycans and glycosaminoglycans in the spongiosa layer of the valve. Although the inciting factor for degenerative valve disease is not certain, high levels of circulating serotonin have been shown to cause valvular changes.

Pathophysiology

Myxomatous lesions of the valve progress over time. These abnormalities also extend to the chordae tendineae. These changes lead to thickening of the free edge of the valve leaflets, and secondary fibrosis causes contracture of the valve leaflets and chordae, preventing normal coaptation. This scenario leads to various degrees of regurgitation, leading to left-sided volume overload and atrial and ventricular enlargement.

Clinical Presentation

The clinical presentation varies with the severity of the disease. Very early in the disease process, the only abnormality on physical examination may be a midsystolic click associated with mitral valve prolapse. In most cases, the first clinical sign is a systolic murmur with a PMI in the region of the mitral valve. Worsening of

the murmur intensity usually coincides with worsening disease severity. Coughing and exercise intolerance are also common presenting complaints. Often dogs will remain preclinical for long periods of time and will only show clinical signs at the onset of CHF (Table 8.9).

Differential Diagnosis

The differential diagnoses for systolic heart murmurs are reviewed in the physical examination section of this chapter. Differential diagnoses for the respiratory signs seen include CHF, pneumonia, compression of the left mainstem bronchus by the enlarged left atrium, tracheal collapse, and primary lower airway disease such as chronic bronchitis.

Diagnosis

The diagnosis of degenerative mitral valve disease is generally easily made based on physical examination findings and patient signalment. However, it is important to confirm the diagnosis with echocardiography. Radiography should also be used to assist in assessing disease severity, presence/absence of CHF, and disease progression. Generalized cardiomegaly with left atrial and left ventricular enlargement is seen radiographically in dogs that are stage B2 and higher. If CHF is present, an interstitial-to-alveolar pattern is commonly seen in the perihilar and caudal lobar regions. Echocardiography will show a thickened and irregular valve (Figure 8.32), valvular insufficiency during systole (Figure 8.33), and atrial and ventricular eccentric hypertrophy depending on the valve(s) affected.

Management

In 2019, the ACVIM released updated guidelines for staging and treatment of degenerative valvular disease, which are briefly summarized as follows:

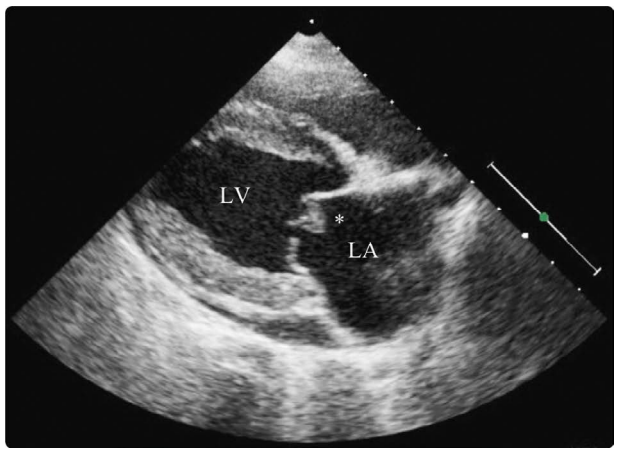


FIGURE 8.32 Right parasternal long-axis echocardiographic view from a dog with severe degenerative mitral valve disease. The septal leaflet of the mitral valve (asterisk) is markedly thickened and prolapses into the left atrium. LA, left atrium; LV, left ventricle.

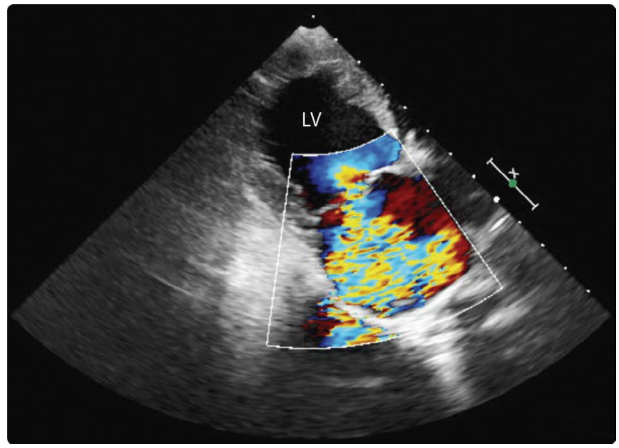


FIGURE 8.33 Color Doppler showing severe mitral valve regurgitation filling more than 50% of the left atrium. The mosaic of color indicates turbulent blood flow. LV, left ventricle.

Stage A classifies dogs that are at risk for developing valvular disease in the future but do not have current clinical signs. This includes all dogs with known breed predispositions to valve disease (such as Cavalier King Charles Spaniels). No medication is warranted, and full physical exam, including careful auscultation, should be performed annually.

Stage B1 classifies dogs with evidence of valvular disease (small breed dog with left apical systolic heart murmur) but who have never had clinical signs associated with heart disease and do not have radiographic or echocardiographic evidence of heart enlargement. Stage B1 also describes dogs who have mild heart enlargement but do not yet qualify for medication (pimobendan).

Stage B2 classifies dogs with valvular disease that have radiographic and echocardiographic evidence of left atrial and ventricular enlargement and who will benefit from medication. Specifically, animals with stage B2 valvular disease have a breed-adjusted VHS > 10.5, moderate left atrial enlargement (LA:Ao > 1.6), and mild left ventricular eccentric hypertrophy (LVIDDN > 1.7). If echocardiography is unavailable, a general VHS > 11.5 or progressive left-sided heart enlargement on radiographs can be used to identify stage B2. Pimobendan (0.25–0.3 mg/kg p.o. q.12h.) should be administered to all stage B2 dogs and has been shown to delay the time to progression to CHF by about 15 months. There is controversy as to whether ACE inhibitors and/or spironolactone should be given to stage B2 dogs, but many cardiologists prescribe these medications, especially if there is evidence of progressive heart enlargement and kidney function is adequate. Surgery can be considered if finances and availability allow.

Stage C classifies dogs with current or former signs of CHF, and stage D classifies those that are refractory to standard treatment. Dogs in these stages should be treated with the appropriate medications to control the signs of CHF (see Congestive Heart Failure, Management).

Prognosis

Disease progression and prognosis are variable, with many dogs remaining asymptomatic for their entire lifetime. However, from onset of CHF, the average survival time is 12–18 months with medical management.

BACTERIAL ENDOCARDITIS

Definition/Overview

Endocarditis corresponds to an infection and secondary inflammation of the endocardial surface following a transient or persistent bacteremia. Vegetative endocarditis occurs when vegetation composed of platelets, fibrin, bacteria, and inflammatory cells are found adhered to heart valves. Clinical signs vary widely and are vague, making recognition difficult. The reported incidence of infectious endocarditis in dogs and cats is very low, with the highest incidence in male, middle-aged, medium-to-large breed dogs, particularly German Shepherd Dogs.

Etiology

Endothelial damage in conjunction with bacteremia is required for infectious endocarditis to develop. The underlying cause of the damage to the endothelium is unproven, although patients with SAS are at increased risk. It is usually not possible to identify the origin of the bacteremia. The most common bacterial isolates are *Staphylococcus* spp. and *Streptococcus* spp., with *Escherichia coli*, *Corynebacterium* spp., and *Erysipelothrix rhusiopathiae* also reported. Recently, *Bartonella* spp. have emerged as important causative agents.

Pathophysiology

In companion animals, infectious endocarditis involves mitral and aortic valve tissue in the majority of cases. Once endothelial damage has occurred, bacteria bind and are covered by fibrin. Additional layers of bacteria and fibrin are deposited to form vegetative lesions, which lead to the destruction of normal valvular and chordal tissue, leading to valvular insufficiency and possible stenosis. These vegetations are friable and commonly embolize to distant sites (Figure 8.34).

Clinical Presentation

The clinical presentation is highly variable and nonspecific, with the most common clinical signs being waxing/waning fever, lethargy, depression, anorexia, weight loss, shifting leg lameness, dyspnea, and tachypnea. These signs can be acute or chronic and are related to the organs affected by bacteremia, septic thrombi, and secondary immune complex formation and deposition.

A new or changing murmur is considered highly suggestive for endocarditis, although lack of a murmur should not preclude the diagnosis. Both systolic (more common) and diastolic murmurs occur, along with arrhythmias. CHF, polyarthritis, and glomerulonephritis are common sequelae.

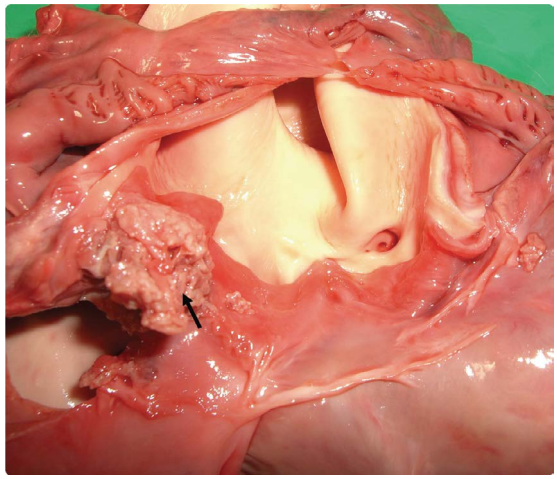


FIGURE 8.34 Vegetative lesion (arrow) on the aortic valve of a dog.

Differential Diagnosis

Differential diagnoses for systolic heart murmurs are reviewed in the physical examination section of this chapter. Infectious, inflammatory, and immune-mediated causes of glomerulonephritis, polyarthritis, and fever of unknown origin should also be ruled out.

Diagnosis

Recognition and diagnosis of endocarditis can be very difficult, in part because of the vague clinical signs and clinicopathologic findings. Radiography may be unremarkable or may show cardiomegaly and signs of left-sided CHF. ECG will often show rhythm disturbances, with ventricular rhythms and AV block being most common. Echocardiography is the gold standard for diagnosis and will often show a hyperechoic, independently oscillating lesion on the affected valve (Figure 8.35). Clinicopathologic laboratory findings can help support the diagnosis but are often nonspecific. They include leukocytosis, nonregenerative anemia, thrombocytopenia, hypoalbuminemia, elevated alkaline phosphatase, and azotemia. Urinalysis may show changes consistent with a glomerulonephritis or bacterial infection, which may be the source of bacteremia or secondary to it. Blood cultures should be taken, although they have both a low sensitivity and specificity. A negative culture should not be used to exclude the diagnosis of endocarditis.

Management

The goals of treatment are to sterilize the vegetative lesion and address cardiac and systemic complications. Bactericidal therapy should be instituted based on culture and sensitivity. Prior to obtaining culture results, or if culture is negative, empiric broad-spectrum coverage with clavulanate-potentiated penicillin,

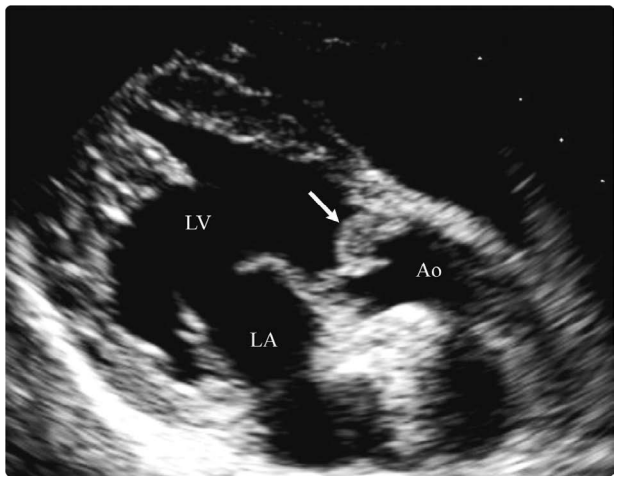


FIGURE 8.35 Right parasternal echocardiographic view from a dog with a vegetative lesion (arrow) on the aortic valve. Ao, aorta; LA, left atrium; LV, left ventricle.

or first- or second-generation cephalosporin along with either a fluoroquinolone or an aminoglycoside should be chosen. Antibiotics at the upper end of the dosing range should be administered orally for a minimum of 6–8 weeks. Parenteral antibiotic therapy is useful especially early in therapy to ensure fast achievement of high serum drug levels. If *Bartonella* is suspected or confirmed, azithromycin (5–10 mg/kg p.o. q.24h. for 7 days, then every other day for 6–12 weeks) or doxycycline should be administered. Treatment with corticosteroids is contraindicated and confers a negative prognosis. Though anticoagulation therapy was proposed in the past, no benefit has been proven, and it may increase the risk of hemorrhage. Cessation of therapy should be determined based on serial monitoring of echocardiograms, body temperature, CBC, and repeat blood and urine cultures.

Prognosis

Prognosis for vegetative infectious endocarditis is guarded to grave in both canine and feline patients. Aortic valve endocarditis, thrombocytopenia, and glomerulonephritis are also associated with worse prognosis.

CANINE CARDIOMYOPATHY

Cardiomyopathies are diseases that affect the heart muscle. When the cause is unknown, the term primary cardiomyopathy is used. When a cause can be identified for the heart muscle disease, the term secondary cardiomyopathy is used. The disease can then be described based on the underlying cause; for example, "Adriamycin (doxorubicin) cardiomyopathy." Cardiomyopathy is one of the most common acquired cardiovascular diseases in dogs, second only to degenerative valve disease and heartworm disease depending on the geographical location. The most common myocardial disease in dogs is DCM.

DILATED CARDIOMYOPATHY

Definition/Overview

Dilated cardiomyopathy (DCM) is a primary myocardial disease characterized by decreased systolic function and subsequent ventricular dilation. This disease is most commonly seen in large breed dogs with Dobermanns, Great Danes, and Irish Wolfhounds being overrepresented. Some medium-size breeds such as Cocker and English Spaniels may also develop the disease. Significant variation of disease presentation, progression, and prognosis can be seen depending on the breed of dog.

Etiology

The cause of DCM is not known, but a genetic cause is suspected. In Dobermanns, DCM has been shown to be inherited as an autosomal dominant trait. A splice deletion in the pyruvate dehydrogenase kinase 4 gene (a gene involved in the regulation of myocardial energy utilization) has been associated with DCM in this breed. More recently, a missense variant in the titin gene of this breed was also identified. The mutation occurs within the immunoglobulin-like domain of the titin protein and is found in cardiac and skeletal muscle. Titin is involved in muscle active contraction and passive stiffness' however, its contribution to DCM is currently unclear.

Over the past few years, diet has been implicated in the development of DCM in unusual breeds. While still under investigation, it is thought that alternative carbohydrate sources such as peas and lentils in diets labeled as "exotic," "boutique," or "grain-free" interfere with the body's ability to manufacture and utilize amino acids, specifically taurine.

Pathophysiology

Myocardial changes secondary to DCM lead to eccentric hypertrophy of the ventricles, which is usually more pronounced on the left side. In addition, left ventricular systolic function is markedly reduced. Over time, left ventricular enlargement leads to dilation of the mitral valve annulus and secondary mitral regurgitation. Left atrial enlargement results from volume overload, impaired ventricular filling, and secondary mitral regurgitation. Ventricular arrhythmias are caused by the disruption of the normal architecture of the ventricular myocardium and various triggers such as increased adrenergic tone, electrolyte imbalances, and hypoxemia. AF is more likely to occur when the left atrium is markedly dilated and fibrotic.

Clinical Presentation

In general, DCM has an adult onset, with male dogs being affected more commonly; however, Portuguese Water Dogs often develop the disease before 12 weeks of age. Clinically, two phases of the disease can be detected: An occult or asymptomatic phase and an overt phase. In the occult phase, there are no clinical signs;

however, arrhythmias or myocardial changes are present. The occult phase is variable and may last months to years. More commonly, the disease is not diagnosed until the overt stage when exercise intolerance, CHF, or syncope is noted. In some dogs, sudden death may be the first and only sign of disease. This is especially true for Dobermanns, in which sudden death can be the first sign of disease in approximately 30%–50% of affected dogs.

Differential Diagnosis

Other causes of left ventricular dilation in large breed dogs, including tachycardiomyopathy, cardiomyopathy secondary to taurine deficiency or doxorubicin toxicity, and myocarditis. Primary mitral valve insufficiency is associated with left ventricular systolic dysfunction, which may mimic DCM. Chronic cardiac changes of left-to-right shunt, especially PDAs in adult dogs, resemble those of DCM.

Diagnosis

During physical examination, a grade 1 to 3/6 systolic murmur (a result of mitral insufficiency due to annular dilation) and/or an S3 gallop sound (indicating left ventricular dilation) may be noted over the left apex. A weak femoral pulse (a result of decreased stroke volume due to poor contractility) is a common finding. An irregular rhythm along with pulse deficits may be present as ventricular arrhythmias and AF are commonly seen in these dogs. Arrhythmias are often an early indication of disease, and breeds predisposed should be screened with ECG and Holter monitor. Detection of ventricular premature complexes in an asymptomatic dog, particularly a Dobermann, should raise a high level of suspicion for occult cardiomyopathy. Sinus tachycardia, AF, and ventricular tachycardia are commonly seen in dogs with DCM. Giant breeds such as the Great Dane and Irish Wolfhound are more likely to develop AF, whereas Dobermanns are more likely to have ventricular arrhythmias. Arrhythmias are often noted around 2–4 years of age and can vary from single ventricular premature complexes to life-threatening ventricular tachycardia. Electrocardiographic changes suggesting left ventricular enlargement (R-wave amplitude > 3.0 mV) and conduction disturbances such as right or left bundle branch block may also be noted. It is important to note that a normal ECG does not rule out the presence of DCM. Thoracic radiography may reveal generalized cardiomegaly; however, radiographs are not sensitive to mild cardiac changes. Therefore, cardiomegaly is better assessed with echocardiography, particularly in the occult stage of the disease. In the overt stage, radiographs are more valuable in helping to diagnose CHF, showing pulmonary venous distension and pulmonary edema. Due to their chest conformation, the degree of cardiomegaly may be underestimated in Dobermanns. Echocardiography is essential for the evaluation of cardiac enlargement and function. The classic sign of DCM on an echocardiogram is systolic dysfunction. This is seen as reduction in fractional shortening (FS) and ejection fraction along with increases in E-point-to-septal separation and left ventricular end-systolic diameter. Increased left ventricular end-diastolic diameter as well as left atrial enlargement are seen as the disease progresses (Figure 8.36a, b). Early in the disease, affected individuals may only have ventricular arrhythmias and normal echocardiograms. Therefore, it is important that when screening for the occult phase of the disease both echocardiogram and Holter monitor evaluation are performed.

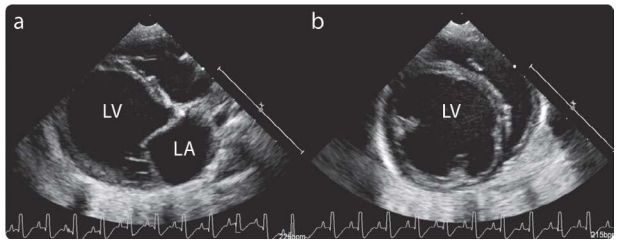


FIGURE 8.36 Right parasternal long-axis **(a)** and short-axis **(b)** views from a dog with dilated cardiomyopathy. The left ventricle appears markedly dilated. The ECG shows sinus tachycardia with wide QRS complexes, consistent with a left bundle branch block. LA, left atrium; LV, left ventricle.

Management

In dogs with DCM and heart failure, standard CHF therapy is initiated, with antiarrhythmic therapy used as needed based on the arrhythmia burden. Administration of pimobendan delays the onset of CHF and extends survival in Dobermanns with occult DCM. Syncope is often the result of rapid ventricular tachycardia in DCM dogs. When this is seen, antiarrhythmic treatment is needed to control the syncope. Antiarrhythmic treatment does not prevent sudden death, and many dogs with syncope will die suddenly, especially Dobermanns. Less likely causes of syncope in DCM include collapse due to decreased cardiac output, vasovagal syncope, or, on occasion, secondary to the onset of AF. Treatment of ventricular arrhythmias includes the use of sotalol monotherapy or a combination of mexiletine and a beta-blocker. A thorough diet history should be performed, and diet change should be considered if a "boutique" or "grain-free" diet is fed. If the owner is unable or unwilling to change diets, taurine should be supplemented.

Prognosis

Prognosis with DCM varies with breed and severity of disease but mostly is considered fair to poor, especially after the onset of CHF. Dobermanns with DCM may carry a worse prognosis compared with other breeds. The majority of dogs with DCM presenting with CHF survive approximately 6–12 months. In some Cocker Spaniels, the disease may be associated with taurine deficiency, and subsequent improvement may occur with supplementation. Diet-associated DCM may also improve with a diet change and initiation of taurine supplementation. Onset of CHF at a young age and the presence of ascites and AF also carry a negative prognosis.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (BOXER CARDIOMYOPATHY)

Definition/Overview

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a myocardial disease dominated by ventricular arrhythmias and clinical signs of syncope. Most dogs have normal ventricular size and function at the time they develop the arrhythmia. The disease is primarily seen in Boxers but has also been documented in other breeds, including English Bulldogs. It is typically an adult-onset disease, but it can be diagnosed in dogs as young as 1 year of age.

Etiology

In humans, mutations in multiple genes coding for intercalated disc proteins have been associated with ARVC. In Boxers, only one genetic mutation has been associated with ARVC to date; it affects the striatin gene. Boxers positive for the striatin mutation have a higher number of VPCs on 24-hour Holter recordings. Boxers without this mutation can also get ARVC.

Pathophysiology

ARVC is characterized by fatty or fibro fatty myocardial replacement, predominantly in the right ventricle and, to a lesser extent, the left ventricle and both atria (Figure 8.37).

Clinical Presentation

Clinically, the disease is characterized by ventricular tachycardia, right ventricular enlargement, syncope, and sudden death. There are three stages to the disease, which may be observed in succession as ARVC worsens: (1) Initially, the patient is asymptomatic, and ventricular arrhythmias are an incidental finding; (2) the patient presents for syncope associated with the ventricular arrhythmias; and (3) the patient presents with signs of CHF secondary to systolic dysfunction and frequently a history of weakness or syncope related to the arrhythmias. Similar to Dobermanns with DCM, in some cases sudden death is the first and only sign of the disease. Sudden death due to ventricular arrhythmias is more common than death associated with complications of CHF.

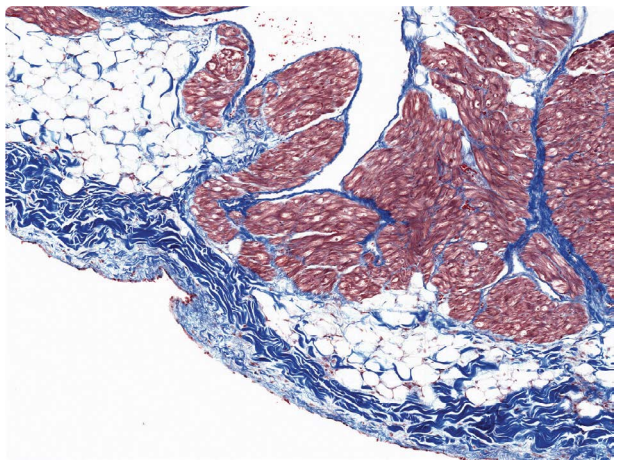


FIGURE 8.37 Histopathology of the myocardium of a Boxer with arrhythmogenic right ventricular cardiomyopathy revealing fatty replacement of the myocytes and interstitial fibrosis. The Masson trichrome stain shows collagen in blue. Magnification ×70.

Differential Diagnosis

Myocarditis and other causes for left ventricular enlargement and arrhythmias, including DCM, tachycardiomyopathy and doxorubicin toxicity.

Diagnosis

The most common physical examination finding reported is the detection of an arrhythmia. This can be either single premature beats or paroxysms of tachycardia. On occasion, the arrhythmia is permanent when AF is present. Another physical examination abnormality common with ARVC is the presence of a systolic murmur on auscultation. Apical systolic murmurs result from mitral or tricuspid insufficiency caused by the annular dilation that accompanies cardiomegaly. Less frequently, a cardiac gallop is detected. Left basilar systolic murmurs may be noted in some Boxers, but these should not be linked to ARVC as they are usually physiologic or secondary to SAS. The most common electrocardiographic change noted is ventricular ectopy in the form of ventricular premature complexes (singles, couplets, triplets, or bigeminy) or ventricular tachycardia. The ventricular ectopic beats tend to arise from the right ventricular myocardium and are classically described as having a left bundle branch block pattern morphology with a predominantly positive deflection of the QRS complex in leads II, III, and a VF. If severe, the ventricular tachycardia can lead to syncopal episodes and potentially sudden death. The frequency of the ventricular beats can have as much as an 80% day-to-day variation with ARVC. To increase the possibility of identifying these arrhythmias, 24-hour Holter monitoring is recommended if there is evidence of arrhythmia on auscultation or a history of clinical signs such as syncope (Figure 8.38). Repeating a Holter recording or the use of an event monitor may increase the likelihood of arrhythmia detection in cases where an arrhythmia is not detected on initial evaluation. Although ARVC is a primary myocardial disease, structural changes may only be present on histopathology and not be evident on echocardiography. The expected findings on echocardiography vary depending on the stage of disease progression. The majority of asymptomatic Boxers, as well as most dogs suffering from syncopal episodes, have normal echocardiograms, but signs of depressed ventricular function and chamber dilation are reported on occasion. Atrial enlargement also develops as a result of ventricular dysfunction and is more pronounced in dogs with CHF.

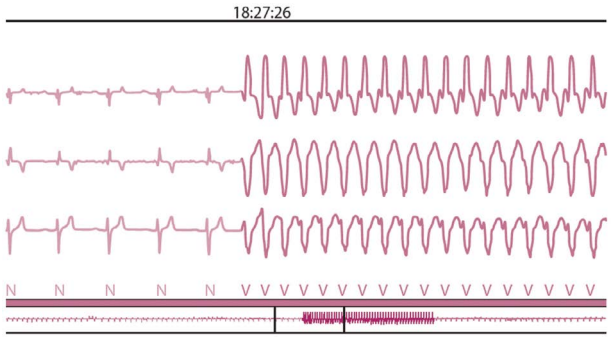


FIGURE 8.38 Holter recording from a Boxer with arrhythmogenic right ventricular cardiomyopathy showing a run of ventricular tachycardia.

Ultimately, disease progression may lead to biventricular failure, making it difficult to distinguish ARVC from idiopathic DCM.

Management

Treatment of ARVC aims at alleviating the clinical signs, as there is no specific treatment for the disease. In the absence of clinical signs and if the arrhythmia burden is mild, no treatment may be necessary. However, if the arrhythmia is of clinical concern, or if there are collapsing episodes, antiarrhythmic therapy is implemented. In dogs, the most common treatment of ventricular arrhythmias consists of sotalol monotherapy. Whenever sotalol alone fails to control the arrhythmia, it is typically combined with mexiletine. Alternatively, mexiletine can be associated with atenolol. The response to antiarrhythmic therapy should be assessed via 24-hour Holter monitoring, since a large daily variation in the number of ventricular arrhythmias may be seen in dogs with ARVC. In cases where CHF is present, standard heart failure therapy is initiated with the need for addition of antiarrhythmic therapy determined by the patient's underlying rhythm. Administration of antiarrhythmic drugs can lead to a reduction in clinical signs and, therefore, improve quality of life, but the risk for sudden death from ARVC is not decreased by these medications.

Prognosis

ARVC progresses over several years, and the rate of progression varies between dogs. In dogs with severe arrhythmia or syncope but normal cardiac function, a 2- to 3-year survival is not unusual when the clinical signs are controlled with antiarrhythmic therapy. Survival is usually less than 1 year once myocardial failure and CHF occur.

HYPERTROPHIC CARDIOMYOPATHY

Definition/Overview

Hypertrophic cardiomyopathy (HCM) is a rare primary myocardial disease in dogs. It is characterized by concentric hypertrophy of the left ventricle in the absence of a reason for the hypertrophy. Therefore, the diagnosis excludes valvular stenosis, hypertension, or other systemic illness that may stimulate left ventricular hypertrophy.

Clinical Presentation

Most dogs with HCM are males and most are diagnosed before 3 years of age. In humans and cats with HCM, asymmetrical hypertrophy of the left ventricle is seen; however, dogs with HCM more commonly have symmetrical hypertrophy of the left ventricle. The vast majority of dogs also have systolic anterior motion of the mitral valve causing dynamic left ventricular outflow tract obstruction (LVOTO). Some dogs may have myocardial hypertrophy as a result of the LVOTO and not because of a primary myocardial disorder such as HCM. Concurrent abnormalities of the mitral valve have been described in patients with HCM and LVOTO. In addition, treatment with beta-blockers causes significant reduction of the LVOTO and may lead to improvement or resolution of the hypertrophy in some cases.

Differential Diagnosis

Rule out systemic hypertension and other causes of increased afterload, such as SAS. Infiltrative myocardial disease, in particular lymphoma, may be responsible for concentric ventricular hypertrophy.

Diagnosis

Diagnosis relies on an echocardiogram to demonstrate left ventricular concentric hypertrophy in the absence of an obstruction to ejection of blood in the aorta or systemic hypertension.

Management

Treatment is primarily aimed at reducing or eliminating the LVOTO with beta-blockers (e.g., atenolol: 1 mg/kg q.12–24h.), which slow the heart rate and decrease contractility.

Prognosis

In most of the described cases, HCM was a fatal disease. The primary concern is sudden death; less commonly, dogs may develop CHF secondary to diastolic dysfunction and severe left atrial enlargement.

INFILTRATIVE DISEASE

Definition/Overview

Infiltrative myocardial disease is infrequent in dogs. The most commonly seen cause is a cardiac tumor. Infiltration by a tumor to the degree that it impairs myocardial diastolic or systolic function is rare.

Etiology

Lymphosarcoma is usually suspected. Lapland dogs have been reported to develop myocardial infiltration with glycogen secondary to glycogen storage disease. These dogs had clinical signs associated with skeletal muscle disease; however, arrhythmias were also noted.

Clinical Presentation

Most often dogs will present with clinical signs related to cardiac arrhythmia, pericardial effusion, and, on occasion, obstruction to blood flow by the cardiac tumor.

Differential Diagnosis

The degree of infiltration of the myocardium can be severe enough to resemble HCM.

Diagnosis

Diagnosis is based on a detailed echocardiographic examination. If pericardial effusion is present, a sample should be obtained via pericardiocentesis and submitted for cytologic evaluation. An abdominal ultrasound and fine-needle aspirates of enlarged organs and lymph nodes may help reach the diagnosis of lymphoma.

Management

Treatment is aimed at addressing the underlying cause for the myocardial infiltration and the use of antiarrhythmic medication determined by the underlying rhythm.

Prognosis

If cardiac lymphoma is diagnosed, survival depends on response to chemotherapy, with some dogs living more than 6 months after diagnosis.

FELINE CARDIOMYOPATHY

Definition/Overview

Cardiomyopathies are diseases of the myocardium associated with cardiac dysfunction and are the most common form of cardiac disease in felines. HCM is associated with increased cardiac mass due to a hypertrophied, nondilated left ventricle in the absence of a hemodynamic load or metabolic cause. It is the most common form of cardiomyopathy in felines (60% of cases) with a higher prevalence in certain breeds (Maine Coon, Ragdoll, Norwegian Forest Cat, British Shorthair, American Shorthair, Sphynx, Siberian, and Persian), although Domestic Shorthairs are seen most commonly. Males are predisposed (65%–70% of cases) possibly related to comodifying genes or hormonal influences. Prevalence within the feline population is estimated to be about 15%, although the criteria for diagnosis vary between studies and prevalence may be higher in some breeds.

Restrictive cardiomyopathy (RCM) is defined as restrictive diastolic filling with normal left ventricular dimensions and wall thickness with accompanying left atrial or biatrial enlargement (myocardial form). An endomyocardial form of this disease also exists wherein an endocardial scar spans the left ventricle, causing a fixed obstruction to blood flow. It is the second most common form of cardiomyopathy (20% of cases). DCM is associated with dilation and impaired contractility of the left ventricle or both ventricles. Arrhythmogenic cardiomyopathy (ACM) is characterized by progressive fibrofatty replacement of the myocardium that is regional or global, leading to a dilated and hypocontractile right ventricle with various arrhythmias and conduction abnormalities. It may also affect the left ventricle. A "nonspecific phenotype" is diagnosed when there is echocardiographic myocardial disease that does not readily fit into other categories.

Etiology

Familial HCM has been documented in Maine Coon cats as an autosomal dominant trait with incomplete penetrance. Separate mutations in different regions of the myosin-binding protein C (MyBPC3) gene are considered causative of HCM in both Maine Coon and Ragdoll breeds. Importantly, these mutations have not been identified in other breeds, and it is likely that other mutations in this gene or in genes for other sarcomeric proteins exist but have not yet been discovered. Over 1,400 mutations in 27 genes coding for sarcomeric or other structural proteins have been identified in humans with HCM. Development of the HCM phenotype is not an inevitable consequence in individuals with an HCM genotype, as there is a low penetrance for the MyBPC3 mutation, and it is likely age related. Additionally, epigenetic factors and environmental influences may affect phenotypic expression.

Myocardial hypertrophy can occur secondary to pressure overload (outflow obstruction, systemic hypertension), hyperthyroidism, hypersomatotropism, and infiltrative diseases of the myocardium. These causes should be excluded as soon as possible before a diagnosis of HCM is made.

The other forms of cardiomyopathy (RCM, DCM, ACM) are idiopathic and likely have a genetic basis. DCM was historically due to a taurine deficient diet and is now rare due to supplementation in commercial diets. Current cases of DCM may be found in feline patients on nontraditional diets (vegetarian diet, home-cooked diet, or being fed canine food). RCM and ACM may be associated with an inflammatory process secondary to infectious, neoplastic, or immune-mediated disorders.

Pathophysiology

In HCM, it is hypothesized that the production of abnormal sarcomeric proteins creates a functional defect in the process of muscle contraction, leading to increased

myocyte stress with subsequent activation of trophic factors (angiotensin II, aldosterone, insulin-like growth factor) that induce myocyte hypertrophy. Early nutrition may also affect circulating growth factors and phenotypic expression of disease. Diastolic dysfunction is the primary mechanism responsible for clinical signs in HCM and RCM. Hypertrophy of the left ventricle wall (HCM) causes impaired or delayed relaxation, and interstitial/endomyocardial fibrosis (HCM and RCM) increases myocardial stiffness and reduces distensibility. These changes impair left ventricular filling and result in filling only at higher pressures. Elevated filling pressures lead to left atrial enlargement, pulmonary venous hypertension, and CHF.

HCM generally leads to normal or increased global systolic performance of the left ventricle; however, regional systolic impairment has been documented in HCM patients using tissue Doppler imaging. Systolic dysfunction may be present in any myocardial disease due to ischemia and replacement fibrosis. Regional systolic impairment may increase regional wall stress and stimulate myocardial hypertrophy. DCM results in left ventricular or biventricular systolic dysfunction. ACM affects systolic performance primarily of the right ventricle and leads to a dilated, thin-walled, hypokinetic right ventricle and may affect the left ventricle. Tachyarrhythmias can affect diastolic performance and lead to myocardial dysfunction.

Clinical Presentation

Most cats with cardiomyopathy are diagnosed at a mean age of 5–7 years (range 3 months to 18 years), and HCM is typically diagnosed at an earlier age than other forms of cardiomyopathy. Certain breeds may present more commonly at a younger age. They may be presented in the asymptomatic phase due to the presence of auscultatory abnormalities such as a heart murmur or gallop sound. Various prevalence studies have shown that nearly 50% of apparently healthy cats with heart murmurs do not have evidence of cardiac disease; however, the presence of a heart murmur warrants further evaluation. In one study, 70% of cats with HCM did not have auscultatory abnormalities, so the absence of these findings does not exclude the presence of cardiac disease. Cats with occult cardiomyopathy (more common for RCM, DCM, ACM, nonspecific phenotype) are often not identified until clinical signs are present, including dyspnea, tachypnea, lethargy, poor appetite, hind limb paresis, collapse, or sudden death. Clinical signs are not an inevitable consequence for individuals with HCM.

Differential Diagnosis

Includes cardiomyopathy secondary to systemic disease (hypertension, hyperthyroidism, hypersomatotropism), degenerative valve disease, congenital heart disease, and myocarditis. Differentials for respiratory signs include feline lower airway disease (feline asthma), pneumonia, noncardiogenic pleural effusion or pulmonary edema, hemorrhage, and PTE.

Diagnosis

Diagnosis is based on the phenotypic expression of disease. HCM, RCM, DCM, ACM, and nonspecific phenotype (previously unclassified cardiomyopathy) are diagnoses based primarily on imaging and electrocardiographic tests as well as elimination of other possible etiologies (hyperthyroidism, systemic hypertension).

Echocardiography is the gold standard for diagnosis and permits evaluation of morphologic and functional abnormalities of cardiac structures. Diagnosis of HCM is based on the identification of a diastolic wall thickness > 6 mm on 2D or M-mode echocardiography, though some cats with HCM will have wall thickness between 5 and 6 mm. Hypertrophy may be diffuse or segmental and may be symmetric or asymmetric (**Figure 8.39**). Other findings on echo may include papillary muscle hypertrophy, end-systolic cavity obliteration, left atrial enlargement (identified as left atrial dimension > 16 mm or LA:Ao > 1.5) or spontaneous echo contrast (SEC, "smoke"). HCM may uncommonly affect the right ventricle. There is a subset of patients with hypertrophic obstructive cardiomyopathy due to obstruction in the left ventricular outflow tract associated with systolic anterior motion of the mitral valve (**Figure 8.40**). It is unclear if the obstruction leads to hypertrophy of the left ventricle or if obstruction is the result of abnormalities in left ventricular geometry, the mitral valve apparatus, or loading conditions associated with hypertrophy of the left ventricle.

Thoracic radiographs may identify cardiomegaly, although changes may be subtle especially if atrial enlargement is not present. The classic valentine shape results from severe biatrial enlargement. Pulmonary venous congestion, a patchy or diffuse interstitial to alveolar pattern, and/or pleural effusion may be present in cats with CHF.

ECG may show evidence of chamber enlargement, though these are not sensitive findings. Various arrhythmias and conduction abnormalities may be present. A

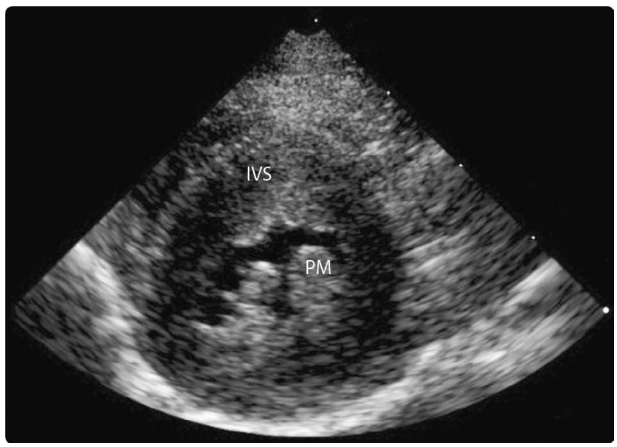


FIGURE 8.39 Right parasternal short-axis echocardiographic view from a cat with hypertrophic cardiomyopathy. There is concentric hypertrophy of the interventricular septum and the left ventricular free wall. The papillary muscles are prominent. IVS, interventricular septum; PM, papillary muscle.

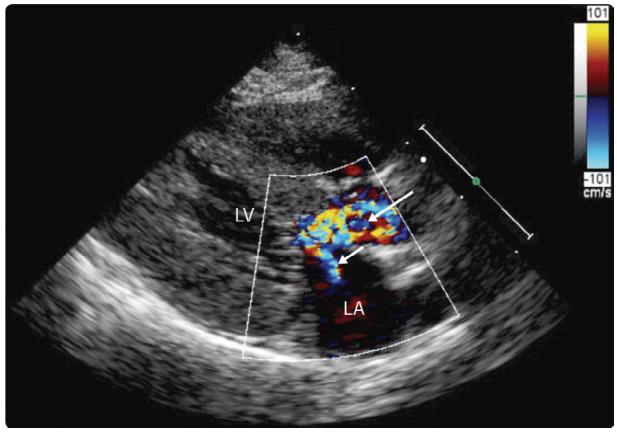


FIGURE 8.40 Color Doppler from a cat with hypertrophic obstructive cardiomyopathy showing two areas of turbulence: One in the left ventricular outflow tract caused by the septal leaflet of the mitral valve (long arrow); the other in the left atrium corresponds to a small amount of mitral regurgitation resulting from the incomplete closure of the mitral valve in systole (short arrow). LA, left atrium; LV, left ventricle.

left anterior fascicular block is the most common finding in cats with HCM (Figure 8.41). Supraventricular tachycardia and, rarely, AF may be present in cats secondary to severe atrial enlargement.

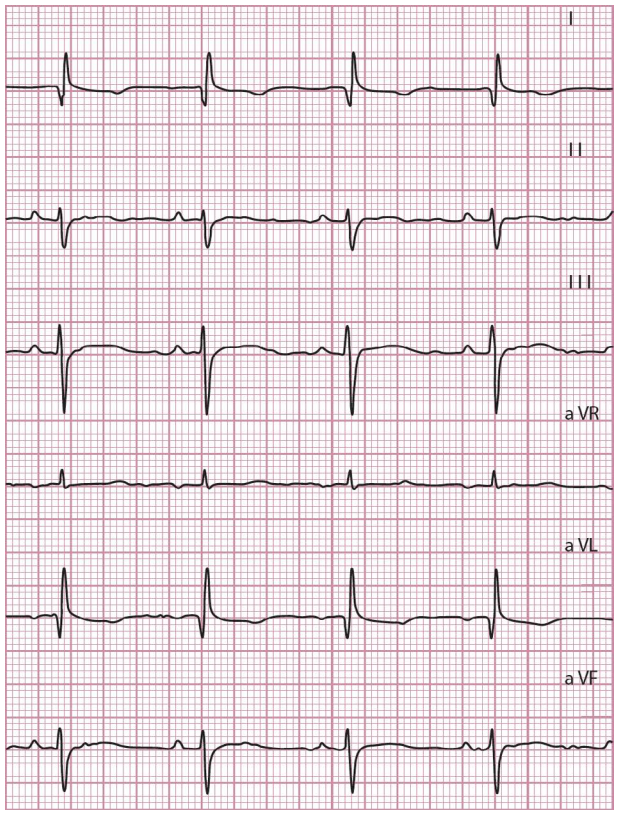


FIGURE 8.41 ECG from a cat with hypertrophic cardiomyopathy showing a sinus rhythm with a left axis deviation (lead I mostly positive, lead a VF mostly negative), also called left anterior fascicular block.

NT-proBNP has been shown to be a fairly sensitive and specific screening tool for the identification of subclinical HCM, though false negatives may occur in cats with mild disease. It has been shown to discriminate between cats with respiratory signs due to CHF and cats with primary respiratory disease. An elevated NT-proBNP warrants further diagnostic evaluation. A normal value should not be used to rule out cardiac disease if other findings are supportive. cTnI may also be elevated in cats with moderate-to-severe HCM with or without CHF.

Genetic testing for a specific genetic mutation is currently only available for Maine Coon and Ragdoll cats. These tests are most useful for identifying breeding cats that carry this mutation, although cats that do not carry the mutation may still develop HCM. Genetic testing should be utilized in addition to echocardiographic screening in breeding cats to avoid the production of individuals homozygous for the mutation.

Management

A new staging system has recently been proposed to classify cats based on their risk and in order to guide therapeutic recommendations. Staging and treatment (Table 8.13) recommendations are summarized as follows:

TABLE 8.13 Drugs used in the management of cardiomyopathy in cats

Drug	Dosage	Comment
Atenolol	0.5–2 mg/kg p.o. q.12–24h.	In cats with dynamic left ventricular outflow tract obstruction with relatively normal LA size Consider long-term treatment if improvement of hypertrophy Start with low dose and increase slowly over a few weeks Consider for complex ventricular arrhythmias
Enalapril, benazepril	0.25–0.5 mg/kg p.o. q.12–24h.	Start q.24h.
Furosemide	1–2 mg/kg IM or IV q.1–8h. 1–3 mg/kg p.o. q.8–24h.	Monitor BUN, creatine, and blood potassium concentration
Torsemide	0.1–0.2 mg/kg p.o. q.24h.	Monitor BUN, creatine, and blood potassium concentration
Pimobendan	0.25 mg/kg p.o. q.12h.	Administered in the absence of significant LVOTO when CHF is present
Clopidogrel	18.75 mg p.o. q.24h.	In cats after episode of thromboembolism or if severe left atrial enlargement +/– visible thrombus or SEC

Stage A classifies cats who are at risk for developing cardiomyopathy (are a breed predisposed to cardiomyopathy). Genetic testing (if Maine Coon or Ragdoll) and routine echocardiograms can be considered for these pets.

Stage B1 classifies cats who have evidence of cardiomyopathy but do not have moderate-to-severe LA enlargement. These cats are considered at low risk for CHF or arterial thromboembolism (ATE). No treatment is generally recommended. Atenolol may be considered in cats who have severe LVOTO, but atenolol has not been shown to prolong survival.

Stage B2 classifies asymptomatic cats with cardiomyopathy who are at increased risk of developing CHF or ATE. Findings on echocardiogram may include moderate-to-severe left atrial (LA) enlargement, low LA FS%, low LA appendage velocities, and SEC. Clopidogrel is warranted in these cats, and other antithrombotic drugs (aspirin, factor Xa inhibitors) can be considered in addition to clopidogrel. ACE inhibitors have not been shown to prolong time to CHF, and studies on pimobendan are currently lacking. Complex ventricular ectopy should be treated with atenolol. AF with fast ventricular response rate should be treated with either diltiazem, atenolol, or sotalol.

Stage C classifies cats that are currently experiencing or have experienced CHF or ATE. Chronic treatment of CHF in cats with cardiomyopathy includes furosemide and clopidogrel. ACE inhibitors are used by some cardiologists, though compelling evidence of their effectiveness is lacking. ACE inhibitors are consistently used in conjunction with furosemide in feline patients that are not of advanced age or significantly azotemic. Pimobendan may be considered in cats without significant LVOTO. Spironolactone may also be considered. Patients presenting with evidence of ATE should be provided pain medication and antithrombotic therapy (clopidogrel, heparin). Taurine should be supplemented in cats with DCM phenotype. Serum creatinine and electrolyte concentrations should be monitored, and potassium supplementation should be initiated in hypokalemic cats.

Stage D classifies cats that are refractory to treatment of CHF. These cats are receiving furosemide doses in excess of 6 mg/kg per day. Furosemide may be replaced with torsemide (starting dose of 0.1–2.0 mg/kg p.o. q.24h.). Pimobendan and taurine are recommended in cats with decreased global systolic function (unless taurine levels are normal).

Prognosis

Prognosis for cats with HCM is variable. Asymptomatic patients may live several years after diagnosis, and there are a modest number of cats with mild HCM that do not experience disease progression and live a normal life span. Other cats experience more aggressive disease progression and die suddenly at a young age, develop CHF, or suffer thromboembolic complications (Figure 8.42). Extreme hypertrophy (> 9 mm), decreased left ventricular systolic function (FS < 30%), and decreased left atrial systolic function (↓ left atrial FS%) are associated with increasing risk of cardiac death.

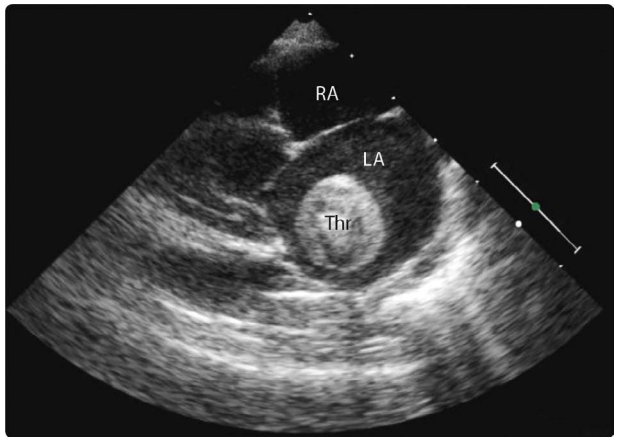


FIGURE 8.42 Right parasternal echocardiographic view of a cat showing a large thrombus in the left atrium. LA, left atrium; RA, right atrium; Thr, thrombus.

In acute CHF, there is an approximate 80% survival to discharge. Patients with systolic dysfunction and CHF have historically had a poor prognosis; however, there may be improved survival with the addition of pimobendan. The prognosis from the first episode of heart failure is generally 6–12 months among the various cardiomyopathies; however, it is quite variable with some patients having shorter survival and others surviving well beyond 1 year (some up to 2–3 years). Cats with thromboembolic complications generally have a poor long-term prognosis, with an average survival of 6 months and up to 30% mortality during the immediate hospitalization period; however, some cats live for several years. Cats who experience CHF as a consequence of stress, fluid administration, general anesthesia, or steroid intolerance tend to have a better prognosis.

MYOCARDITIS

Definition/Overview

Myocarditis is defined as an inflammation of the myocardium associated with myocyte necrosis. Although myocardial inflammation is present in all forms of cardiac disease, the term myocarditis is reserved for inflammation of the heart as the result of pathogens (viruses, bacteria, parasites), drug exposure, or immune-mediated diseases. The expression traumatic myocarditis is also used for inflammation of the myocardium following blunt trauma.

Etiology

Myocarditis in dogs (Table 8.14) and cats (Table 8.15) may be secondary to pathogens (viruses, bacteria, parasites, fungal), immune-mediated diseases, drug toxicity, or trauma. *Trypanosoma cruzi* (Chagas disease) is one of the pathogens most commonly recognized as a cause of myocarditis in endemic areas, particularly in

TABLE 8.14 Etiology of canine myocarditis

Infectious
- Bacteria
  - *Bartonella vinsonii* spp. *berkhoffi*
  - *Bacillus piliformis*
  - *Citrobacter koseri*
  - *Borrelia burgdorferi*
- Viruses
  - West Nile virus
  - Adenovirus type 1
  - Parvovirus
  - Canine herpesvirus
  - Canine distemper virus
- Parasites
  - *Trypanosoma cruzi* (Chagas disease, **Figure 8.43**)
  - Leishmaniasis
  - *Neospora caninum*
  - *Babesia*
  - *Toxocara canis*
  - *Fungal disease:* Blastomycosis, cryptococcosis, coccidioidomycosis, aspergillosis

Immune-mediated
- Lymphocytic nonsuppurative myocarditis
- Myocarditis associated with polymyositis

Drug reaction
- *Anthracyclines:* Doxorubicin

TABLE 8.15 Etiology of feline myocarditis

Infectious
- Bacteria
  - *Bartonella henselae*
  - Other bacteria
- Viruses
  - Parvovirus (panleukopenia virus)
  - Other virus (Herpes or calicivirus)
- Parasites
  - *Toxoplasma gondii*

Immune-mediated
- Eosinophilic syndrome

Drug reaction
- Anesthesia

Unknown
- Transmissible myocarditis–diaphragmitis of cats

the southern part of the United States (**Figure 8.43**). In patients from nonendemic areas, myocarditis has been seen secondary to systemic bacterial infection and septicemia.

In cats, transmissible myocarditis–diaphragmitis is reported to affect adult cats in California and Florida during the summer months and has been associated with *Bartonella henselae* and other infectious causes. Unfortunately, identifying the definitive cause of myocarditis remains unsuccessful in most cases.

Pathophysiology

Myocardial lesions can be a direct effect of infectious agents or drugs, but they can also be secondary to an immune response. Viruses can enter myocytes and interfere with cell metabolism, which may induce cell death, hypertrophy, or dysfunction. By modifying the myocyte cytoskeleton, viruses can lead to cardiac dysfunction with echocardiographic characteristics of DCM. The immune response can lead to cytokine release and enzyme activation. During the inflammatory process, activated collagenase and elastase enzymes contribute to cardiac remodeling. Activation of specific cytokines, especially transforming growth factor-beta, may predispose to pathologic fibrosis.

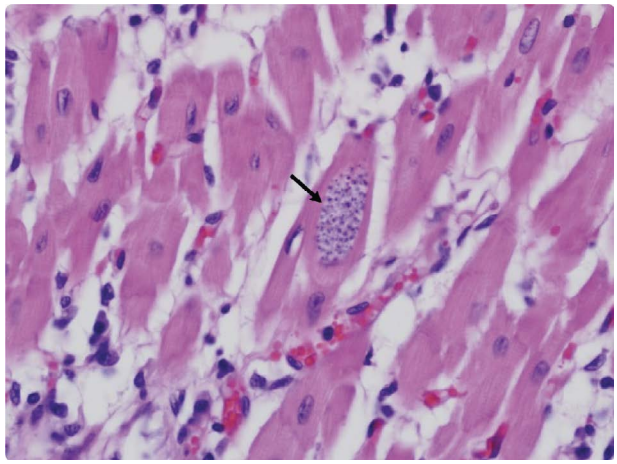


FIGURE 8.43 Histologic section of a canine heart infected with *T. cruzi*. H&E stain. Magnification ×40.

Clinical Presentation

Myocarditis can affect dogs and cats of all ages. However, several diseases are more likely in the young dog (Chagas disease, parvovirus) or in immunocompromised animals (e.g., leishmaniasis, toxoplasmosis). Obtaining a complete history is essential because living conditions or travel to endemic area may help the clinician identify an etiologic factor for a specific disease.

Dogs and cats with myocarditis can present with signs of CHF such as weakness, syncope, exercise intolerance, respiratory difficulties, and/or abdominal distension. Clinical signs are most commonly acute, but these signs can be insidious (e.g., chronic phase of Chagas disease). Fever and a heart murmur are common findings. Complex arrhythmias are frequent and should alert the clinician to the possibility of myocarditis when they occur in a breed that is not predisposed to cardiomyopathy. Tachyarrhythmias (ventricular or supraventricular) and bradyarrhythmias (most commonly second- or third-degree AV block) are reported. Systolic dysfunction is the most common echocardiographic finding. Left- and right-sided CHF are complications of myocarditis.

Differential Diagnosis

Myocarditis is characterized by nonspecific clinical signs; therefore, differential diagnoses include other cardiac diseases and other cause of arrhythmias.

When myocarditis is associated with both systolic dysfunction and ventricular and/or supraventricular arrhythmias, the differential diagnosis should include DCM, tachycardia-induced cardiomyopathy, and infiltrative cardiomyopathy (e.g., lymphoma). However, myocarditis is usually acute compared with other causes of systolic dysfunction.

It is suspected that in cats as in humans, myocarditis may also lead to myocardial concentric hypertrophy. Differential diagnosis for feline ventricular hypertrophy includes HCM, systemic hypertension, hyperthyroidism, acromegaly, muscular dystrophy, myocarditis, and cardiac lymphoma. Therefore, the differential diagnosis of myocarditis in cats should include all causes of ventricular hypertrophy and other cardiomyopathies.

Diagnosis

Myocarditis is usually suspected in dogs and cats (especially in young animals) with acute clinical signs consistent with arrhythmias and systolic dysfunction, especially in those with a fever and new heart murmur. A complete biochemistry profile and hemogram are necessary to assess organ dysfunction, inflammation, or the presence of blood parasites. The most common bloodwork findings are a neutrophilia with a left shift, monocytosis, anemia, increased ALT, and azotemia.

In all dogs and cats with suspected myocarditis, an ECG (+/– Holter recording) should be performed, especially if arrhythmias are detected during physical examination, or if the reason for the consultation includes weakness, exercise intolerance, or syncope. A complete echocardiogram is essential to exclude other cardiac diseases and evaluate systolic function. cTnI serum level increases secondary to massive myocardial cell death. A marked elevation in circulating cTnI level is common with myocarditis.

Thoracic radiography is indicated if respiratory signs are present to evaluate the possibility of pulmonary edema or pleural effusion. Any pleural, pericardial, or abdominal fluids removed should be submitted for bacterial culture and cytology. Any accessible lesions should be aspirated or biopsied for analysis.

Diagnosis of Chagas disease can be made by direct observation of *Trypanosoma cruzi* on a stained blood smear or buffy coat smear, on lymph node aspirates, or in abdominal effusion. PCR is sensitive in the acute phase, but the sensitivity decreases with chronicity. Antibody titer is usually positive by 3 weeks post infection. The most commonly used serologic tests are the indirect immunofluorescent antibody test and the ELISA test (possible cross reaction with *Leishmania*).

Management

Treatment should be directed at improving cardiac function, decreasing arrhythmia burden, controlling CHF, and treating the underlying cause if possible. Inotropes (pimobendan) are indicated to improve systolic function. Diuretics (furosemide) should be used with pimobendan if CHF is present. Abdominocentesis and thoracocentesis should be performed in all animals with ascites or pleural effusion. Pericardiocentesis should be performed if a large amount of effusion is present. High-grade second- and third-degree AV blocks do not respond to medical treatment; therefore, pacemaker implantation is needed to increase the heart rate and improve cardiac output in these cases. Tachyarrhythmias are treated according to the underlying mechanism involved (see Tachyarrhythmias).

No effective treatment is currently available to treat Chagas disease in dogs. Nifurtimox, benzimidazole, itraconazole, and allopurinol have been used with varying success. Prednisolone (0.5–1 mg/kg p.o. q.12–24h.) may increase survival. Because the immune system is involved in the mechanism of myocardial lesions even in infectious myocarditis, glucocorticoids are often recommended to reduce inflammation. Antibiotics can be effective against bacterial myocarditis, and the choice of antibiotic should ideally be made on the basis of blood culture results.

Prognosis

Prognosis is generally guarded and unpredictable. Chagas disease is usually associated with poor outcomes because even if a dog survives the acute phase, the chronic phase may induce severe cardiac dysfunction. Young dogs have a worse prognosis (< 5 months survival) than adult or old dogs (30–60 months survival), probably because of a different immune response to the disease.

Most of the time, puppies that develop myocarditis secondary to parvovirus die in a few days because of severe myocardial necrosis. However, myocarditis can also resolve in a few days or a few weeks without specific treatment or with empirical treatment with broad-spectrum antibiotics. Some authors report that cats may develop myocardial hypertrophy and CHF secondary to anesthesia or surgery and occasionally recover spontaneously.

PERICARDIAL DISEASES

Definition/Overview

The most common manifestation of pericardial disease is pericardial effusion. Cardiac tamponade describes pericardial effusion associated with clinical signs because a large volume of effusion is present or because fluid has accumulated very fast. Constrictive pericarditis is caused by a markedly thickened pericardial sac that prevents adequate cardiac filling.

Etiology

Pericardial effusion in dogs is frequently caused by cardiac tumors. Cardiac hemangiosarcoma is the most common tumor responsible for cardiac tamponade. Golden Retrievers and German Shepherd Dogs are overrepresented. Brachycephalic breeds are predisposed to

chemodectomas. Other tumors include mesothelioma, lymphoma, and ectopic thyroid carcinoma. Idiopathic pericardial effusion is another common cause of cardiac tamponade. Unusual causes for tamponade include trauma, coagulation disorders, and an atrial tear in dogs with severe mitral valve regurgitation and a dilated left atrium. Pericardial effusion is less common in cats and is usually associated with CHF. Tamponade is rare in cats but could result from lymphosarcoma or feline infectious peritonitis (FIP). Constrictive pericarditis can be a complication of any chronic effusion or pericarditis. It has been described as a complication of *Coccidioides immitis* infections.

Pathophysiology

Pericardial fluid has little effect on cardiac function unless the intrapericardial pressure equals or exceeds cardiac diastolic pressure. The pericardium can accommodate a moderate amount of fluid that accumulates slowly with little change in pericardial pressure. However, large amounts of fluid, or even small amounts that accumulate quickly (hemorrhage), can cause a significant increase in pericardial pressure leading to cardiac tamponade. Tamponade impedes diastolic filling. As a result, cardiac output falls. When pericardial fluid accumulates over days or weeks, this decrease in cardiac output results in increased adrenergic tone and activation of neurohormonal mechanisms. This includes activation of the RAAS, leading to increased circulating angiotensin II, aldosterone, and vasopressin. This results in an increase in heart rate and fluid retention. Renal fluid excretion is not promoted because there is no increase in secretion of atrial natriuretic peptide. Over time, right-sided CHF occurs. Conversely, when hemorrhagic pericardial effusion accumulates within a few seconds, there is no time for water retention to occur and prevent a rapid drop in cardiac filling. Subsequently, an important reduction in cardiac output occurs. Cardiogenic shock is, therefore, the typical consequence of acute cardiac tamponade. Reduced coronary perfusion during tamponade can also impair ventricular systolic function.

Clinical Presentation

Clinical signs of cardiac tamponade are consistent with right-sided CHF and reduced cardiac output. History may include weakness, lethargy, exercise intolerance, collapse, syncope, abdominal distension, and tachypnea, as well as weight loss in chronic cases. Signs of right-sided CHF predominate. Physical examination may reveal jugular vein distension, weak femoral pulses, and muffled heart sounds (Beck triad). Also, a positive hepatojugular reflux, hepatomegaly, ascites, tachypnea, and dyspnea can be present. Pleural effusion from right-sided CHF may also muffle heart sounds and lung sounds ventrally. Sinus tachycardia, pale mucous membranes, and prolonged CRT are common due to increased sympathetic tone. A murmur may be present if there is underlying cardiac disease; however, pericardial effusion will not cause a heart murmur on its own. Pulsus paradoxus is not always present but is characteristic of pericardial effusion. It results in weaker femoral pulses during inspiration and stronger pulses during expiration.

Differential Diagnosis

Congenital causes of canine pericardial disease include pericardial cysts, partial/total pericardial agenesis, and peritoneopericardial diaphragmatic hernia (PPDH). PPDH is the most common congenital pericardial disease in cats. Causes of acquired pericardial disease and pericardial effusion in dogs include hemangiosarcoma, heart base tumor, idiopathic pericardial effusion, malignant mesothelioma, hypoalbuminemia, uremia, CHF, septic pericarditis (bacterial, fungal [coccidiomycosis], protozoal [leishmaniasis]), left atrial rupture, trauma, and hemorrhage (coagulopathy). Causes of acquired pericardial disease in cats include CHF, feline infectious peritonitis (FIP), hypoalbuminemia, idiopathic, and lymphosarcoma.

Diagnosis

Radiography

Radiographic findings are not always reliable for diagnosing pericardial effusion. The typical, large, globoid cardiac silhouette results when there is a moderate accumulation of chronic effusion. Acute effusions causing clinical signs of cardiac tamponade may not always be evident on thoracic radiographs.

Radiographs of animals with PPDH show convergence of the cardiac silhouette and the diaphragm. GI segments may be evident as gas opacities within the pericardial space, and depending on the amount of organ displacement, the abdomen may be partially devoid of intestinal segments or other organs. Liver and omental fat are most commonly herniated through the defect. Sternal defects are often found concurrently with PPDH. Other congenital cardiovascular defects have also been reported in dogs and cats with PPDH.

Electrocardiography

Animals with cardiac tamponade are tachycardic. In addition, low-amplitude QRS complexes are common in animals with a moderate amount of pericardial effusion. Electrical alternans (a beat-to-beat variation in the R-wave amplitude) is less common (Figure 8.44).

Echocardiography

Two-dimensional echocardiography is the most sensitive, noninvasive test for confirming the presence of pericardial effusion and elucidating the cause. Pericardial effusion is seen as an anechoic space between the epicardium and the pericardium (Figure 8.45). The amount of effusion can be roughly quantitated, and signs of cardiac tamponade can be identified. The areas of the right atrium/auricle, heart base, and main pulmonary



FIGURE 8.44 ECG (lead II) from a dog with cardiac tamponade. There is sinus tachycardia with a beat-to-beat variation in QRS complex amplitude, called electrical alternans.

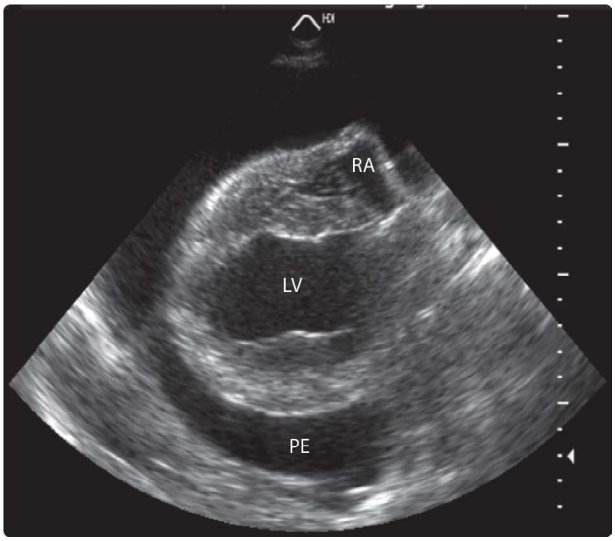


FIGURE 8.45 Echocardiographic view from a dog with pericardial effusion. The effusion is seen as an anechoic space around the heart. LV, left ventricle; PE, pericardial effusion; RA, right atrium.

artery should be examined carefully since these are common locations for cardiac masses (Figure 8.46). The specific tumor type can often be suspected based on location. Overall, echocardiography is estimated to be 90% sensitive for detecting cardiac masses. Heart base tumors are commonly found adjacent to the aorta on standard transthoracic views. Right atrial/auricular masses (commonly hemangiosarcoma) may be difficult to see, so the absence of a mass in this location does not necessarily rule neoplasia out. Transesophageal echocardiography may more easily reveal masses, but this technique requires special equipment and general anesthesia. False-positive findings have been reported, and normal cardiac structures can be misidentified as a mass when imaged in oblique positions, especially by inexperienced echocardiographers. In cases of cardiac tamponade, the ventricular walls may show pseudohypertrophy due to external compression and collapse of the right atrial and ventricular walls during diastole. The myocardial texture should be observed for any signs of tumor infiltrate (primary or metastatic neoplasia such as lymphoma). In the case of a left atrial tear, a clot may be visualized in the pericardial space along with the pre-existing valvular disease.

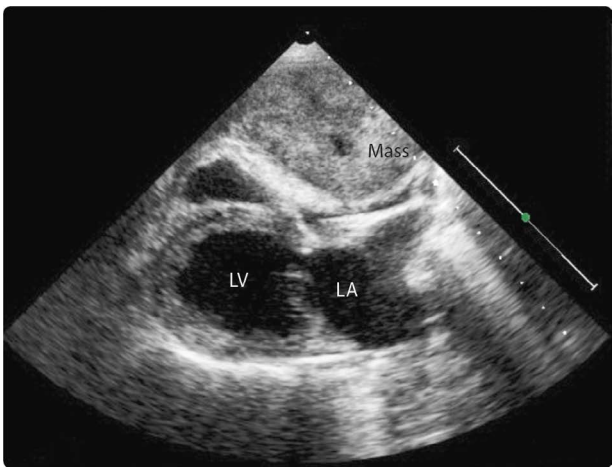


FIGURE 8.46 Right parasternal echocardiographic view from a dog with a large cardiac mass expanding along the right atrium and ventricle. The mass is so large that it is compressing the right atrium and ventricle. LA, left atrium; LV, left ventricle.

Pericardial Fluid Analysis

Pericardiocentesis is frequently necessary for emergency stabilization of a patient with pericardial effusion and cardiac tamponade; however, fluid analysis is rarely diagnostic. Fluid samples are often hemorrhagic or serosanguineous, sterile, inflammatory exudates. Not surprisingly, hemangiosarcoma and aortic body tumors are rarely confirmed on cytologic examination of pericardial fluid. Less common causes of pericardial effusion, such as lymphosarcoma or infectious pericarditis, are more reliably diagnosed with pericardial fluid analysis.

Management/Prognosis

Acute management of pericardial effusion requires pericardiocentesis in most cases. The pericardium should be approached from the right side to reduce the risk of lacerating a coronary vessel. Many animals will tolerate the procedure without sedation, but a sedative such as butorphanol can be used. The right thorax is clipped and aseptically prepared. The ideal location for entry can be determined with ultrasound. Typically, a 14- or 16-gauge over-the-needle catheter is used along with an extension set and a three-way stopcock. The skin, intercostal muscles, and parietal pleura are infiltrated with local anesthetic. The catheter is then inserted while applying negative pressure. Once the needle enters the pericardium and fluid flows into the extension set, the catheter can be advanced. To distinguish red pericardial fluid from blood within the heart or blood vessels, a sample of fluid is collected in

an activated clotting time tube. Blood should normally clot within 60–90 seconds, unlike sanguineous body cavity effusions in which clotting factors and platelets are depleted. Ventricular arrhythmias are common during this procedure, so ECG monitoring should be available. The treatment and prognoses for specific pericardial diseases are described here.

Hemangiosarcoma

Cardiac hemangiosarcoma has usually metastasized by the time of diagnosis. Commonly, palliation with pericardiocentesis alone is elected; however, the fluid and cardiac tamponade can return quickly and result in death or euthanasia. Median survival time for dogs treated with pericardiocentesis alone is approximately 2 weeks. Other aggressive therapies include tumor resection, pericardectomy, chemotherapy, and splenectomy. Some dogs live up to 3–6 months. Adjuvant chemotherapy has been shown to provide little survival advantage.

Heart Base Tumors

Complete surgical resection of these tumors is usually impractical because they are highly vascular and surround major blood vessels. Palliation with pericardectomy alone commonly results in prolonged survival with good quality of life, sometimes over 2 years after pericardectomy. Radiation therapy and chemotherapy with toceranib phosphate (Palladia) have emerged as viable treatment options.

Mesothelioma and Other Cardiac Tumors

There are only a few case reports of successful treatment for mesothelioma. However, complete pericardectomy followed by intracavitary cisplatin and IV doxorubicin have been reported to result in a disease-free state 2 years later. Patients may also require periodic thoracocentesis for pleural effusion. Since mesothelioma can be difficult to diagnose even with histopathology, accumulation of a large amount of pleural effusion 4–6 months after pericardectomy increases the suspicion for the disease. Cardiac lymphosarcoma, rhabdomyosarcoma, and fibrosarcoma are rare. Cardiac lymphosarcoma is treatable with chemotherapy.

Infectious Pericarditis

Bacterial infections of the pericardium are thought to arise most commonly from foreign body penetration, often migrating foxtails (*Hordeum* spp.). Therefore, pericardectomy and removal of the foreign body is crucial for resolution of the disease. Therapy, including pericardectomy, removal of any foreign bodies, and long-term antibiotic therapy (up to 6 months), results in a good prognosis. Treatment for coccidioidomycosis is similar except that antifungal medications replace antibiotics. Prognosis for *Coccidioides* infection involving the pericardium is guarded, as constrictive pericarditis is a common complication after the fungal infection is treated.

Idiopathic Pericardial Effusion and Constrictive Pericarditis

Idiopathic pericardial effusion is a diagnosis of exclusion and often not completely distinguishable from mesothelioma. Animals with idiopathic pericardial effusion can develop effusive–constrictive pericarditis over time with repeated thoracocentesis. For this reason, pericardectomy is recommended. Many animals go on to do well after successful surgery.

PULMONARY HYPERTENSION

Definition/Overview

Pulmonary hypertension (PH) is defined as pathologically elevated blood pressure within the pulmonary vasculature with a mean pulmonary artery pressure of ≥ 25 mmHg. Recognition of PH has increased since the widespread availability of Doppler echocardiography. PH occurs most commonly in middle-aged to older small breed dogs but can be seen in canine patients of any age and less commonly in cats.

Etiology

The etiology of PH is multifactorial and requires multidisciplinary collaboration for appropriate diagnosis and medical management. PH can be classified based on anatomical location: Precapillary causes wherein an increase in pulmonary vascular resistance is observed without an increase in left atrial pressures verses post capillary causes which occur secondary to an increase in pulmonary artery wedge pressure observed secondary to left heart enlargement and increased left atrial pressure.

Pathophysiology

The pulmonary vasculature is normally a low-pressure system with minimal resistance and high capacitance (highly distensible). Disruption of the pulmonary circulation can cause an increase in pulmonary blood flow, pulmonary vascular resistance, or pulmonary venous pressures, which can secondarily lead to architectural changes typical of PH. Increased flow causes vascular endothelial damage, vasoconstriction, and remodeling of small pulmonary arteries leading to development of PH; irreversible damage to the pulmonary vasculature may occur. Hypoxia and release of vasoactive substances from activated platelets causes reactive vasoconstriction, increasing pulmonary vascular resistance. Post capillary PH causes increased filling pressure, which impedes drainage of the pulmonary capillaries and leads to a compensatory increase in pulmonary artery pressure to maintain forward flow. Chronic post capillary PH may lead to irreversible changes within the pulmonary vasculature consistent with precapillary PH, and thus, a combination of precapillary and post capillary PH may occur. PH creates a pressure overload on the right ventricle, leading to right heart enlargement, right ventricular dysfunction, and tricuspid valve

insufficiency. It may progress to right-sided CHF. PH may also limit preload (filling) to the left ventricle, decreasing cardiac output to the systemic circulation.

PH was recently separated into 6 major groups based on primary underlying etiology. Primary pulmonary arterial hypertension (group 1) is very uncommon in veterinary patients. Specific etiologies include idiopathic PH, drug-induced PH, congenital heart shunts, pulmonary vasculitis or amyloid deposition, pulmonary veno-occlusive disease, or pulmonary capillary hemangiomatosis. PH secondary to increased left atrial pressure (group 2) is the most common cause of PH and occurs secondary to cardiac diseases, including mitral valve insufficiency, DCM, and myocarditis. Primary lung pathology (group 3) is the second most common cause for PH in veterinary patients. This group is expansive, including numerous etiologies such as obstructive airway disease (tracheal or mainstem bronchi collapse, bronchomalacia), interstitial lung diseases (fibrotic lung disease, eosinophilic disorders), diffuse neoplasia, obstructive sleep disorders and brachycephalic airway syndrome, high altitudes, and bronchiolar diseases, among others. Hypoxia secondary to these disorders leads to pulmonary arteriolar constriction as an adaptive mechanism to shunt pulmonary blood flow to regions of the well-oxygenated lung tissue. The pulmonary vasculature may also be distorted and pulmonary arterioles narrowed secondary to chronic lung diseases. PH from either acute or chronic pulmonary thromboembolism is classified under group 4. Group 5 includes PH due to *Dirofilaria immitis* and *Angiostrongylus vasorum*. Lastly, group 6 encompasses PH secondary to more than one cause listed in groups 1–5, a mass compressing the pulmonary artery, or PH for which an underlying etiology cannot be identified.

Clinical Presentation

Clinical signs that are strongly suggestive of PH include syncope, respiratory distress at rest, or activity ending in respiratory distress. Findings possibly suggestive of PH include tachypnea at rest, increased respiratory effort at rest, or prolonged tachypnea after activity. Nonspecific clinical signs such as lethargy, hyporexia, or cough may also be observed. Patients with mild-to-moderate PH are often asymptomatic. Like clinical signs, physical exam findings are dependent on the underlying disease and could include systolic heart murmurs due to tricuspid or mitral valve insufficiency, a diastolic murmur of pulmonic insufficiency, split S2 sound, jugular distension or pulsation, abdominal distension or fluid wave with right-sided CHF, cyanosis, tachypnea, increased respiratory effort, crackles, wheezes, or increased bronchovesicular sounds.

Differential Diagnosis

Differentials for respiratory signs include PTE, pneumonia, CHF, pleural effusion, chronic bronchitis, pulmonary hemorrhage or contusions, and lung lobe torsion. Differentials for syncope or exercise intolerance include arrhythmias, cardiomyopathy, vasovagal syncope, hypotension, acute pericardial effusion, and anemia.

Diagnosis

The gold standard diagnostic test is right heart catheterization and direct measurement of pulmonary pressures; however, this technique is impractical in most clinical situations. Doppler echocardiography is an excellent, noninvasive method of estimating pulmonary pressures and is considered the practical diagnostic of choice in veterinary medicine. In the absence of pulmonic stenosis, the velocity of tricuspid valve regurgitation is used to estimate the right ventricular end-systolic pressure (RVESP). The systolic pulmonary artery pressures are then calculated using the modified Bernoulli equation ($P = 4v^2$) where P is the pressure gradient between the right ventricle and right atrium, and v is the velocity of the regurgitant jet (**Figure 8.47**). Pulmonic valve insufficiency may be used to estimate diastolic pulmonary artery pressure (PAP). While historically classified as mild, moderate, or severe (RVESP 36–60 mmHg, 60–80 mmHg, and ≥ 80 mmHg, respectively), newer recommendations propose a pressure gradient of > 46 mmHg as the cutoff to indicate a high probability of PH. Other echocardiographic changes that may be observed with PH include interventricular septal flattening (**Figure 8.48**), paradoxical septal motion, decreased left ventricular size, right ventricular eccentric or concentric hypertrophy, right atrial enlargement, caudal vena cava enlargement, pulmonary artery to aorta ratio > 1.0, pulmonic regurgitation velocity > 2.5 m/s, right pulmonary artery distensibility index < 30%, dilation of the main pulmonary artery (**Figure 8.49**), or type II or III pulmonary artery systolic flow profile. If PH is due to left-sided heart disease, evidence of significant structural disease should be present.

Ancillary diagnostics should start with a full systemic evaluation by means of CBC, biochemistry, urinalysis, heartworm antigen test, and thoracic radiographs. Evidence of right heart enlargement, main pulmonary artery bulge, dilation of lobar pulmonary arteries, or pulmonary disease may be identified on

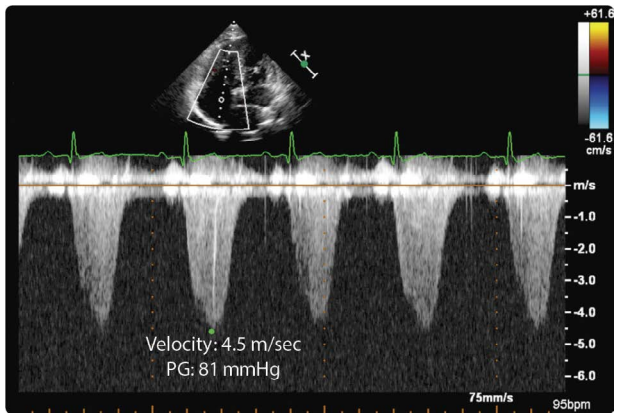


FIGURE 8.47 Spectral Doppler of a tricuspid valve regurgitation jet consistent with severe pulmonary hypertension.

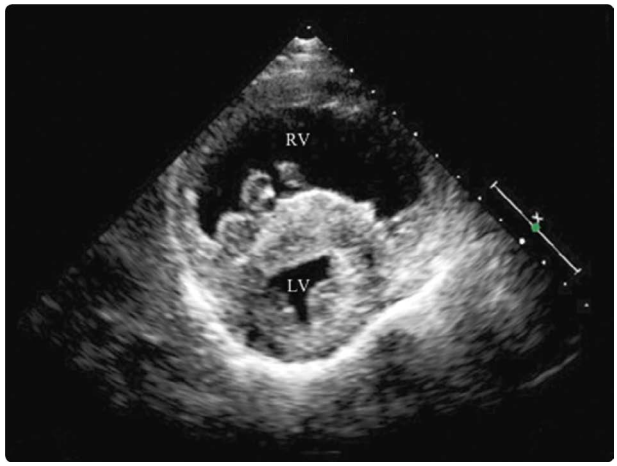


FIGURE 8.48 Echocardiographic short-axis view from a dog with severe pulmonary hypertension. The right ventricle is severely dilated. There is marked thickening of the interventricular septum, with prominent papillary muscles on the right side. The left ventricle is small as a result of decreased filling. LV, left ventricle; RV, right ventricle.

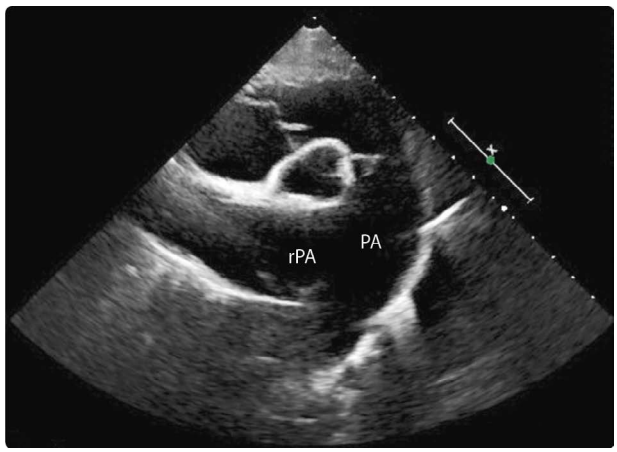


FIGURE 8.49 Echocardiographic view of the main pulmonary artery of a dog with pulmonary hypertension. There is severe dilation of the main and right pulmonary arteries. PA, pulmonary artery; RPA, right pulmonary artery.

thoracic radiographs. Further diagnostic testing may be indicated based on the suspected differentials after initial evaluations. These tests include arterial blood gas, abdominal ultrasound, urine protein-to-creatinine ratio, fluoroscopy, thoracic CT, angiography, bronchoscopy, bronchoalveolar lavage, and a coagulation profile, including D-dimers or thromboelastography.

Management

Treatment is directed at resolving or treating the underlying cause of PH if one is identified. Supplemental oxygen, which can directly improve PH by causing pulmonary artery dilation, and sedatives (opioids) should be provided to patients in respiratory distress. Patients with PH from diseases in group 1 could benefit from congenital shunt repair (if possible) or therapeutic phlebotomy plus/minus hydroxyurea for treatment of erythrocytosis. PH due to left-sided heart disease often improves with standard treatment of CHF. Treatment for PH from diseases in group 3 varies vastly but could include antibiotics, steroids, and chemotherapeutic agents. Anticoagulants such as heparin, factor Xa inhibitors like rivaroxaban, and antithrombotics like aspirin or clopidogrel are necessary for patients with thromboembolic disease. Due to the low shear conditions, anticoagulants are preferred to antithrombotic drugs but are typically more cost prohibitive. Lastly, the underlying helminthic infection should be treated for patients in group 5. The majority of patients with PH will benefit from the implementation of a phosphodiesterase-5 inhibitor such as sildenafil or tadalafil. These drugs cause pulmonary vasodilation associated with the nitric oxide pathway. However, they should be avoided with suspected pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, or significant left-sided heart disease because the increased blood return to the left side of the heart may result in fatal pulmonary edema.

Prognosis

Prognosis is related to the underlying disease process and response to treatment. PH can rarely be completely reversed unless it is due to a left-to-right shunt that can be surgically corrected (such as a PDA). Due to the progressive nature of a majority of the processes leading to PH, the prognosis for long-term survival is generally considered poor. There is a paucity of information regarding prognosis, and confounding factors such as client funds may make determining this more difficult. However, data shows that dogs with primary respiratory disease and a tricuspid regurgitation pressure gradient of > 47 mmHg have a low probability of long-term survival. Conversely, patients with these diseases treated with PDE-5 inhibitors experience longer survival times. Lastly, the development of right-sided congestive heart failure may limit survival.

SYSTEMIC HYPERTENSION

Definition/Overview

Systemic hypertension is defined as a systolic blood pressure > 160 mmHg or diastolic pressure > 100 mmHg. Hypertension is divided into three categories: Situational, secondary, or idiopathic ("primary" or "essential").

Etiology

Systemic hypertension has been documented in veterinary patients most commonly from secondary disease processes and is rarely essential/primary. Causes of secondary hypertension can be classified as volume-loading hypertension or not. Diseases that result in increased circulating blood volume or peripheral vasoconstriction include hyperaldosteronism, hyperthyroidism, primary renal disease, diabetes mellitus, Cushing's disease,

pheochromocytoma, hyperviscosity syndrome (polycythemia, multiple myeloma, macroglobulinemia), and acromegaly. These diseases result in either activation of the RAAS at different levels or osmotic increases due to glucose, steroids, red blood cells, proteins, or growth hormones. Essential hypertension has been documented in a line of Siberian Husky mixed breed dogs.

Pathophysiology

Systemic hypertension is associated with increased systemic vascular resistance. Four target organs are particularly affected by a chronic elevation in blood pressure: The heart, kidneys, eyes, and brain.

Clinical Presentation

Most hypertensive dogs and cats are middle aged to older. Signs reported by the owner are usually caused by the various diseases that lead to systemic hypertension or by evidence of target organ damage. For example, hypertensive animals may develop acute blindness or seizures. Target organ consequences caused by uncontrolled hypertension are listed in Table 8.16. Physical examination may reveal epistaxis, a palpable thyroid slip, a gallop rhythm, and/or heart murmur.

Differential Diagnosis

Differential diagnosis for pathologic systemic hypertension includes physiologic hypertension from stress (situational hypertension).

Diagnosis

Diagnosis of systemic hypertension is based on invasive or noninvasive measurements of blood pressure. Invasive blood pressure measurements are made most commonly with the animal restrained in lateral recumbency and a 22- to 25-gauge catheter inserted into the femoral artery connected by a heparinized saline-filled tubing to a physiologic pressure transducer and hemodynamic oscilloscope recorder. Tubing should not be excessively long and should be kept at the level of the heart.

CHF, congestive heart failure; CKD, chronic kidney disease.

Noninvasive blood pressure measurement can be obtained by auscultation of Doppler signals with Korotkoff sounds when blood flow to a limb or the tail is obstructed with an appropriately sized and inflated cuff. The choice of cuff is based on the patient's distal limb size. Additionally, noninvasive oscillometric blood pressure measurement is a common technique that relies on detection of arterial pulsation through the use of an automatically inflating and deflating cuff that is wrapped around a distal limb or tail. The accuracy of such devices may be limited in smaller patients, where Doppler measurement is preferred. Consistency in personnel, equipment, and technique is critical to obtain accurate measurements.

Systemic hypertension is currently classified as falling into one of three groups:

1. Prehypertension (140–159 mmHg)
2. Moderate hypertension (160–179 mmHg)
3. Severe hypertension (> 180 mmHg)

Diagnostic tests for secondary causes of systemic hypertension are listed in Table 8.17.

TABLE 8.16 Target organ consequences of systemic hypertension

Target organ	Consequences
Cardiovascular	– Left ventricular concentric hypertrophy – Aortic valve insufficiency – Arteriosclerosis – Atherosclerosis – CHF (uncommon) – Aortic dissection/aneurism (rare)
Cerebrovascular	– Encephalopathy – Cerebrovascular accidents (strokes)
Renal	– Progression of CKD – Proteinuria
Intraocular	– Blindness – Retinal detachment, hemorrhage, and/or hyphema – Choroidopathy

TABLE 8.17 Diagnostic tests for hypertensive diseases

Disease	Test
Thyroid disease	T4, free T4, antibody panel
Hyperadrenocorticism	ACTH stimulation test, dexamethasone suppression test, urine cortisol-to-creatinine ratio, abdominal ultrasound
Pheochromocytoma	Abdominal ultrasound, plasma/urinary catecholamine levels
Hyperaldosteronism	Serum sodium and potassium levels, aldosterone assay, abdominal ultrasound
Renal disease	CBC, chemistry, urinalysis, urine culture, urine protein-to-creatinine ratio, abdominal ultrasound, renal biopsy, creatinine clearance
Polycythemia	Primary versus secondary, CBC, erythropoietin assay, bone marrow biopsy, cardiopulmonary evaluation, abdominal radiographs and ultrasound
Hyperviscosity	Chemistry, protein electrophoresis, bone marrow biopsy
Intracranial disease	MRI
Acromegaly	Growth hormone assay, clonidine stimulation test
Hyperestrogenism	Estrogen assay, abdominal ultrasound

TABLE 8.18 Emergency treatment of systemic hypertension*

Autonomic independent vasodilators	– Nitroprusside IV CRI at 0.5–1 µg/kg/min carefully titrated to effect by increasing by 1 µg/kg/min increments every 15 minutes as long as the blood pressure decreases to desired degree (usually 2–5 µg/kg/min with upper limit of 8–10 µg/kg/min) – Hydralazine (loading dosage of 0.1 mg/kg IV over 2 minutes, followed by a CRI of 1.5-5.0 µg/kg/min) or 0.5–2 mg/kg p.o. q.12h.
Calcium channel blockers	– Amlodipine 0.2–0.4 mg/kg p.o. q.24h.
Dopamine-1 Agonist	– Fenoldopam IV CRI at 0.1 µg/kg/min with frequent (every 10 minutes) BP monitoring – Titrate dose up by 0.1 µg/kg/min increments every 15 minutes to the desired SBP – Maximum dose: 1.6 µg/kg/min

* All doses are for canines unless otherwise indicated.

Management

Underlying causes of secondary systemic hypertension should be treated if possible. Additionally, medical management with antihypertensive medications may be needed acutely and in the long term for treatment of hypertension, with the goal of avoiding target organ damage. Emergency treatment for severe hypertension is described in Table 8.18. The goal of emergency treatment is a gradual decrease in blood pressure rather than an acute fall to normal blood pressure. Emergency treatment of hypertension should take place at a facility that provides 24-hour care. Drugs commonly used for treatment of hypertension are listed in Table 8.19.

Prognosis

Prognosis for systemic hypertension is good if an underlying cause is identified and treated appropriately and if end-organ damage is minimal.

HEARTWORM DISEASE

Heartworm disease (or dirofilariasis) occurs worldwide. The dog is the typical host of the parasite, but cats can also develop infection. Heartworm disease has been diagnosed in all 50 states and around the globe. It is critical to administer year-round chemoprophylaxis, which is highly effective at protecting dogs and cats from heartworm disease.

CANINE HEARTWORM DISEASE

Etiology

Heartworm disease is caused by *Dirofilaria immitis*, a filarial nematode that resides in its adult form in the pulmonary arteries of canids and uses several species of mosquitoes as vector. Adequate temperature and humidity are necessary to support a viable mosquito population and allow maturation of the heartworm larvae to the infective stage.

Pathophysiology

Infected mosquitoes deposit 1-mm long stage 3 larvae on the dog's skin at the time of a blood meal. Larvae reach the dog's subcutaneous tissues and muscle from the puncture side and then molt to stage 4 larvae by day 3. Larvae then migrate between muscle fibers where they mature to immature adult worms that enter the circulatory system, which transports them to the pulmonary artery by day 70. Worms measure 10 cm and become sexually mature 6–7 months post infection. Mature females release microfilariae, a prelarval stage, into the bloodstream where they are picked up by mosquitoes, which completes the worm's life cycle. Microfilariae first appear in the circulation 6 months post infection. Microfilariae live up to 2.5 years. Heartworms harbor an endosymbiotic bacterium, *Wolbachia* spp. Elimination of *Wolbachia* has negative effects on *Dirofilaria immitis* fecundity and

TABLE 8.19 Treatment of systemic hypertension*

ACE inhibitors	Benazepril 0.5 mg/kg p.o. q.12–24h. Enalapril 0.5 mg/kg p.o. q.12–24h.
Angiotensin receptor blocker	Telmisartan 1 mg/kg p.o. q.24h.
Calcium channel blocker	Amlodipine 0.1–0.25 mg/kg p.o. q.24h. (Cat: 0.625–1.25 mg per cat q.24h.)
Beta-adrenergic receptor blockers	Atenolol 0.25–1.0 mg/kg p.o. q.12h. (Cat: 0.625–1.25 mg per cat q.24h.) Propranolol (beta 1 and 2) 0.25–1.0 mg/kg p.o. q.8h. (titrate to effect)
Alpha-adrenergic receptor blockers	Prazosin 0.5–2 mg/kg p.o. q.8–12h. (Cat: 0.25–0.5 mg per cat q.24h.)
Vasodilators	Hydralazine 0.5–2.0 mg/kg p.o. q.12h. (start at low range)
Diuretics	Furosemide 1.0–4.0 mg/kg p.o. q.8–24h. Spironolactone 1.0–2.0 mg/kg p.o. q.12h. Hydrochlorothiazide 2–4 mg/kg p.o. q.12–24h.

* All doses are for canines unless otherwise indicated.

development. It is also believed that *Wolbachia* trigger an immune response in the dog, which may be responsible for some of the clinical signs associated with heartworm disease.

Live worms cause vascular inflammation with thickening of the pulmonary artery wall and pneumonitis. Additional thromboembolic lesions occur when the worms die, and worm fragments obstruct branches of the pulmonary arteries. Over time, lung lesions result in the development of PH and, in severe cases, congestive right heart failure.

Clinical Presentation

Most dogs with heartworm disease do not have clinical signs. When present, typical signs include cough, tachypnea, dyspnea, and exercise intolerance. Rarely, syncope associated with exercise, hemoptysis, and CHF (ascites) are observed.

Caval syndrome occurs when adult worms move into the right ventricle and atrium where they interfere with tricuspid valve closure (Figure 8.50). Caval syndrome is most likely triggered by a profound alteration in hemodynamics, such as the one that accompanies a PTE, and usually a large worm burden. Most dogs with caval syndrome usually show signs of poor perfusion (weakness, tachycardia), dyspnea, tachypnea, ascites, and hemoglobinuria.

Differential Diagnosis

Other causes of PH, including PTE, and angiostrongylosis where it is prevalent (historically Europe and parts of Canada, though infections have been reported in the United States and South America). *Angiostrongylus vasorum*, also referred to as the French heartworm, resides in the pulmonary arteries of dogs. Infected dogs may show respiratory signs, including chronic cough, dyspnea, and exercise intolerance. Others develop PH. Diagnosis is by detection of larvae in feces. Cross-reactions with the *Dirofilaria* antigen tests have been reported.

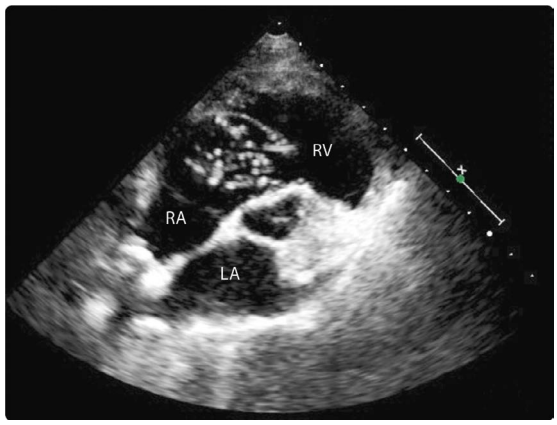


FIGURE 8.50 Echocardiographic view from a dog with caval syndrome. Worms are visible within the right cardiac chambers. The reflection of the ultrasound on the surface of segments of the worms give this typical image of an "= sign." LA, left atrium; RA, right atrium; RV, right ventricle.

Diagnosis

Heartworm disease is usually detected during routine yearly screening. The heartworm antigen test, which detects circulating adult female antigens, is a very sensitive and specific test as long as it is performed at least 6 months after infection. A test in an infected dog may be falsely negative if it is performed too early, if only male worms and/or nonreproductive females are present, or if there is a small worm burden.

Microfilariae can be detected in some dogs in the peripheral circulation on a direct blood smear or using a Knott's test. However, many dogs experience occult heartworm infections (i.e., microfilariae are not present in the circulation). It is currently recommended to test for both heartworm antigen and microfilaria annually.

Thoracic radiographs, blood work, and urinalysis are usually performed in heartworm-positive dogs to determine the severity of the disease. Radiographs may reveal large and tortuous pulmonary arteries, interstitial to alveolar lung patterns, and, on occasion, right-side cardiomegaly. Eosinophilia and basophilia can be identified on CBC, and proteinuria secondary to heartworm-induced glomerulonephritis may be detected on urinalysis. Echocardiography is indicated in dogs presenting with severe signs of heartworm disease. Adult worms are sometimes visible in the right and main pulmonary arteries. The presence of worms in the right cardiac chambers is diagnostic for caval syndrome. In these dogs, a loud intensity right-sided apical systolic murmur, caused by tricuspid valve regurgitation, is usually present.

Management

In infected dogs, the goal of therapy is to kill the adult worms in order to prevent additional damage to the lung vasculature. All dogs with heartworm disease should be treated, and the treatment should include adulticide therapy. The only adulticide currently available is melarsomine dihydrochloride (Immiticide). Before treatment with melarsomine, preventive medications should be administered for 2–3 months to prevent reinfection and allow heartworm larvae to mature to a young adult stage, which is more sensitive to the effects of melarsomine. A tapering dose of prednisone (0.5 mg/kg b.i.d. first week, 0.5 mg/kg once daily for the second week, 0.5 mg/kg every other day for the 3rd and 4th weeks) as well asdoxycycline (10 mg/kg p.o. q.12h.) should be given for 1 month to eliminate *Wolbachia* spp. Melarsomine is administered following a three-dose protocol (one injection followed by two injections 24 hours apart 1 month later) and 2 months of strict exercise restriction starting the day of the first injection in order to limit the risk of thromboembolism. Animals should be monitored for side effects for a few hours following injection of melarsomine. Dogs should be retested with a heartworm antigen test and microfilaria test 6–9 months later to confirm successful treatment.

Caval syndrome is managed by surgical extraction of the heartworms. Access to the right heart chambers

is obtained from a jugular vein. Wire baskets designed for endoscopy inserted in the right atrium and right ventricle under fluoroscopy guidance can be used to fish the worms out. Despite surgical extraction, the mortality of dogs with caval syndrome approaches 40%–50%. It is usually not necessary to extract worms that are visible in the pulmonary arteries on echocardiography. Adulticide therapy must be initiated as soon as the animal has recovered from the surgical extraction in order to eliminate the worms still present in the distal pulmonary vessels.

In all dogs that test negative for heartworm disease, macrocyclic lactones (ivermectin, selamectin, moxidectin, milbemycin) are used to prevent the development of stage 3 and stage 4 larvae after mosquito bites. Macrocyclic lactones also have adulticide properties. For example, ivermectin has been shown to kill adults in 31 months. Macrocyclic lactones may not eliminate microfilariae at preventive doses. Year-round prophylaxis is recommended, and most drugs are approved for monthly administration. We recommend reviewing updated guidelines for the treatment and prevention of heartworm diseased regularly published by the American Heartworm Society.

Heartworm Resistance

Most cases of drug failure to prevent heartworm infection can be traced back to poor owner compliance. However, there has been documented resistance to macrocyclic lactones in some regions. One cause for resistance might be the chronic use of macrocyclic lactones in heartworm-positive dogs, which selects a resistant population of microfilariae. Results from experimental studies suggest that the resistance is heritable. It is, therefore, important to not only eliminate adult worms but also eliminate microfilariae with microfilaricidal doses of macrocyclic lactones.

Prognosis

Dogs with low-burden infection and limited lung lesions may fully recover after adulticide therapy. However, dogs with severe lesions and PH may develop right-heart failure over time. Once ascites is present, survival is usually less than 1 year.

FELINE HEARTWORM DISEASE

Introduction/Overview

Heartworms rarely develop to the adult stage in cats. Most commonly, the manifestations of feline heartworm disease are described as heartworm-associated respiratory disease (HARD), which occurs in response to an inflammatory response to larvae and mimics the signs of feline asthma.

Pathophysiology

In regions where canine heartworm disease is present, prevalence in unprotected cats is between 5% and 15% of their canine counterparts. In cats, development of the worms usually stops at larval stage 5 (immature worms), and the presence of adult worms is uncommon. Despite incomplete worm development and the absence of long-lasting infection, pulmonary vascular and parenchymal inflammatory lesions are responsible for clinical signs. In cats with mature infection, thromboembolism from dead worms, fatal acute lung injury, and PH causing right-sided heart failure are major complications of the disease. Finally, aberrant larval migration is more common in cats than dogs, resulting in neurologic signs if larvae reach the central nervous system.

Clinical Presentation

It is important to distinguish cats with mature heartworm infection and cats exposed to larvae that failed to develop into adult worms. HARD occurs in response to the short-lived presence of larvae in the pulmonary vasculature. Its clinical manifestations are similar to feline bronchial disease, including dyspnea and wheezes. Cough is frequent. When a small number of adult worms survive in the pulmonary circulation, cats usually develop severe respiratory signs, PH, right heart failure, syncope, and sudden death.

Differential Diagnosis

It is challenging to differentiate HARD from feline bronchitis and asthma.

Diagnosis

It is difficult to establish a definitive diagnosis of heartworm disease in cats because most of the available tests lack sensitivity or specificity. Antigen tests, which only detect mature female heartworms, are rarely positive in cats because they typically only harbor fewer than six worms and sometimes all males. Antibody tests, when positive, indicate that the cat has been exposed to heartworm disease, and larvae have developed at least to stage 5 (immature worms). However, they do not indicate the presence of adult worms nor that the infection is ongoing. A negative antibody test usually rules out the presence of adult worms. It is usually recommended to start with an antibody test and perform an antigen test when the antibody test is positive. The presence of circulating microfilariae in the peripheral circulation of cats is unusual. Indirect signs of heartworm disease, such as eosinophilia and basophilia, enlarged pulmonary arteries and bronchointerstitial lung pattern on chest radiographs, and echocardiographic evidence of adult worms in the branches of the pulmonary artery, are inconsistent. Therefore, when HARD or adult worm infection is suspected, diagnosis of heartworm disease relies on suggestive clinical signs, in particular cough, and the results of laboratory tests and imaging.

Management

HARD usually responds to medications used for the treatment of feline asthma, including steroids and

bronchodilators. If adult worms are present, the high incidence of life-threatening complications associated with use of melarsomine limits the use of this drug in cats. Alternatively, cats can be administered monthly preventive therapy, and steroids should be used to control inflammation. The authors use doxycycline for 1 month. Sildenafil can be used if severe PH is present. Surgical removal can be considered, but fatal complications are common if worms are not removed intact.

Prognosis

Mortality is high in cats that harbor adult worms.

BRADYARRHYTHMIAS

Bradycardia corresponds to a heart rate less than 60 bpm in dogs and approximately 100 bpm in cats. Bradyarrhythmias can result from an increase in vagal tone, drugs, electrolyte abnormalities, inflammation or infiltration of the myocardium, and degenerative disease of the conduction system. Although the etiology frequently remains unclear, the clinician needs to determine from the ECG and the clinical signs whether extracardiac factors are the cause for the arrhythmia, if treatment is needed, and how to choose between medical and pacemaker therapy.

SICK SINUS SYNDROME (SINUS NODE DYSFUNCTION)

Definition/Overview

Sick sinus syndrome is a disease of the conduction system in dogs characterized by periods of normal sinus rhythm or sinus bradycardia interspersed with long periods of sinus arrest or block that can last up to 10–12 seconds. The pauses result from a failure of the junctional and ventricular pacemakers to initiate escape beats, indicating that this disease involves the conduction system beyond the sinus node (Figure 8.51). A variant of the disease, sometimes called tachy–brady syndrome, is characterized by periods of paroxysmal supraventricular tachycardia followed by a temporary failure of the sinus rhythm to resume when the tachycardia abruptly terminates.

Etiology

The cause for sick sinus syndrome is unknown. However, there is a breed predisposition, with Miniature Schnauzers and West Highland White Terriers being overrepresented, and the condition typically occurs in older dogs.

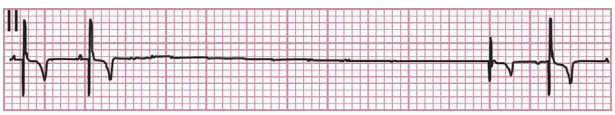


FIGURE 8.51 ECG (lead II) from a dog with sick sinus syndrome. The initial sinus rhythm is followed by a long period of sinus arrest that is interrupted by a junctional escape beat.

Clinical Presentation

Exercise intolerance, lethargy, and weakness are some of the clinical signs reported with sick sinus syndrome. Syncope occurs when periods of sinus arrest last more than 6–8 seconds. The use of opioids as sedatives frequently results in a prolongation of the periods of asystole, and dogs that were asymptomatic while awake may commonly become hemodynamically unstable after sedation or general anesthesia.

Differential Diagnosis

Other bradyarrhythmias that may cause clinical signs, in particular those resulting from high vagal tone in the presence of GI, respiratory, neurologic, and ocular diseases. Marked vagotonia may cause sinus bradycardia, pronounced respiratory sinus arrhythmia, and occasionally second-degree AV block, which may mimic a mild form of sick sinus syndrome.

Diagnosis

In older small breed dogs, the suspicion of sick sinus syndrome is usually confirmed on an ECG recording. To differentiate sick sinus syndrome from vagally induced bradycardias, response to the administration of parasympatholytic medications can be evaluated. A rapid increase in heart rate following IV administration of atropine (0.04 mg/kg) or glycopyrrolate (0.01 mg/kg) strongly suggests the contribution of vagal tone to the bradyarrhythmia. However, an increase in heart rate may also be observed in dogs with sick sinus syndrome. It is, therefore, recommended to evaluate the ECG over a longer period of time using a 24-hour Holter recording.

Management

Temporary response to terbutaline (0.2 mg/kg p.o. q.8–12h. or 0.01 mg/kg IV), a selective beta-2 agonist commonly used as bronchodilator, or theophylline (5–10 mg/kg p.o. q.12h.), a phosphodiesterase inhibitor and bronchodilator with mild chronotropic effect, is observed in some dogs with sick sinus syndrome. However, dogs frequently develop side effects with chronic use of these drugs, and the clinical signs frequently recur as the disease progresses (Table 8.20).

Permanent pacemaker implantation is indicated in dogs that display clinical signs. The simplest and most commonly used type of pacing in veterinary patients involves a single lead placed in the right ventricle via the jugular vein and a generator placed subcutaneously in the cervical region. Pacemakers are able to detect spontaneous activity and stimulate cardiac contraction if the heart rate drops below a preprogramed number. In dogs with sick sinus syndrome, the pacemaker maintains a regular rhythm and adequate cardiac output during periods of sinus arrest. Because the rhythm abnormalities associated with sick sinus syndrome are intermittent, the pacemaker is usually activated less than 50% of the time in these dogs. It, therefore, mimics a ventricular escape rhythm with an adjustable rate.

TABLE 8.20 Drugs for the treatment of bradycardia

Drug	Dosage	Indications
Atropine	0.02–0.04 mg/kg SC, IM, IV (D,C)	Sinus bradycardia Sick sinus syndrome first- and second-degree AV block
Glycopyrrolate	0.005–0.01 mg/kg SC, IM, IV (D,C)	Sinus bradycardia Sick sinus syndrome first- and second-degree AV block
Terbutaline	0.2 mg/kg p.o. q.8–12h. (D) 0.625 mg p.o. q.8–12h. (C) 0.01 mg/kg IV (D,C)	Sinus bradycardia Sick sinus syndrome
Isoproterenol	0.04–0.09 µg/kg/min, to effect (D,C)	Second- and third-degree AV block
Aminophylline Theophylline	10 mg/kg p.o. q.12h. (extended release) (D,C) 5–10 mg/kg IV (D)	Sick sinus syndrome

AV, atrioventricular; C, cat; D, dog.

Prognosis

Clinical signs worsen as the disease progresses, and without treatment, some dogs experience several syncopal episodes daily. Sudden death can occur, but it is common for dogs with sick sinus syndrome to experience signs for months and even years before they die. Long-term prognosis is good after pacemaker implantation if complications associated with the procedure do not occur within 1 month and in the absence of underlying structural heart disease, such as degenerative mitral valve disease. Major but rare pacemaker complications include lead dislodgement during the first 4 weeks following implantation, device infection that is more likely to occur during the first year, and hemodynamically significant tricuspid valve regurgitation.

ATRIOVENTRICULAR BLOCK

Definition/Overview

AV block corresponds to a delay of conduction or the inability for an impulse originating from the atrium to cross the AV node. The AV node is the only pathway for electrical impulses to travel from atrium to ventricle.

Etiology

Fibrosis of the AV node is the most common cause for AV block in older dogs and cats. Inflammation and infiltration of the AV node by neoplastic cells (e.g., lymphoma) may also be seen. Elevated vagal tone can delay AV node conduction. Drugs such as beta-blockers and calcium-channel blockers can also cause AV block.

Pathophysiology

Three forms of AV block corresponding to different degrees of disease severity are recognized. In the mild form of the disease, all impulses originating at the supraventricular level (usually the sinus node) cross the AV node but with some delay (first-degree AV block). As the disease progresses, some impulses are unable to reach the ventricles (second-degree AV block). In the most severe form of the disease, there is complete dissociation between impulses in the atrium and an escape rhythm originating in the ventricles that maintains a low heart rate and a decreased cardiac output (third-degree AV block). Clinical signs occur when too many supraventricular impulses are blocked at the AV node, which results in the absence of ventricular contraction for 4–8 seconds, or when the slow ventricular escape rhythm does not maintain adequate cardiac output

Clinical Presentation

Animals with first-degree AV block do not display clinical signs, as all the impulses from the atrium are transmitted to the ventricles with a short delay. Clinical signs of lethargy, weakness, or syncope only occur in the severe forms of second-degree AV block and third-degree AV block. Surprisingly, some dogs with third-degree AV block and an average heart rate between 20 and 60 bpm do not show overt clinical signs. Cats commonly lack clinical signs because the ventricular escape rhythm is usually around 100 bpm in this species. However, if a slow heart rate persists for several months, it will lead to progressive cardiac enlargement and possibly CHF (usually right-sided).

Differential Diagnosis

Other cardiac causes of syncope and lethargy.

Diagnosis

Diagnosis is usually easily reached with an ECG. With first-degree AV block all the atrial impulses are conducted to the ventricles, but the PR interval is prolonged (PR > 130 ms in dogs, PR > 90 ms in cats). Second-degree AV block is diagnosed when some P waves are not followed by a QRS complex on the surface ECG (Figure 8.52).

Two types of second-degree AV blocks are recognized. Mobitz type I second-degree AV block is characterized by a progressive increase or variable PR interval duration ending with a blocked P wave, known as Wenckebach phenomenon. It usually results from a combination of AV node fibrosis and a progressive increase in vagal tone. This

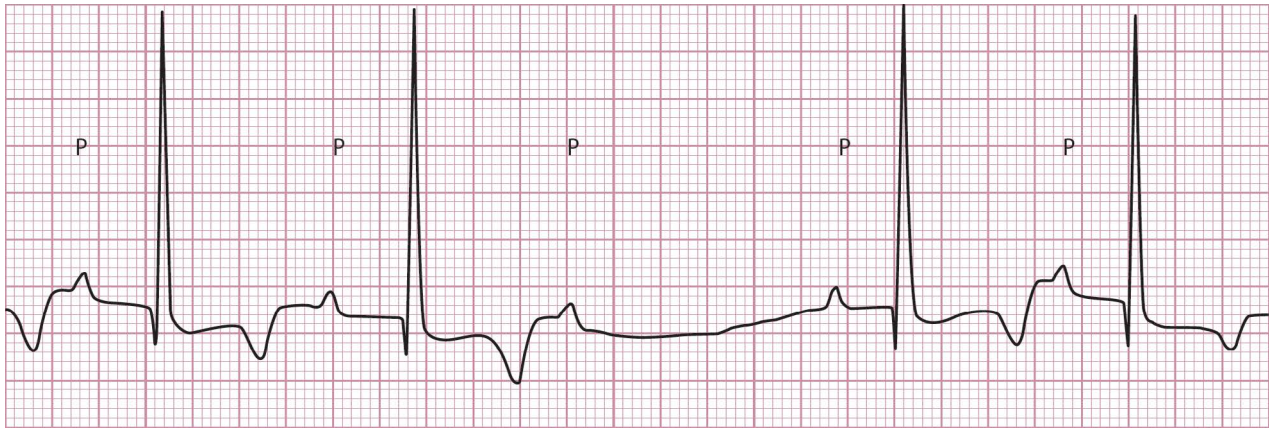


FIGURE 8.52 ECG (lead II) from a dog with first-degree and Mobitz type I second-degree atrioventricular block. The baseline PR interval is prolonged. There is one nonconducted P wave consistent with second-degree atrioventricular block. Note the variable PR interval indicating the effects of vagal tone on atrioventricular conduction.

form of AV block is usually benign and does not require specific treatment. Mobitz type II second-degree AV block is characterized by the unexpected occurrence of blocked P waves. PR intervals before and after the blocked P waves are identical. The QRS complexes of conducted beats can be wide when the area of block is below the His bundle, causing bundle branch blocks and intraventricular conduction delays. This form of block is more likely to worsen and result in clinical signs. Administration of atropine (0.04 mg/kg IV) can help the clinician differentiate between the two forms of block. Type I usually improves after atropine and type II worsens.

Third-degree or complete AV block is characterized by an absence of conducted P waves to the ventricles (Figure 8.53). The ECG displays independent atrial and ventricular activities. Cardiac output is dramatically reduced. In response, the atrial rate, which is under control of the adrenergic tone, is elevated. Electrical activation of the ventricles is dependent on an escape rhythm beyond the site of the block. The QRS complexes are generally wide and bizarre at rates of around 20–60 bpm in dogs and 60–120 bpm in cats. In addition, the ventricular rate is regular unless ventricular premature beats originating from an ischemic myocardium are present.

A 24-hour Holter recording is sometimes necessary to identify occasional second-degree AV block as the cause for syncope. An echocardiogram is always indicated to identify a tumor as the cause for AV block and identify concomitant structural cardiac disease. AV block is often associated with structural cardiac disease in cats. Although a mild elevation of serum cTnI concentration is common in dogs with third-degree (complete) AV block, a marked increase in concentration suggests myocarditis as the cause for the arrhythmia.

Management

Pacemaker implantation is usually the best treatment option when clinical signs are present. AV node conduction may improve in some dogs with second-degree AV block after administration of theophylline or terbutaline.

Prognosis

Good after pacemaker implantation in dogs with clinical signs. Some dogs with myocarditis spontaneously return to sinus rhythm.

ATRIAL STANDSTILL

Definition/Overview

Atrial standstill corresponds to the absence of visible atrial electrical activity (and therefore contraction) on the ECG. It can be permanent or temporary. Permanent atrial standstill is rare.

Etiology

Permanent atrial standstill affects young dogs, and a genetic etiology is likely. It may be more prevalent in English Springer Spaniels. Hyperkalemia is the cause for temporary atrial standstill.

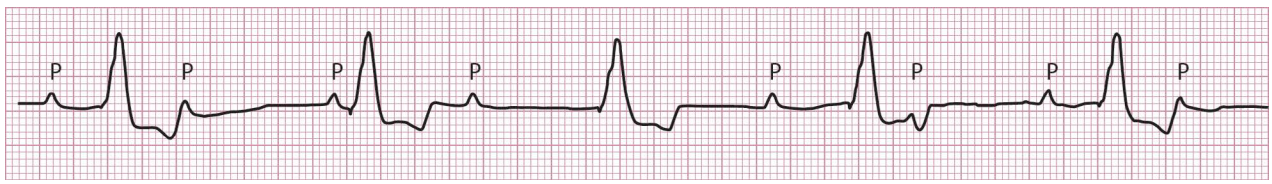


FIGURE 8.53 ECG (lead II) from a dog with third-degree atrioventricular block. There is complete dissociation between the P waves and QRS complexes. Some P waves overlap T waves.



FIGURE 8.54 ECG (lead II) from a dog with atrial standstill. There are no visible P waves, and the ventricular rhythm is regular.

Clinical Presentation

Dogs with permanent atrial standstill usually present with signs associated with severe bradycardia. Animals with hyperkalemia have signs caused by the underlying disease, including hypoadrenocorticism, urinary tract obstruction or rupture, severe arterial thromboembolism in cats, and tumor lysis syndrome.

Diagnosis

Permanent atrial standstill is recognized on the ECG as a lack of P waves with a regular ventricular or AV nodal escape rhythm at rates of 20–60 bpm in dogs (Figure 8.54). The ECG changes of hyperkalemia include a narrowing and increased amplitude of the T wave as plasma concentration of potassium increases above 5.5 mmol/L. As potassium continues to rise, it leads to a decrease in heart rate associated with reduced P-wave amplitude and a widening of the QRS complexes. P waves then become invisible, consistent with a sinoventricular rhythm that cannot be distinguished from atrial standstill.

Management

Permanent atrial standstill requires permanent pacemaker implantation. Successful management of hyperkalemia results in return of normal cardiac rhythm and ECG trace.

Prognosis

Permanent atrial standstill carries a poor prognosis, as the disease affecting the atrium and causing a progressive replacement of the myocytes by fibrous tissue seems to progress to the rest of the myocardium.

TACHYARRHYTHMIAS

Tachycardia is defined by a heart rate typically greater than 180–200 bpm in dogs and greater than 220–240 bpm in cats. Tachyarrhythmias are divided into supraventricular tachycardia, which originates from structures above the ventricles (sinus node, atrial myocardium, AV node), and ventricular tachycardia. AF, a form of supraventricular tachycardia, and ventricular tachycardia are the most common types of tachyarrhythmias. Other types of supraventricular tachycardias are rare and can usually be managed in the same way as AF (Table 8.21).

ATRIAL FIBRILLATION

Definition/Overview

Atrial fibrillation (AF) is characterized by uncoordinated atrial activation from multiple simultaneous electrical wavelets resulting in inadequate mechanical contraction of the atrium and an irregular ventricular response rate.

Etiology

Atrial dilation is a risk factor for developing AF. Therefore, AF commonly occurs in large breed dogs with only mild-to-moderate atrial dilation but is rarely present in small breed dogs with degenerative mitral valve disease despite extreme atrial dilation. It is rarely diagnosed in cats. Fibrosis, inflammation, and autonomic imbalances are other important contributors to the initiation of AF.

Pathophysiology

Most dogs with AF have underlying primary cardiac disease in the form of dilated cardiomyopathy (DCM) or degenerative mitral valve disease. The atrial enlargement provides the substrate for maintenance of the arrhythmia. During AF, the AV node is bombarded

TABLE 8.21 Drugs for the treatment of supraventricular tachycardia

Drug	Dosage	Comment
Digoxin	0.005 mg/kg p.o. q.12h. (D)	AF (rate control)
Diltiazem	0.1–0.4 mg/kg IV over 5 min (D,C) 0.05–0.15 mg/kg/h CRI (D,C) 1–2 mg/kg p.o. q.8h. (D,C) 3 mg/kg p.o. q.12h. (extended release) (D) 15–30 mg p.o. q.12–24h. (extended release) (C)	SVT (rate control or conversion) AF (rate control)
Atenolol	0.2–1 mg/kg p.o. q.12–24h. (D) 6.25–12.5 mg p.o. q.12–24h. (C)	SVT (rate control or conversion) AF (rate control)
Esmolol	0.2–0.5 mg/kg IV over 1 minute, repeat q.5 min (D,C)	SVT conversion
Procainamide	5–15 mg/kg IV over 1 minute (D) 1–2 mg/kg IV (C) 20–50 µg/kg/min CRI (D)	SVT conversion
Lidocaine	2 mg/kg IV over 30 sec Maximum 3 boluses (D) 0.25–0.5 mg/kg IV (C)	SVT conversion Vagally mediated AF conversion
Sotalol	1–3 mg/kg p.o. q.12h. (D,C)	SVT conversion SR maintenance

AF, atrial fibrillation; C, cat; D, dog; SR, sinus rhythm; SVT, supraventricular tachycardia.

by hundreds of impulses originating from the atria. Because the AV node has the role of a filter, only some of the impulses are able to reach the ventricles, with an irregular response to the supraventricular impulses. In the presence of heart failure, elevated adrenergic tone decreases the filtering property of the AV node, resulting in tachycardia. Less commonly, "lone" AF occurs in giant breed dogs with structurally normal hearts. In this instance, vagal tone, which is typically high in dogs in the absence of heart failure, increases the filtering effect of the AV node, resulting in a heart rate within the normal range for dogs. AF is rarely identified in cats. However, most cats with AF have underlying structural cardiac disease with atrial enlargement. Many of these cats also show signs of CHF. Once initiated, AF does not spontaneously resolve.

Clinical Presentation

The vast majority of dogs with AF are giant and large breed dogs. In the giant breed group, Irish Wolfhounds, Mastiffs, Newfoundlands, Rottweilers, and Great Danes are overrepresented, with a male predisposition. Cats with AF are usually older males. Most dogs with lone AF are asymptomatic. Conversely, some dogs with compensated cardiac disease and AF show signs of lethargy, exercise intolerance, and, rarely, anorexia, cough, or syncope. When AF occurs in the presence of CHF, generalized weakness, dyspnea, cough, and abdominal distension from ascites are usually present. Cats frequently show signs of an underlying cardiac disease, including dyspnea and arterial thromboembolism. However, AF can also be an incidental finding on auscultation in this species.

Differential Diagnosis

Other permanent tachyarrhythmias. The distinctive feature of AF is that it is irregular, whereas most sustained tachyarrhythmias are regular.

Diagnosis

On physical examination, AF is identified as a sustained and "irregularly irregular" rhythm accompanied by pulse deficits. A murmur may be auscultated, as underlying cardiac disease is common in dogs with AF.

On the surface ECG, AF is an irregular tachyarrhythmia, with usually narrow QRS complexes and no P waves, which can be replaced by an undulation of the baseline, or F waves (Figure 8.55). It is also permanent, indicating that sinus rhythm never spontaneously resumes following initiation of AF, and the average heart rate is typically > 180–200 bpm. The rate is much lower with lone AF, usually approaching 100–120 bpm at rest. Although AF is a supraventricular tachycardia, lesions of the ventricular conduction system (bundle branch block) may result in a widening of the QRS complexes, which may resemble those of ventricular tachycardia.

Determination of the average ventricular rate during AF provides critical information in deciding on a treatment strategy. Unfortunately, brief ECG recordings obtained in an unfamiliar environment do not adequately reflect the daily variations of heart rate. Heart rate is, therefore, better assessed from a 24-hour Holter recording. For reference, the average heart rate of healthy dogs varies between 85 and 100 bpm. Conversely, it is approximately 120 bpm in dogs with lone AF, 155 bpm in dogs with underlying cardiac disease, and 200 bpm in dogs with CHF.

Management

A rate-control strategy is usually applied to the treatment of AF. The rate-control approach aims at slowing ventricular rate in response to the rapid supraventricular impulses. However, this does not terminate the arrhythmia. Rate control is based on using drugs to decrease the ability of the AV node to conduct impulses. Ideally, the need for pharmacologic control of the heart rate is determined from the heart rate distribution obtained from a baseline 24-hour Holter recording. The effect of rate-control drugs is then assessed on a follow-up Holter 2 weeks after treatment initiation. As for defining adequate control, an average heart rate of no more than 120–140 bpm is considered adequate to observe clinical improvement. If the average heart rate is considered too high, drug dosages are increased by small increments, with close monitoring of the animal's clinical status, as the response to antiarrhythmics varies between patients. In contrast, medical therapy is usually not needed in dogs with lone AF; in these dogs, AF can be reverted to normal rhythm using direct-current (DC) electrical cardioversion.

Diltiazem is widely used for the management of AF. A graded dose of diltiazem results in a decrease in ventricular response rate because of slower action potential propagation in the AV node. Oral formulations include an extended-release form. A dose of 3–4 mg/kg p.o. q.12h. of the extended-release formulation usually achieves satisfactory rate control. Better rate control, especially during periods associated with high adrenergic tone, can be obtained by adding digoxin to the



FIGURE 8.55 ECG (lead II) from a dog with atrial fibrillation. Noted here is an irregular tachycardia. The QRS complexes are narrow, indicating that it is supraventricular in origin. In addition, there are no visible P waves.

treatment regimen. Calcium channel blockers decrease ventricular contractility and may cause hypotension when used in animals with severely depressed cardiac function.

The range of indications and side effects for beta-blockers are very similar to those of calcium channel blockers. Beta-1 selective agents, such as atenolol, are preferred to nonselective agents that can cause bronchospasm (Table 8.21).

Prognosis

Long-term prognosis is good for dogs with lone AF; however, in some breeds, in particular Irish Wolfhounds, it may be an early sign of DCM. In dogs with AF with underlying structural heart failure, median survival has been reported to be 32 months; however, it was only 5 months when CHF was present. In cats, treatment targeted at AF is rarely required as their ventricular response rate usually approaches the heart rate recorded in cats with sinus rhythm and heart failure.

VENTRICULAR TACHYCARDIA

Definition/Overview

Ventricular tachycardia is a rapid rhythm originating from the ventricles. A ventricular rhythm with a rate above the typical ventricular escape rhythm seen with AV block, but slower than ventricular tachycardia, is called accelerated idioventricular rhythm.

Etiology

Ventricular tachycardia is usually diagnosed in Boxers and English Bulldogs with ARVC and in Dobermanns with DCM. It can also occur in the presence of myocarditis, infiltrative cardiac disease, electrolyte imbalances, pheochromocytoma, or hypoxemia/ischemia. Cats are rarely diagnosed with ventricular tachycardia that requires treatment. In this species, it is associated with HCM and hyperthyroidism. Accelerated idioventricular rhythm is triggered by episodes of ischemia/reperfusion involving extracardiac tissues (e.g., gastric dilatation volvulus, trauma, arterial thromboembolism, or pancreatitis).

Pathophysiology

The two factors that determine the clinical consequences of ventricular tachycardia are rate and duration. Ventricular tachycardia must be sustained (more than 30 seconds) and rapid (usually more than 220–240 bpm) to cause clinical signs. Some forms of ventricular tachycardia can degenerate into ventricular fibrillation, resulting in sudden death.

Clinical Presentation

Dogs with intermittent ventricular premature contractions do not show clinical signs. It is only when the rate of the ventricular tachycardia is rapid (> 250–300 bpm) that signs of poor cardiac output may be present, and syncope may occur. Clinical signs will also be influenced by the degree of underlying heart disease. Thus, a patient with systolic dysfunction and ventricular arrhythmia may exhibit clinical signs at a slower rate of ventricular firing than a patient without underlying myocardial disease and ventricular tachycardia.

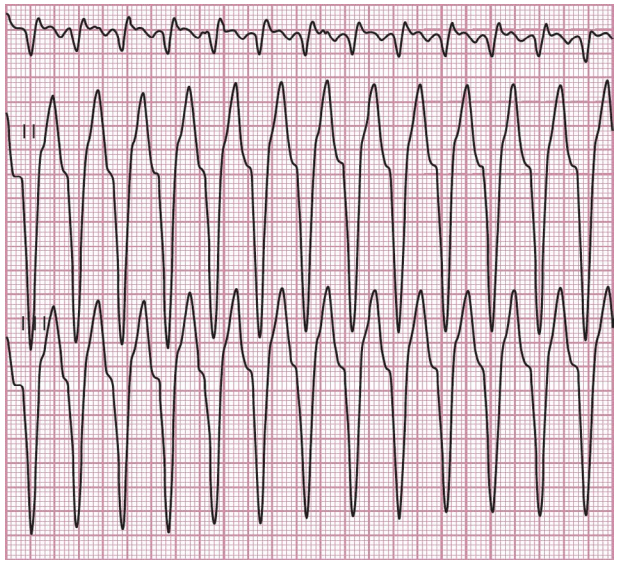


FIGURE 8.56 ECG from a dog with ventricular tachycardia. The QRS complexes are "wide and bizarre," and the rhythm is regular.

Diagnosis

Ventricular arrhythmias are diagnosed on ECG by the presence of wide and bizarre complexes (Figure 8.56). Beats originating in the ventricles are wide because the electrical impulse depolarizing the ventricles does not use the specialized cells of the conduction system. The QRS complex of ventricular beats is followed by a large T wave opposite to the direction of the QRS complex. Ventricular tachycardia is usually regular. It can last for a few seconds or be sustained for hours. A 24-hour Holter recording is indicated to evaluate the frequency of the arrhythmia and determine if its severity explains the clinical signs present. An echocardiogram is recommended to identify underlying structural heart disease and measure the left ventricular function. Thoracic radiographs and blood work are indicated to rule out any extracardiac cause for the arrhythmia, especially in the presence of an idioventricular accelerated rhythm.

Management

Treatment of ventricular tachycardia is justified when it causes hemodynamic compromise and clinical signs (Table 8.22). Hemodynamic compromise is typically related to the rate of the tachycardia and its duration. Sometimes treatment is initiated in apparently nonclinical animals based on the arrhythmia burden in on a

TABLE 8.22 Drugs for the treatment of ventricular tachycardia

Drug	Dosage
Amiodarone	10–20 mg/kg p.o. q.24h. for 7–10 days then reduce to 3–15 mg/kg p.o. q.24–48h. thereafter (D)
Atenolol	0.2–1 mg/kg p.o. q.12–24h. (D) 6.25–12.5 mg p.o. q.12–24h. (C)
Esmolol	0.2–0.5 mg/kg IV over 1 min, repeat q.5 min (D,C)
Lidocaine	2 mg/kg IV over 30 seconds Maximum 3 boluses (D) 0.25–0.5 mg/kg IV (C) 25–80 µg/kg per min CRI (D)
Mexiletine	4–8 mg/kg p.o. q.8h. (D)
Procainamide	5–15 mg/kg IV over 1 minute (D) 1–2 mg/kg IV (C) 20–50 µg/kg per minute CRI (D)
Sotalol	1–3 mg/kg p.o. q.12h. (D,C)

C, cat; D, dog.

Holter recording and the concern that the arrhythmia could worsen or result in sudden death. The risk of sudden death is likely higher in the presence of structural cardiac disease.

For a dog presented in an emergency with rapid sustained ventricular tachycardia, initial treatment with lidocaine boluses is recommended. It is important to measure serum potassium concentration, as lidocaine works better with normal potassium levels. Procainamide is an alternative to lidocaine when it fails to terminate the arrhythmia. Lidocaine should be used carefully in cats because they are more likely to develop neurologic side effects.

Long-term management of ventricular tachycardia is based on oral drugs and frequent monitoring with 24-hour Holter recordings to evaluate response to treatment. Sotalol, which shares antiarrhythmic and beta-blocking properties, is usually very effective at controlling ventricular arrhythmias in dogs. Mexiletine is another good antiarrhythmic agent but has become increasingly difficult to obtain for veterinary patients and has several times come off the market. It can cause significant gastrointestinal upset and has historically been difficult to obtain. It is often used in combination with atenolol or sotalol for resistant arrhythmias or as an initial antiarrhythmic agent for dogs with systolic dysfunction. Amiodarone appears to be effective for arrhythmias refractory to other drugs; however, it has been reported to have significant and severe side effects in dogs. The low end of the dosage range should be used first and titrated upwards only if necessary. Amiodarone very commonly causes adverse clinical signs with chronic use. It may cause anorexia due to elevated liver enzymes. Liver enzymes should be evaluated prior to initiating therapy, periodically while receiving amiodarone, and any time anorexia develops. It may also cause neutropenia of unknown clinical significance and neurologic signs and/or ataxia, especially at higher doses and with prolonged use. IV antiarrhythmic agents are rarely needed in the cat. Oral products, in particular atenolol and sotalol, are usually sufficient for clinical needs (Table 8.22).

Prognosis

Prognosis depends more on the underlying etiology than the tachycardia itself.

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CHAPTER 9

Digestive Diseases

Frédéric Gaschen

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PART 1: DISEASES OF THE PHARYNX, MASTICATORY MUSCLES, AND SALIVARY GLANDS

DYSPHAGIA

Definition/Overview

The word "dysphagia" is derived from Greek and means difficulty in eating and swallowing. A closely related term is odynophagia, which describes pain while eating/swallowing. The three phases of the normal swallowing reflex are described in Table 9.1.

Etiology and Pathophysiology

Three types of dysphagia are recognized.

Oral Dysphagia

Oral dysphagia relates to a difficulty prehending food and forming a bolus of food. It can occur with most oral and dental diseases. Additionally, cleft palate, tongue atrophy or paralysis, and diseases of the masticatory muscles, retrobulbar space, and temporomandibular joint can also lead to oral dysphagia.

Pharyngeal Dysphagia

Pharyngeal dysphagia is characterized by abnormal passage of food through the oropharynx. It may occur with pharyngeal diseases such as pharyngeal edema, trauma and foreign bodies, intraluminal masses, and extraluminal masses (e.g., grossly enlarged lymph nodes, retropharyngeal abscess, salivary gland enlargement), or result from abnormalities in the tightly regulated swallowing reflex. Affected animals may show numerous unsuccessful attempts to swallow, regurgitate immediately, gag, cough, and experience nasal reflux. Aspiration pneumonia is a common complication. Diagnosis is confirmed by a video fluoroscopic swallow study (VFSS) that shows failure of the pharynx to constrict and the upper esophageal sphincter (UES) to relax. In the absence of an obvious cause for dysphagia, rabies should be considered in unvaccinated dogs. Dogs

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TABLE 9.1 Physiology of swallowing

Oropharyngeal phase	– Voluntary oral stage – Formation of food bolus in the oropharynx, passage to the base of tongue, pharyngeal peristaltic contractions, bolus propelled to the laryngopharynx
	– Pharyngeal phase – Contraction of oral and tongue muscles with closure of pathway between oral cavity and pharynx, elevation of the soft palate, glottis closure, and tipping of the epiglottis after rostral displacement of the larynx
	– Cricopharyngeal phase – Relaxation of the UES (cricopharyngeal and thyropharyngeal muscles) to allow food bolus to be propelled into the upper esophagus
Esophageal phase	– A primary peristaltic wave is generated in the pharynx and propagated through the esophagus to propel the bolus to the LES – If the primary wave is not successful, a secondary wave is quickly generated by esophageal distension
Gastroesophageal phase	– Relaxation of the LES and passage of the bolus into the stomach

LES, lower esophageal sphincter; UES, upper esophageal sphincter.

with laryngeal paralysis, hypothyroidism, or myasthenia gravis may show concurrent pharyngeal dysphagia. If no cause can be identified, the prognosis of pharyngeal dysphagia is generally poor.

Cricopharyngeal Dysphagia

Cricopharyngeal dysphagia (CD) is characterized by a failure of the UES to relax (achalasia) or a lack of coordination between pharyngeal contraction and UES relaxation (dyssynchrony). Clinically, it may be difficult to differentiate CD from pharyngeal dysphagia. CD is rare and usually observed in puppies at the time of weaning or before the 1 year of age. Affected dogs may show nasopharyngeal reflux and nasal discharge. Detailed oropharyngeal inspection yields no abnormal findings. Diagnosis is confirmed with VFSS showing that the food bolus is unable to move past the UES despite normal pharyngeal motility. A congenital neurologic disorder is suspected. In the absence of complicating factors, the prognosis for dogs with confirmed cricopharyngeal achalasia is good after myotomy or myectomy of the cricopharyngeal muscle. Injection of botulinum toxin A into the muscle through an oral approach with endoscopic guidance has been anecdotally successful. However, this method is only performed at few referral centers worldwide and its effect is limited to 2–4 months.

Breed Predispositions

A congenital pharyngeal myopathy has been described in Bouvier des Flandres dogs. Cricopharyngeal achalasia is most observed in Dachshunds, Cocker Spaniels, Maltese Terriers, and Springer Spaniels. Golden Retrievers are overrepresented among dogs with cricopharyngeal dyssynchrony. Large breed dogs are also predisposed to laryngeal paralysis, a disease more commonly associated with pharyngeal and upper esophageal dysfunction.

Clinical Presentation

- *Oral dysphagia:* Dogs and cats are reluctant or unable to chew properly. They may show halitosis and oral pain or be painful on opening their mouth.
- *Pharyngeal or oropharyngeal dysphagia:* Animals are unable to swallow the food bolus in spite of repeated attempts. If the affected animal takes a quick breath of air between swallowing actions, food may enter the larynx and trachea, eliciting a cough. Dogs will try again and again and will sometimes succeed in achieving a more adequate swallowing action. They regurgitate the food bolus, which is covered with saliva. Their ability to drink from a water bowl may be maintained or impaired as well. Animals are generally hungry, and weight loss, lean body condition, and small stature (in puppies) are common. Other signs include coughing in case of aspiration and nasal discharge in association with nasopharyngeal reflux.

Diagnosis

Diagnosis relies on clinical signs (Box 9.1). A thorough oral and pharyngeal examination, ideally in the sedated animal, is often valuable. Radiographs of the pharynx are recommended in animals with suspect foreign body (FB) or other causes of obstruction. To confirm the type of dysphagia, VFSS can be very useful but is only available in referral centers. If aspiration pneumonia is suspected, chest radiographs are helpful to evaluate the severity and extent of the process.

Management

Nonspecific measures include optimizing the consistency of the food (generally, moist food is best tolerated). Specific treatments correcting the primary disease

Box 9.1 Practical tip on the clinical approach to dysphagic dogs and cats

First, observe the animal while it is eating. Videos filmed by the owner can be helpful as well. This allows recognizing the different types of dysphagia and designing a targeted further approach.

are most helpful if available. Additionally, in severe or untreatable cases, endoscopically or surgically placed low profile gastrostomy tubes allow bypass of the pharynx and proximal esophagus in order to provide enteral nutrition.

PHARYNGITIS AND TONSILLITIS

Definition/Overview

Inflammation causes hyperemia and swelling of the pharyngeal mucosa, which may be associated with tonsillar enlargement and protrusion of the tonsils out of the palatine fossae. Tonsillitis is not uncommon in the dog, particularly in young miniature and toy breeds but is quite rare in the cat. The inflammation is usually bilateral; however, it may be unilateral in association with FBs such as grass blades, pieces of wood, and grass seeds.

Etiology

Acute pharyngitis with or without secondary tonsillitis may occur following trauma, foreign bodies, insect stings, snake bites, allergic reactions, chemical or thermal injuries, and viral infection of the upper respiratory tract (cat). Additionally, disorders causing chronic vomiting, gagging, coughing, or regurgitation may be associated with acute tonsillitis.

Clinical Presentation

Coughing, gagging, retching, or expectorating white foamy mucus (which may be confused with vomiting by the pet's owner) are commonly reported. Dysphagia, repeated swallowing attempts, odynophagia, hypersalivation, excessive licking, and pica can also be observed. Some animals can present with decreased appetite, malaise, and fever. Pharyngeal examination reveals a hyperemic (dog) or injected (cat) pharynx, possibly with enlarged tonsils protruding out of the palatine fossae. Hyperemia, mottled appearance, petechiation, and white specks are reliable signs of acute inflammation. Chronically inflamed tonsils may just be enlarged with an irregular surface.

Differential Diagnosis

Tonsillitis should be differentiated from tonsillar neoplasia such as lymphoma (unilateral or bilateral enlargement [Figure 9.1]) or squamous cell carcinoma (SCC) (unilateral, highly malignant).

Diagnosis

Diagnosis is based on the abnormal appearance of the pharynx and tonsils in association with the existence of compatible clinical signs. Secondary tonsillitis is common, and a thorough search for a primary underlying disease should be performed. Radiographs of the pharynx and retropharyngeal area may reveal the presence of FBs or space-occupying processes (Figures 9.2 and 9.3).



FIGURE 9.1 Bilaterally enlarged tonsils in a middle-aged mixed-breed dog. Cytology from a fine needle aspirate revealed lymphoma. (*Courtesy of R. Husnik.*)



FIGURE 9.2 Proximal cervical radiograph from a 5-year-old Belgian Shepherd Dog taken 2 hours after the owner pulled a stick that appeared to be stuck in the dog's throat. There is retropharyngeal accumulation of air. Persistent wood fragments cannot be ruled out based on these films. Esophagoscopy was negative, and the dog recovered with antibiotic treatment.



FIGURE 9.3 Proximal cervical radiograph of an 8-year-old Bernese Mountain Dog with dysphagia. A space-occupying lesion is pushing the pharynx, esophagus, and trachea ventrally. Fine-needle aspiration revealed histiocytic sarcoma.

Fine-needle aspiration or brush cytology may help rule out neoplasia and confirm inflammation.

Management

For acute cases, treatment usually consists of a 7- to 14-day course of antibiotics (e.g., amoxicillin and clavulanic acid), possibly with analgesics if indicated. In chronic cases with significantly enlarged tonsils, tonsillectomy may be required if the tonsils become an obstacle preventing passage of food into the pharynx.

Prognosis

Good, although acute tonsillitis may recur. The disorder usually resolves spontaneously with time.

DISEASES OF THE SALIVARY GLANDS

The four salivary glands of dogs and cats are the submandibular (located rostrolateral from the submandibular lymph node), sublingual, parotid (under mandibular ramus), and zygomatic (infraorbital) glands. Salivary gland diseases are uncommon in dogs and very rare in cats.

MUCOCELE, SIALOCELE

Definition/Overview

Sialocele is the most frequently diagnosed salivary gland disorder of dogs. It consists of an accumulation of saliva in the periglandular tissues due to salivary duct obstruction and/or rupture. The wall of the mucocele is not epithelial; therefore, mucoceles are not true salivary gland cysts. They can occur in the vicinity of each salivary gland; however, the sublingual and submandibular glands are the most frequently affected. German Shepherd Dogs and Poodles appear to be more susceptible to developing sialoceles.

Etiology

Trauma is thought to be the most frequent cause of sialocele (direct trauma, FB, sialadenolith), although signs of original trauma have usually resolved by the time the sialocele is diagnosed.

Clinical Presentation

A large, usually nonpainful mass is observed in the upper cervical region, the pharynx, or the oral cavity (Figure 9.4). Oral and pharyngeal sialoceles may cause dysphagia and oral bleeding following self-trauma. Pharyngeal and cervical mucoceles can occasionally cause dyspnea.



FIGURE 9.4 A ranula or sialocele affecting the sublingual salivary gland is visible at the base of the tongue of this dog (arrows). (*Courtesy of R. Husnik.*)

Differential Diagnosis

Other causes of salivary gland enlargement such as inflammation (sialadenitis) and neoplasia.

Diagnosis

Diagnosis is based on history, physical examination, and results of fine-needle aspiration of the mucocele with a large-bore needle (blood-tinged, thick mucoid fluid with few neutrophils). Diagnostic imaging (ultrasound, sialography) can help confirm which gland is involved.

Management

Treatment consists of removal of the ipsilateral sublingual and submandibular gland as well as drainage of the fluid accumulation.

Prognosis

Prognosis is good following surgery.

SIALADENITIS

Sialadenitis describes inflammation of the salivary glands. A syndrome of inflammation and necrosis is occasionally observed in dogs. The condition leads to enlargement of one or several glands (e.g., zygomatic or mandibular gland). In the presence of severe inflammation and swelling, pain and dysphagia can occur. Confirmation of diagnosis may require fine-needle aspirate for cytology, cross-sectional imaging, and/or surgical biopsy. Therapy for sialadenitis usually includes antibiotics and pain management. In severe cases, surgical removal of the gland may be indicated. Sialadenosis is a nonpainful, noninflammatory swelling that may

cause lip smacking, hypersalivation, retching, and gulping and seems to respond to phenobarbital therapy.

SALIVARY GLAND NEOPLASIA

Salivary gland neoplasia occurs rarely (more frequently in cats than in dogs). The submandibular gland is most commonly affected. Adenocarcinoma is the most common type.

MASTICATORY MYOSITIS

Definition/Overview

Masticatory myositis is a common focal inflammatory myopathy of dogs. It selectively affects the muscles of mastication, including temporalis, masseter, pterygoid, and rostral digastricus muscles, while sparing the spinal and limb muscles. The disease is discussed in further details in Chapter 14.

PART 2: DISEASES OF THE ESOPHAGUS

Overview

Esophageal diseases occur relatively commonly in dogs but are infrequent in cats. They may have serious implications and severely debilitate affected animals. The resulting esophageal dysfunction may lead to regurgitation of undigested food with a high risk of food inhalation and aspiration pneumonia. Additionally, chronic esophageal problems may lead to undernourishment and associated complications. Foreign bodies, strictures, and neoplasia may cause intraluminal obstructions. Vascular abnormalities with compression of the esophagus may also compromise the esophageal lumen. Esophagitis is a frequent complication of esophageal diseases and gastroesophageal reflux and vomiting. Severe cases may result in development of strictures. Congenital or acquired functional disorders cause esophageal dysmotility and may eventually result in megaesophagus (ME).

Esophageal Anatomy

The UES consists of striated muscle fibers of both cricopharyngeal and esophageal origin. The two spirally arranged muscularis layers of the esophagus wind in opposite directions. In cats, they consist of striated muscle fibers in the proximal third of the esophagus (cervical segment), while they only contain smooth muscle fibers in the distal two-thirds of the esophagus (thoracic segment). In contrast, the muscularis layers of the canine esophagus are made exclusively of striated muscle fibers over the whole length of the esophagus. The lower esophageal sphincter (LES) is a thickening of the esophageal muscle located before the gastroesophageal junction.

TABLE 9.2 Clinical signs associated with esophageal diseases in dogs and cats

- Regurgitation
- Dysphagia
- Swallowing attempts “on empty”
- Halitosis
- Excessive salivation
- Odynophagia (esophagitis)
- Anorexia/inappetence (esophagitis)
- Ravenous appetite (motility disorders, megaesophagus)
- Tachypnea, dyspnea, cough, exercise intolerance, fever (aspiration pneumonia)

Normal Esophageal Function

Esophageal motility is triggered by passage of a food bolus through the pharynx (Table 9.1). Afferent impulse is conducted by the glossopharyngeal and vagus nerves to the nucleus solitarius in the brainstem. The information is processed with the help of the reticular formation and the nucleus ambiguus, where the motor neurons are located. These are activated and transmit impulses to the vagus nerve.

Clinical Presentation

The clinical signs consistent with esophageal disease are summarized in Table 9.2. Regurgitation describes passive retrograde evacuation of undigested food or liquids and may be associated with pharyngeal or esophageal dysfunction. Differentiation of regurgitation and vomiting relies on several well-defined clinical parameters but can be challenging at times (Table 2.14.1).

ESOPHAGEAL OBSTRUCTION

ESOPHAGEAL FOREIGN BODY

Esophageal FBs are a common problem in dogs while they are infrequently diagnosed in cats.

Etiology

In dogs, esophageal FBs are frequently observed in small breeds but may occur in any size dog. The foreign material often consists of beef, pork, veal, or chicken bone(s) coated with various amounts of connective tissue. Dog treats swallowed with insufficient chewing have also been reported. Fishing hooks when swallowed also get stuck in the esophagus. Esophageal FBs are most often located at one of three sites: Thoracic inlet, heart base, or cranial to the lower esophageal sphincter.

Clinical Presentation

Animals are often presented with a suggestive history (e.g., ingestion of bones, toys missing). The clinical signs typically include regurgitation, excessive drooling, odynophagia, halitosis, hyporexia/anorexia, and retching. Additional signs (e.g., lethargy, dyspnea, shock

associated with systemic inflammatory response syndrome [SIRS], or sepsis) may occur in association with complications such as esophageal perforation with mediastinitis or pleuritis or aspiration pneumonia.

Differential Diagnosis

Other esophageal diseases: Stricture, esophagitis, ME, and esophageal tumors. Additionally, differentiation between clinical signs of esophageal FB and those of vomiting and associated diseases can be difficult at times (Table 2.14.1).

Diagnosis

The presence of an esophageal FB is best confirmed using chest radiographs that reveal a soft-tissue mass in the esophagus at the level of the obstruction (Figures 9.5 and 9.6). In most instances, the use of barium sulfate is not required, and risks associated with its use can be avoided (aspiration pneumonia, damage to endoscopic equipment if esophagoscopy is performed soon after the esophagram). It is important to evaluate radiographs for the presence of free air in the mediastinum and pleural effusion, as these may indicate esophageal perforation or rupture.

Management/Prevention

Treatment consists of extracting the FB under endoscopic or fluoroscopic guidance as soon as possible (Figure 9.7). If extraction through the oral cavity is too difficult, the FB can be pushed into the stomach. Bone, cartilage, and fibrous tissue material can generally be digested by gastric juice and eliminated naturally. If passage through the pyloric canal seems impossible, gastrotomy and extraction of the FB is performed.

In case of esophageal perforation or rupture, a surgical approach is generally necessary. If severe esophageal mucosal lesions are present following extraction, a 24- to 48-hour fasting period is recommended. In the most severe cases, endoscopic placement of a regular or low-profile gastrostomy tube is required to provide nutrition without compromising mucosal healing for the period following FB removal. Additionally, treatment of esophagitis and

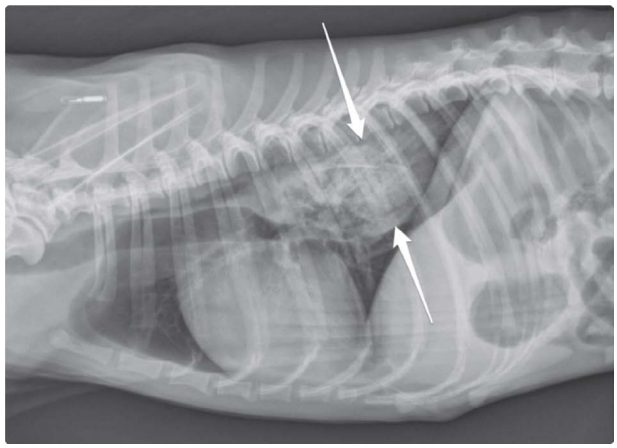


FIGURE 9.5 Four-year-old male Papillon Spaniel. Right lateral thoracic radiograph. A large soft tissue opacity is visible in the caudal half of the thoracic esophagus (dorsal and ventral limits shown by arrows). Interpretation: Esophageal foreign body without indication of esophageal perforation and pleuritis.

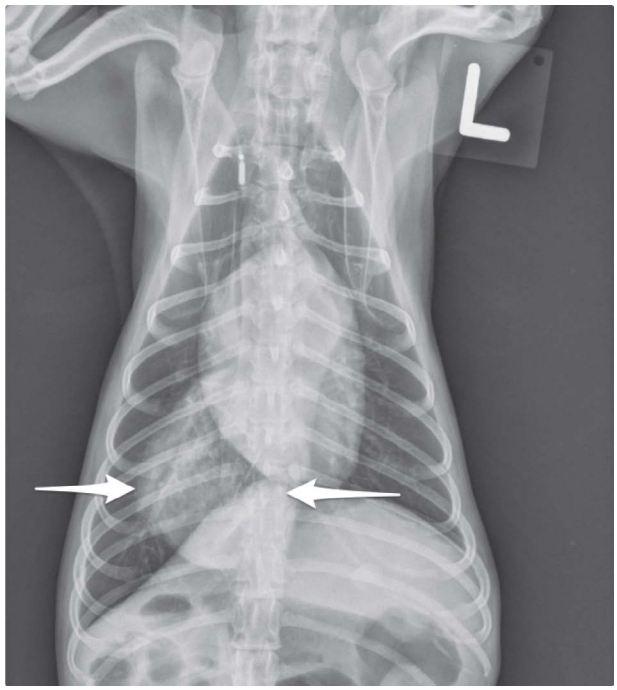


FIGURE 9.6 Four-year-old male Papillon Spaniel (same dog as Figure 9.5). The ventrodorsal thoracic radiograph shows the same soft tissue opacity in the esophagus caudal to the heart base (arrows).



FIGURE 9.7 Esophagoscopy showing a bone foreign body in the caudal thoracic esophagus (same dog as Figures 9.5 and 9.6).

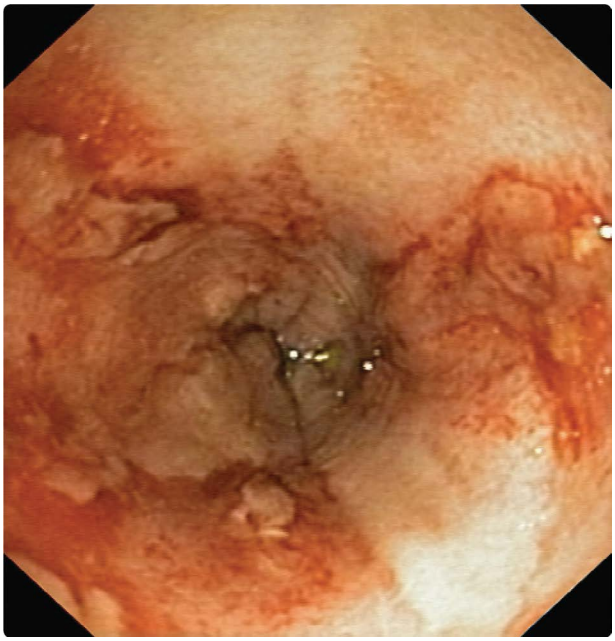


FIGURE 9.8 Endoscopic view of moderate esophageal mucosal lesions located cranial to the lower esophageal sphincter after removal of an esophageal foreign body in a dog. (*Courtesy of R. Husnik.*)

prevention of gastroesophageal reflux and further esophageal mucosal damage is recommended (see Esophagitis).

Access to bones or disproportionately large pieces of meat that are unlikely to reach the stomach should be restricted if the dog does not chew them. Approximately 5–6 mL of water should be administered with a syringe after pilling cats with any drug, particularly doxycycline and clindamycin tablets.

Prognosis

Generally, the prognosis for esophageal FB after nonsurgical removal is good to excellent. Esophagitis is present in up to 80% of dogs after FB removal (Figure 9.8) but seems to resolve relatively rapidly. Esophageal strictures are a feared complication that may develop over time, particularly in dogs with severe esophageal mucosal lesions.

BENIGN ESOPHAGEAL STRICTURE

Strictures occur less commonly than FBs in dogs and in cats.

Etiology/Pathophysiology

Benign strictures are a complication of severe esophagitis (FB, gastroesophageal reflux, dry swallow of pills to cats, ingestion of caustic substances). They occur with deep inflammation when lesions extend to the submucosa and muscularis layers of the esophageal wall. They are characterized by excessive scar tissue formation with narrowing of the esophageal lumen and resulting partial or total obstruction.

Clinical Presentation

The history often reveals esophageal disease (e.g., esophageal FB) or general anesthesia (with gastroesophageal reflux) prior to the development of signs. The animal shows frequent regurgitation, which can be associated with a particular food consistency. A dog with esophageal stricture may regurgitate dry food but not a puréed diet. Moreover, the clinical signs typical of esophagitis may also be present.

Differential Diagnosis

See Esophageal Foreign Body.

Diagnosis

Thoracic radiographs are useful to rule out other causes of esophageal obstruction (e.g., esophageal FB, external compression). Diagnosis is confirmed either by esophagoscopy (see Case 9.1) or contrast esophagram. Administration of contrast agents may lead to aspiration pneumonia and may damage endoscopic equipment if an esophagoscopy is performed soon after the contrast study. If esophageal perforation is suspected, and an esophagram is indispensable, low osmolar iodinated contrast agents are preferred over barium sulfate. It is essential to differentiate stricture of the esophageal lumen from external compression.

Management

Treatment involves dilating the stricture(s) under endoscopic or fluoroscopic control using balloons of different diameters (Figure 9.9) or "bougies" of different sizes. Multiple sessions at intervals of 1–2 weeks are often necessary. Submucosal injection of triamcinolone at the level



FIGURE 9.9 A balloon catheter filled with saline is in place to dilate an esophageal stricture.

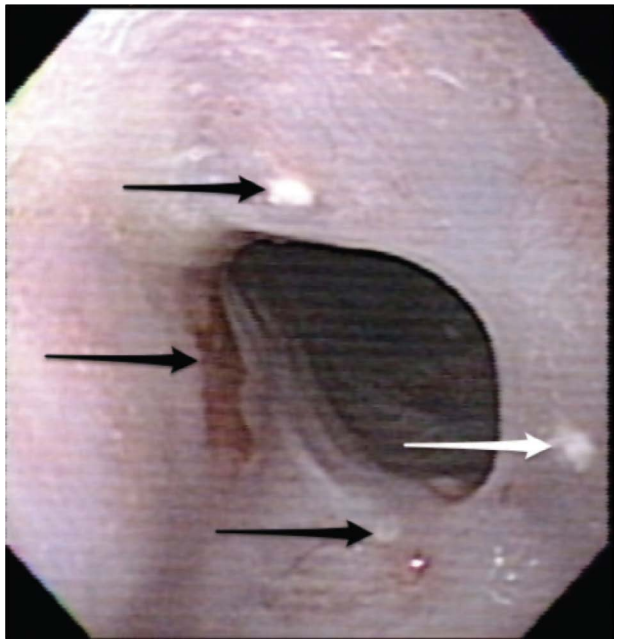


FIGURE 9.10 Triamcinolone acetate was injected submucosally in four sites at the base of the stricture in this dog (arrows).

of the stricture prior to or after dilation or bougienage can help reduce the number of procedures required (Figure 9.10). Drug therapy is similar to that for esophagitis. Systemic administration of prednisone/prednisolone is ineffective. Esophageal stenting is an option to consider in cases refractory to dilation attempts.

Prognosis

Without treatment, the prognosis is poor to grave due to the risk of aspiration pneumonia and esophageal perforation. After stricture dilation, the prognosis is guarded to good. Several dilation attempts may be required to re-establish patency of the lumen for a normal-size food bolus. In some instances, patency can only be partially restored, thus requiring liquid or moist food (and not dry kibbles) to be fed. Occasional regurgitation episodes may not be avoidable.

OTHER CAUSES OF OBSTRUCTION

VASCULAR RING ANOMALIES

Vascular ring anomalies cause entrapment of the esophagus at the level of the heart base. The most common vascular ring anomaly is persistent right aortic arch (PRAA), which is characterized by the presence of a fibrous band that connects the main pulmonary artery and the anomalous aorta and causes extraluminal compression and entrapment of the esophagus. Regurgitation typically occurs when puppies or kittens are weaned to solid food, and aspiration pneumonia is a common complication. Affected puppies are generally

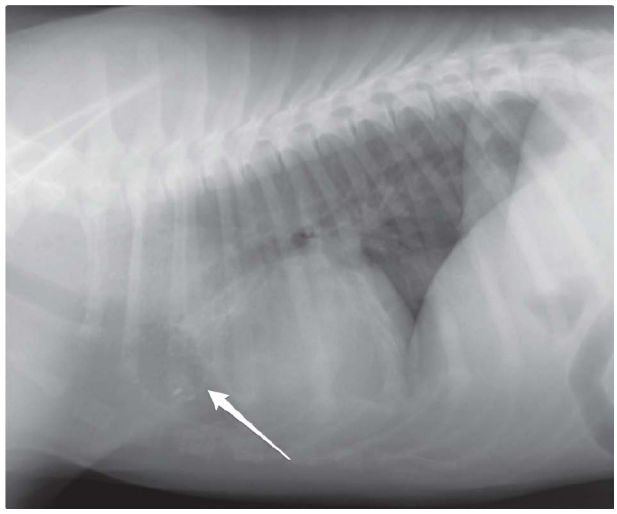


FIGURE 9.11 A 3-month-old German Shepherd Dog with a persistent right aortic arch. Lateral radiograph. The dilated esophagus is seen as a soft tissue opacity in the cranial mediastinum that displaces the trachea ventrally. Note the presence of granular material in the dilated esophagus cranial to the cardiac silhouette (arrow).

hungry and with time become malnourished and lose weight. Diagnosis relies on the typical history and clinical signs and is confirmed with thoracic radiographs that reveal esophageal dilation cranial to the heart base and deviation of the trachea to the left, cranial to the cardiac silhouette that is visible on ventrodorsal

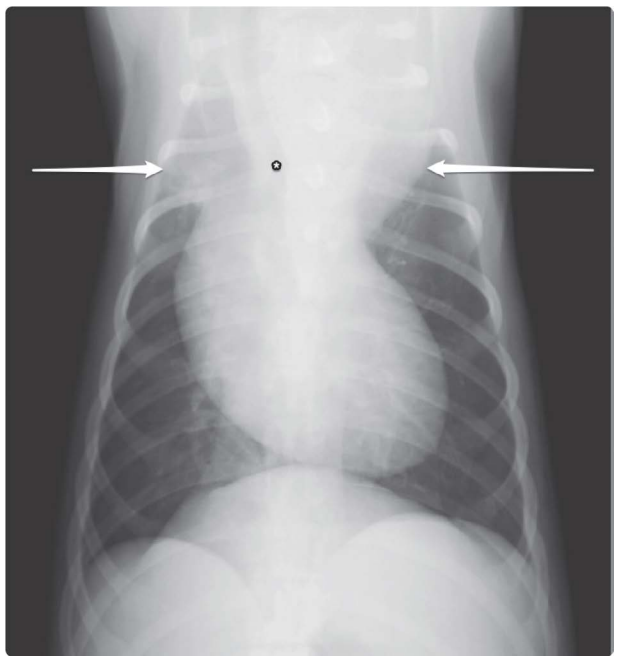


FIGURE 9.12 A 3-month-old German Shepherd Dog with a persistent right aortic arch (same dog as Figure 9.11). Ventrodorsal radiograph. The dilated esophagus is recognizable as a structure of soft tissue density in the cranial mediastinum (white arrows). Note the deviation of the trachea to the left cranial to the heart base (asterisk).

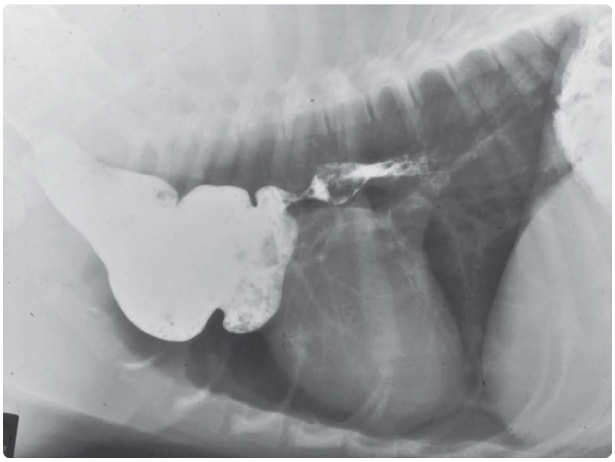


FIGURE 9.13 Contrast esophagram of a dog with a persistent right aortic arch. The dilated esophageal pouch located in the cranial mediastinum is clearly visible.

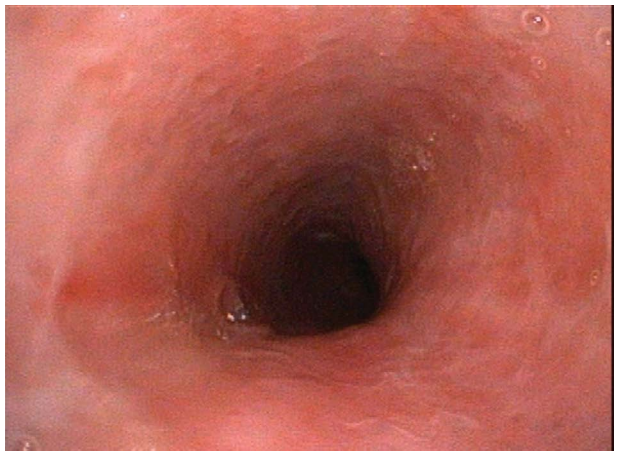


FIGURE 9.14 Esophagoscopy showing severely inflamed esophageal mucosa with multiple ulcerations at the level of the heart base in a dog with esophagitis following severe vomiting due to pancreatitis.

or dorsoventral views (Figures 9.11–9.13). Treatment of vascular ring anomalies consists of thoracotomy and transection of the compressive fibrous band. Prognosis of PRAA is generally good after surgery. In some cases, normal motility may not return if the cervical esophagus was severely dilated or if an esophageal diverticulum was formed. While most dogs are reported to do well, some may need continuous support such as upright feeding (see Megaesophagus, Management).

ESOPHAGEAL TUMORS

Esophageal tumors occur rarely. Leiomyoma is the most common benign neoplasm in dogs and often occurs in the caudal esophagus. Fibrosarcoma and osteosarcoma may develop in dogs infected with *Spirocerca lupi*. Other tumors include leiomyosarcoma, lymphoma, and metastatic lymphoma. The most common primary esophageal neoplasia of cats is squamous cell carcinoma (SCC). Clinical signs may be very discrete unless the tumor causes significant luminal obstruction. Diagnosis relies on radiographs, which may show esophageal dilation cranial to the mass. A contrast esophagram may be helpful. Esophagoscopy is required for final confirmation, with collection of biopsies for histopathologic analysis. Tumor excision with esophageal resection and anastomosis can be attempted, but the surgical procedure may be associated with postoperative morbidity. Esophageal stenting is a palliative option to consider.

ESOPHAGITIS

Definition/Overview

Esophagitis is a disease characterized by inflammation of the esophageal mucosa. It may occur in dogs and cats, and mild cases may go unnoticed.

Etiology/Pathophysiology

Noninfectious Inflammation

The esophageal mucosa may easily be damaged by gastric acid, pepsin, and bile in gastroesophageal reflux disease, as they induce the formation of proinflammatory cytokines in the esophageal mucosa (Figure 9.14). Esophagitis may be a complication of LES relaxation during general anesthesia. Esophagitis may also occur in animals with frequent and severe vomiting. In addition, esophageal FBs and swallowing of caustic substances may cause esophageal mucosal inflammation. In cats, administration of doxycycline, clindamycin, and other drugs in the form of oral tablets without subsequent water flush may cause severe esophagitis and possibly esophageal stricture.

Infectious Inflammation

In endemic areas (worldwide tropical and subtropical regions), *Spirocerca lupi* is a common cause of esophagitis. The ingested larvae migrate extensively and eventually mature into adults after a prepatent period of 3–9 months. The adult worms generally inhabit the esophageal submucosa and adventitia and cause the formation of granulomatous nodules of less than 1 cm to more than 4 cm diameter in the caudal esophageal wall. Esophageal infections with the oomycetal agent *Pythium insidiosum* occur infrequently in endemic areas (worldwide tropical and subtropical regions) and may cause severe esophagitis.

Clinical Presentation

Clinical signs are characteristic of esophageal diseases (Table 9.2). Mild cases of esophagitis may remain subclinical, or mild signs may go unnoticed by the owners.

Differential Diagnosis

Includes all the other esophageal diseases described in this chapter.

Diagnosis

A tentative clinical diagnosis is made on the basis of clinical signs and history. Confirmation of diagnosis and assessment of the extent and severity of lesions requires endoscopic examination. Collection of esophageal wall biopsies is often challenging, but histologic evaluation may yield additional information on the cause of the esophagitis. For the diagnosis of spirocercosis, diagnostic tests have the following sensitivities: Esophagoscopy 100%, presence of parasite ova on fecal flotation 80%, and radiographic detection of esophageal nodules 50%. Diagnosis of esophageal pythiosis relies on histopathology and immunochemical stains of esophageal biopsies. The typical esophageal wall thickening with involvement of local lymph nodes may be apparent on thoracic radiographs, ultrasound, and CT (Figure 9.15). An enzyme-linked immunosorbent assay (ELISA) test for serum antibodies is available.

Management

Symptomatic treatment of esophagitis is focused on protection of the mucosa against further damage and facilitation of mucosal healing. Fasting for 24–48 hours is recommended, if feasible without compromising the dog's condition. In severe cases, placement of a gastrostomy tube via endoscopy or surgery is beneficial to provide enteral nutrition and prevent complications associated with malnutrition. A diet low in fat is recommended because high-fat diets may be associated with increased episodes of gastroesophageal reflux.

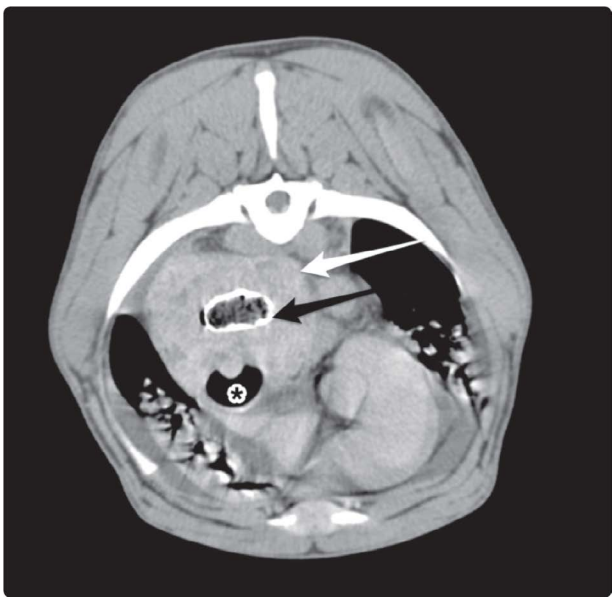


FIGURE 9.15 Mixed-breed dog with dysphagia and esophageal obstruction. Post-contrast CT scan of the cranial mediastinum. The esophageal wall is severely and irregularly thickened (white arrow, serosal surface; black arrow, mucosal surface covered with a fine layer of barium; asterisk, trachea). Infection with *Pythium insidiosum* was confirmed at necropsy. (*Courtesy of LSU SVM Diagnostic Imaging Service.*)

Sucralfate suspension is used to promote mucosal healing (1 g q.8h. for large dogs, 0.5 g q.8h. for smaller dogs). Inhibitors of gastric acid secretion, preferably a proton pump inhibitor such as omeprazole (1 mg/kg p.o. q.12h.), and a prokinetic agent that accelerates gastric emptying (metoclopramide, 0.5 mg/kg p.o., SC q.8h., or CRI of 1–2 mg/kg over 24 hours) or promotes gastric emptying and increases the distal esophageal sphincter tone (cisapride, 0.5–1 mg/kg p.o. q.8h.) should be administered, preferably 30–60 minutes before meals.

Treatment of spirocercosis consists in administration of specific parasiticides. Doramectin is an avermectin licensed for use in cattle but used off-label in dogs. Recommended protocols include 0.2–0.4 mg/kg SC every 14 days for 3–6 injections, or 0.5 mg/kg p.o. q.24h. for 6 weeks. These very high doses of avermectins must not be administered to Collies and other herding breeds that are prone to develop potentially lethal central nervous complications due to a mutation in the MDR-1 gene.

Treatment of esophageal pythiosis is challenging. Surgical excision of the lesion with safe tissue margins is the preferred treatment of gastrointestinal (GI) pythiosis but is not feasible in the esophagus. Medical treatment of unresectable pythiosis is often unrewarding (itraconazole, 10 mg/kg p.o. q.24h. and terbinafine, 5–10 mg/kg p.o. q.24h.). Anti-inflammatory doses of prednisone can be used in the hope of decreasing local inflammation and to palliate clinical signs.

Prognosis

Noninfectious Inflammation

Mild and moderate cases generally have a good prognosis. Severe inflammatory mucosal lesions may lead to esophageal stricture development.

Infectious Inflammation

Esophageal neoplasia (osteosarcoma, fibrosarcoma) is a common complication of *S. Lupi* infection and requires a surgical approach if the mass significantly obstructs the esophageal lumen. Esophageal pythiosis carries a poor to grave prognosis.

MEGAESOPHAGUS

Definition/Overview

Megaesophagus (ME) is characterized by generalized dilatation of the esophagus. It is the most common cause of regurgitation and a common esophageal disease in dogs but is a rare occurrence in cats.

Etiology

Congenital ME occurs in puppies and rarely in kittens, while acquired ME is seen mostly in middle-aged to older adult animals. The diseases frequently associated with ME in the dog are listed in Table 9.3. Among those, idiopathic ME and ME secondary to focal myasthenia

TABLE 9.3 Causes of megaesophagus in the dog

Congenital megaesophagus
- Congenital myasthenia gravis
- Congenital neuropathy

Acquired megaesophagus
- Idiopathic megaesophagus
- Myasthenia gravis
- Esophagitis
- Endocrine diseases (hypoadrenocorticism, possibly hypothyroidism)
- LES-achalasia-like syndrome
- Toxicosis (e.g., lead toxicity)
- Polymyositis, polyneuropathy
- Less common causes: Other neurologic diseases (botulism, tetanus, dysautonomia, rabies), systemic lupus erythematosus

gravis (MG) are most common. Acquired ME is also a feature of feline and canine dysautonomia.

Pathophysiology

With the exception of focal MG, the pathogenesis of canine and feline ME has not been fully elucidated. In dogs with MG, autoantibodies are formed against nicotinic acetylcholine receptors located at the neuromuscular junction in striated muscle. MG is discussed in further detail in Chapter 14. Congenital ME and other forms of acquired ME most likely result from malformation or changes in the complex neural network responsible for esophageal innervation. Recently, a syndrome resembling achalasia (or failure to relax) of the lower esophageal sphincter (LES) called LES-achalasia-like-syndrome has been described and may account for an important proportion of dogs previously diagnosed with idiopathic ME.

Miniature Schnauzers, Fox Terriers, German Shepherd Dogs, Great Danes, Irish Setters, Labrador Retrievers, Shar Peis, and Newfoundlands are at increased risk for development of primary idiopathic ME.

Clinical Presentation

The clinical signs are similar to those of other esophageal diseases (Table 9.2), and regurgitation is the most frequent complaint in dogs with ME. Secondary esophagitis is a common complication. The risk of aspiration pneumonia is high. Accordingly, affected animals may present with exercise intolerance, cough, tachypnea, and dyspnea.

Differential Diagnosis

Includes all the other esophageal diseases described in this chapter.

Diagnosis

The first step in the diagnostic approach is to rule out esophageal obstruction (FB, stricture) by taking a detailed history and obtaining good quality thoracic radiographs. A generalized dilatation of the esophagus is usually easily identified on the thoracic films

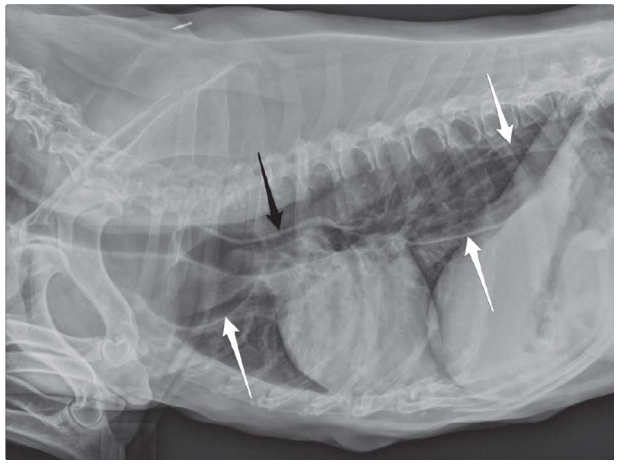


FIGURE 9.16 Nine-year-old female spayed Basset Hound with megaesophagus due to focal myasthenia gravis. Right lateral radiograph. The white arrows point to the dorsal and ventral walls of the esophagus, which are both clearly visible. The black arrow points to summation of the dorsal tracheal and ventral esophageal walls (tracheal stripe sign).

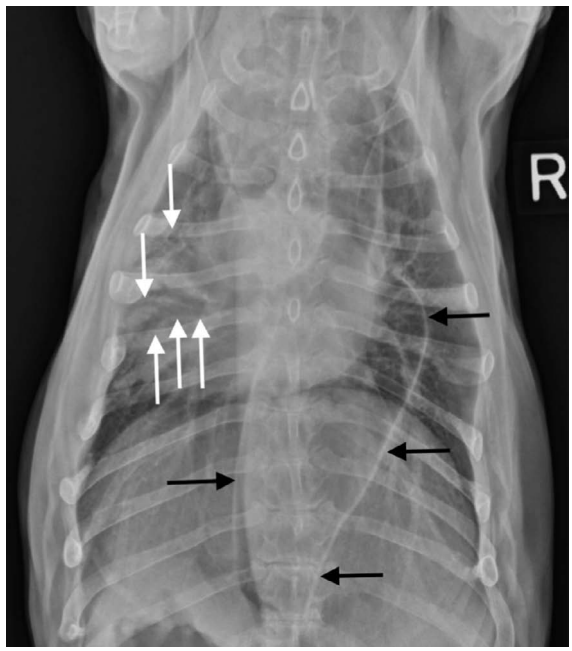


FIGURE 9.17 Nine-year-old female spayed Basset Hound with megaesophagus due to focal myasthenia gravis (same dog as Figure 9.16). Ventrolateral radiograph. The walls of the dilated esophagus are clearly visible in the caudal mediastinum (black arrows). Air bronchograms are visible in the caudal and cranial subsegments of the left cranial lung lobe (white arrows) together with increased opacity of the lung parenchyma.

(Figures 9.16 and 9.17). It is important to carefully check for aspiration pneumonia in these patients. This is best done by thoroughly examining the ventral parts of the lung lobes, in particular the right middle and left and right cranial lobes for presence of interstitial or alveolar infiltrate (Figure 9.17). VFSS is required to confirm the diagnosis of LES-achalasia-like syndrome.

The systematic approach is continued by screening animals for primary diseases associated with secondary ME. A minimal database consisting of complete blood count (CBC), biochemistry panel (including serum creatinine kinase [CK]), and urinalysis is recommended. Next, screening for endocrinopathies (basal serum cortisol concentration, possibly serum thyroxine and endogenous thyroid-stimulating hormone [TSH]), and a search for opacities in the cranial mediastinum (looking for possible thymoma associated with MG) are recommended. A sensitive and specific serum assay documenting the presence of autoantibodies against nicotinic acetylcholine receptors is available for the diagnosis of MG (http://vetneuromuscular.ucsd.edu). Endoscopic examination of the esophagus may be useful in unclear cases to allow visualization of the extent and severity of the esophagitis, if present. In cases with suspected polymyositis or polyneuropathy, electrodiagnostics (electromyogram [EMG], nerve conduction studies) and collection of muscle and nerve biopsies for histopathologic evaluation should be considered.

Management

Dietary management is essential. It is important to try various options such as dry food kibble, canned food formed into meatballs, and food blended with water in different consistencies (thick or thin slurry) because each animal may respond differently. Dogs and cats with ME should be fed a calorie-dense diet in a vertical position and be maintained in that position for 10–15 minutes after the meal to use gravity to facilitate aboral movement of the food bolus. Small dogs can be held on a person's lap for that time. Medium-size and large dogs can be fed on stairs and maintained with their forelimbs higher than their hind limbs. The Bailey chair is a useful device to keep medium-size and large dogs in a vertical position during and after meals (**Figure 9.18**). This aspect of treatment can be a challenge for older dogs with pre-existing orthopedic diseases such as coxofemoral arthritis.

In severe cases, placement of a gastrostomy tube may be beneficial to ensure appropriate nutrition and timely delivery of oral medications to the stomach and prevent aspiration pneumonia.

Identified underlying diseases need to be treated. For instance, the recommended treatment of MG includes administration of the acetylcholinesterase inhibitor pyridostigmine (1–3 mg/kg p.o. q.12h., start with a low dose to minimize risk of cholinergic crisis) and immunosuppressive doses of prednisone or prednisolone (e.g., 1 mg/kg p.o. q.12h.).

In dogs, there is no drug treatment that can successfully increase esophageal motility. In recent years, sildenafil, a phosphodiesterase-type 5 (PDE-5) inhibitor which relaxes smooth muscle, has been anecdotally used in dogs with ME under the assumption that LES relaxation would facilitate the passage of ingesta into the stomach. It was shown to decrease the frequency of regurgitation episodes, cause weight gain, and reduce esophageal diameter on radiographs in dogs with congenital ME (1 mg/kg p.o. q.12h.). In LES-achalasia-like



FIGURE 9.18 A 10-year-old female spayed Border Collie with idiopathic megaesophagus eating in a custom-made Bailey's chair. The dog is kept in an upright position in the chair for 20 minutes after each meal.

syndrome, recent research has documented the value of endoscopically guided LES balloon dilation and *C. botulinum* toxin A injection into the sphincter in providing time-limited improvement of clinical signs and identifying patients that would respond to surgical myotomy and fundoplication. In cats, cisapride may be useful as prokinetic agent for the distal esophagus. Because of the high prevalence of esophagitis in patients with ME, sucralfate suspension maybe beneficial to facilitate mucosal healing (0.5–1.0 g/dog q.8h., 0.25–0.5 g/cat q.8–12h.).

Treatment of aspiration pneumonia is mostly supportive. If secondary bacterial infection is suspected, antibiotic treatment is best based on culture and sensitivity from a bronchial wash; however, empiric treatment with a broad-spectrum antibiotic may be necessary in some cases (e.g., amoxicillin and clavulanic acid, ampicillin and sulbactam).

Home management of pets with ME is complex and time-consuming. Owners may feel overwhelmed and discouraged at first. Therefore, optimal communication between the veterinary care team and the animal's owners is essential for successful management of this condition (**Box 9.2**).

Prognosis

Studies from Scotland and Germany reported a short median survival time of 3 months after diagnosis

Box 9.2 Practical tip for support of owners of dogs with megaesophagus

The management of dogs with megaesophagus requires considerable dedication from the pet's owners and can be overwhelming at times. Clients should be made aware of the existence of support groups on the web or on social media. These owner-driven groups provide useful tips to optimize the quality of homecare and to make it possible for owners to include these new tasks in their busy daily routines.

regardless of the etiology in dogs with ME. In the Glasgow study, only 41% of dogs survived 1 year, 31% were alive at 2 years, and 22% survived for 5 years. Identified risk factors for shorter survival were dogs older than 13 months of age at the time of diagnosis and presence of aspiration pneumonia at diagnosis. However, ME may be reversible when associated with a treatable underlying disease.

HIATAL HERNIA

Definition/Overview

Hiatal hernia (HH) involves herniation of parts of the stomach through the esophageal hiatus into the mediastinum. Four types of hiatal hernias have been described in people, and most cases documented in dogs and cats are type I or sliding HH.

Etiology/Pathogenesis

Type I HH are usually due to a congenital weakness of the esophageal hiatus. They have been reported most frequently in brachycephalic breeds and also in cats. Acquired type I HH may occur following trauma or in combination with obstructive upper respiratory disease and abnormally high negative intrathoracic pressure during inspiration, such as may occur in dogs with brachycephalic syndrome and laryngeal paralysis.

Clinical Presentation

Common clinical signs are due to the secondary reflux esophagitis and include regurgitation, hypersalivation, vomiting, dysphagia, dyspnea, anorexia, and weight loss. Puppies and kittens with congenital HH are often presented at the time of weaning to solid food, but onset of clinical signs can also be delayed into adulthood. In some cases, acquired HH may remain subclinical. Aspiration pneumonia is possible and affected animals may show typical respiratory signs.

Differential Diagnosis

Esophageal diseases, in particular esophageal obstruction (FB, stricture), vascular ring anomaly in puppies, and acute or chronic gastritis.

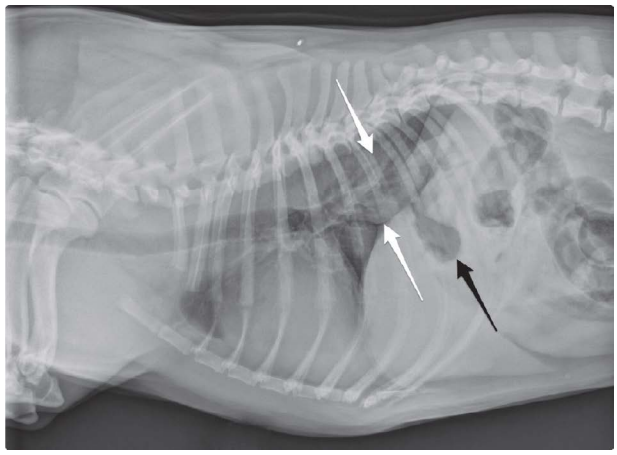


FIGURE 9.19 Right lateral thoracic radiograph of a 1-year-old male French Bulldog with hiatal hernia. The stomach is not in a normal anatomic position within the abdomen (black arrow) and is displaced cranially into the caudal thorax and confluent with the soft tissue opacity in the region of the esophagus (white arrows). (*Courtesy of LSU SVM Diagnostic Imaging Service.*)

Diagnosis

Diagnosis is confirmed with survey thoracic radiographs (Figure 9.19) and positive contrast esophagram (Figure 9.20) to confirm the type of HH. Sliding hernias may not be visible at the time of the examination, and fluoroscopy may be required for confirmation. The HH may also be viewed using ultrasound from an abdominal approach. Esophagoscopy allows visualization of the extent and severity of the esophagitis.

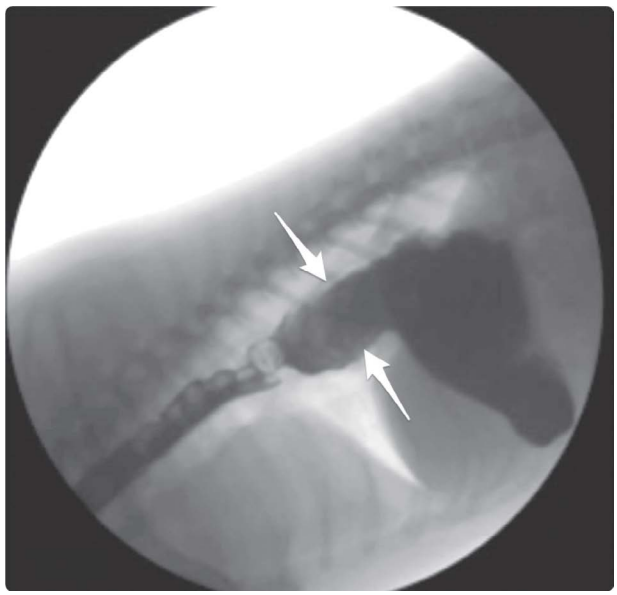


FIGURE 9.20 Right lateral view from a 6-year-old male neutered Welsh Corgi with dysphagia. The dog was given a kibble meal mixed with barium. A sliding hiatal hernia is visible. The arrows show the dorsal and ventral walls of the herniated stomach.

Management

Medical management is aimed at treating the secondary esophagitis and protecting esophageal mucosa from further damage (see Esophagitis, Management). A 30-day trial of medical therapy is often recommended prior to making plans for surgical correction as it may cause clinical signs to abate with restitution of adequate quality of life in a significant proportion of dogs. However, medical treatment was not successful in a series of Shar Peis presented before the age of 5 months, and surgery was recommended with no delay in such puppies. Surgical techniques include reduction of the abnormal diaphragmatic hiatus (phrenoplasty), esophagopexy, and left-sided gastropexy used alone or in combination. Surgical management of brachycephalic obstructive airway syndrome, if present, should be considered as well. Clinical signs may persist after surgical reduction until resolution of secondary esophagitis.

Prognosis

Prognosis for dogs and cats with HH is generally good. Animals that respond to medical management will probably require long-term treatment (continuous or intermittent). If medical treatment fails, surgical correction has a favorable outcome in most cases.

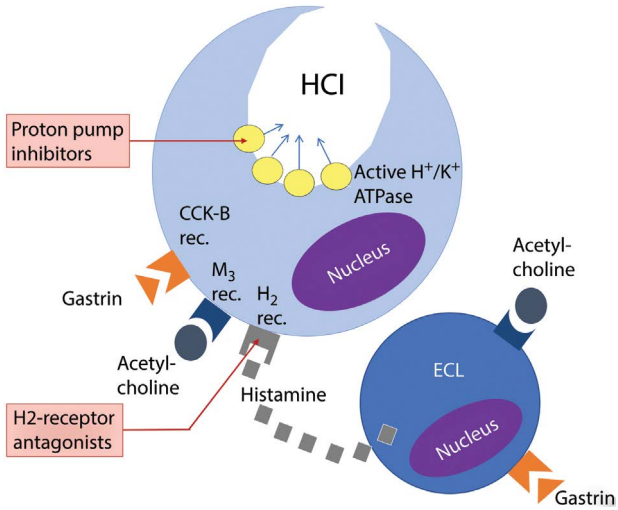


FIGURE 9.21 Schematic representation of a canine parietal cell and its neighboring enterochromaffin-like cell (ECL). Apical proton pumps actively secrete protons into the glandular lumen under stimulation by one of three basolateral receptors: CCK-B (gastrin), M_3 (acetylcholine), and histamine type 2. The ECL releases histamine in response to stimulation with acetylcholine or gastrin. The site of action of proton pump inhibitors and H_2 histamine receptor antagonists is illustrated. Rec, receptor.

PART 3: DISEASES OF THE STOMACH

Overview

Gastric diseases are common in dogs and cats. The stomach plays a key role in the digestive process through gastric acid and pepsinogen production. It functions both as a storage organ (fundus and body) and as a grinder (antrum), reducing the size of food particles until they are small enough to pass through the pyloric sphincter, and be further processed in the small intestine.

Gastric Anatomy

The stomach can be divided into five anatomic parts: Cardia, fundus, body, pyloric antrum, and pylorus. The mucosa of the fundus and body folds into countless gastric glands that are lined with cells responsible for secretion of acid (parietal cells), mucus (neck cells), pepsinogen (chief cells), and GI hormones (endocrine cells). The pyloric mucosa is thinner and contains a lower density of glands. Pyloric glands mostly consist of mucous cells and endocrine cells (many of them producing gastrin).

Normal Gastric Function

Acid and Enzyme Production

While unstimulated gastric acid production is minimal in dogs and cats, postprandial acid production is considerable, with gastric acidity reaching a pH as low as 1 or less. Acid is produced in the parietal cells in response to three types of stimuli: Activation of histamine type 2 receptors by histamine produced by neighboring enterochromaffin-like cells; muscarinic type 3 receptors activated by vagal nerve endings; or gastrin receptors (also called CCK type 2 receptors) activated by gastrin produced by antral G-cells (Figure 9.21). Enzyme secretion is limited to pepsinogen, released by chief cells, and broken down to the proteolytic enzyme pepsin, and gastric lipase.

Gastric Motility

After ingestion of solid food, the gastric antrum acts as a pump from which peristaltic waves originate while the gastric body acts as a high compliance reservoir. The mechanical action of the antral pump is divided into three phases: (1) Propulsion, (2) emptying of fine particles into the duodenum and mixing, and (3) retropulsion of particles > 1–2 mm for continued grinding. In dogs, complete emptying of the stomach is followed by synchronized housekeeping contractions (phase III migratory motor complexes).

GASTRITIS

ACUTE GASTRITIS

Definition/Overview

Acute gastritis is a clinical syndrome that occurs commonly in dogs and occasionally in cats. The diagnosis is rarely confirmed histopathologically, and affected

animals are usually treated symptomatically with good success.

Etiology

The most common cause of acute gastric inflammation is dietary indiscretion or food intolerance. Other common causes include gastric FBs (including hairballs), drugs (e.g., antibiotics, nonsteroidal anti-inflammatory drugs [NSAIDs]), toxins (plant material, bleach, cleaners, heavy metals), bacteria (*Helicobacter* spp.), toxins, and viruses. Additionally, acute gastritis may also be associated with diseases primarily affecting other organs (e.g., hypoadrenocorticism, acute kidney injury, acute hepatitis, cholangitis, cholecystitis).

Clinical Presentation

Sudden-onset vomiting, possibly associated with hyporexia/anorexia and lethargy. Hematemesis may occur as well. The history may reveal exposure to spoiled food, drugs, or toxins. Untreated animals become dehydrated and hypovolemic. Hypokalemia may occur as well due to potassium loss associated with vomiting and onset of metabolic alkalosis.

Differential Diagnosis

Other diseases causing sudden-onset vomiting such as GI FB, acute pancreatitis, endocrine diseases (e.g., hypoadrenocorticism, diabetic ketoacidosis), acute kidney injury (e.g., toxicosis with ethylene glycol or grapes/raisins, Easter lily, leptospirosis), acute hepatitis, cholangitis, or cholecystitis.

Diagnosis

History and clinical signs are usually suggestive. Abdominal radiographs should be obtained in order to rule out the presence of a GI FB. Underlying diseases should be ruled out, particularly in older animals or in atypical cases, with the help of a minimal database (CBC, serum biochemistry, urinalysis).

Management

Treatment is mostly symptomatic and consists of antiemetics, parenteral fluids to correct fluid and electrolyte deficits, and analgesia with opiates in case of abdominal pain. Animals usually benefit from a short fast (12 hours) until vomiting has subsided, followed by frequent feedings of small quantities of an easily digestible bland food (e.g., boiled chicken and rice or commercial prescription food) for 2–3 days. Once the animal feels better, the usual diet can be reintroduced progressively over 2–3 days.

Prognosis

Most dogs and cats with acute gastritis respond very well to symptomatic treatment. In cases with severe underlying conditions, the prognosis of the primary disease is determinant.

CHRONIC GASTRITIS

Definition/Overview

Chronic gastritis is a common disease in dogs with clinical signs such as chronic vomiting. Histopathologic lesions of gastric inflammation can also be present in significant numbers of asymptomatic dogs. The prevalence of chronic gastritis in cats has not been established.

Etiology

Possible causes of chronic gastritis include infectious agents or parasites, drugs (see Gastric Ulcers and Erosions), or chronic FBs (see Gastric Outlet Obstruction). In many cases, a specific cause cannot be identified, and the term idiopathic gastritis is used. Food intolerance or allergy, occult parasitism, or other mechanisms are thought to play a role in the pathogenesis of idiopathic gastritis.

Ollulanus tricuspis is the small gastric worm that infests the feline stomach. It is 0.7–1 cm in length and is transmitted directly from cat to cat through ingestion of vomitus. Depending on the severity of the infestation, cats may remain subclinical or show severe signs of chronic gastritis. *Physaloptera* spp. are larger (2–6 cm long) and may be found in dogs and cats (Figure 9.22), although their final host appears to be the coyote. *Pythium insidiosum* is an oomycetal microorganism that may infect the canine GI tract in subtropical climates (such as the southeast and Gulf of Mexico regions of the United States) and sporadically in other areas. Young, large breed dogs with access to the outdoors are most commonly affected and typically vomit regularly without losing their appetite. Gastric pythiosis is characterized by severe transmural antral thickening

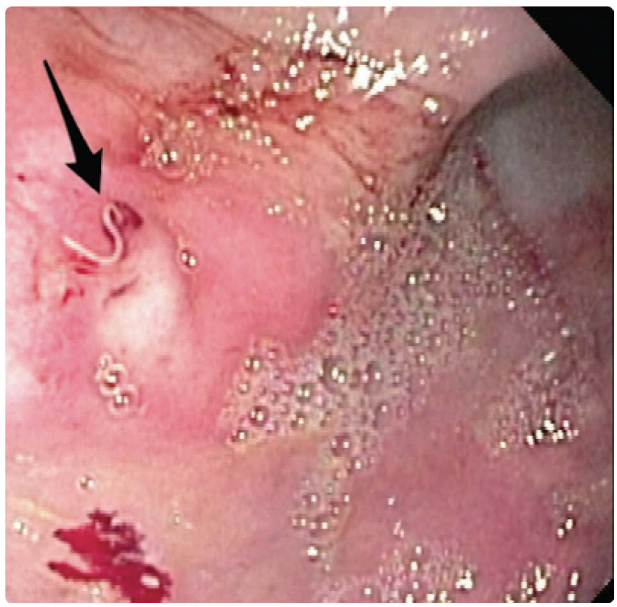


FIGURE 9.22 Endoscopic view of a *Physaloptera* worm (arrow) found in the gastric mucosa of a young adult male dog with chronic vomiting. (*Courtesy of K. Harkin.*)

and possible gastric outflow obstruction and may be difficult to differentiate from gastric antral neoplasia. *Helicobacter* infection is discussed in further detail on page 305.

Clinical Presentation

Chronic or chronic-intermittent vomiting of food and/or bile is the main clinical sign associated with chronic gastritis. Depending on the severity of the disease, varying combinations of hyporexia, weight loss, melena, or hematemesis may be observed.

Differential Diagnosis

All diseases that may cause chronic vomiting need to be considered. These include chronic enteropathies (vomiting, hyporexia, and/or weight loss may be the only signs of inflammatory bowel disease [IBD] in cats), chronic pancreatitis, chronic diseases of the liver and biliary tree, chronic kidney disease, and endocrinopathies (dog: hypoadrenocorticism, cat: hyperthyroidism).

Diagnosis

A minimum database consisting of CBC, biochemistry panel, and urinalysis is useful to assess the presence of underlying conditions with secondary gastritis and the systemic impact of gastritis. For instance, eosinophilia may be suggestive of parasites, allergic reactions, hypoadrenocorticism, or mast cell tumor. Hypoalbuminemia may occur with severe GI bleeding or with concurrent small intestinal involvement. Abdominal radiographs may reveal delayed gastric emptying (i.e., presence of food in the stomach after a 12-hour fast). Abdominal ultrasound is useful to assess antral wall thickness and overall gastric motility. Fecal flotation is not very helpful for diagnosis of *Ollulanus* or *Physaloptera*. In dogs with history, physical examination, and abdominal imaging findings suggestive of gastric pythiosis, serum ELISA documenting the presence of specific antibodies may be helpful. In cases refractory to symptomatic treatment, gastroscopy allows visualization of the gastric lesions (**Figure 9.23**) and collection of gastric mucosal biopsies, which are evaluated histopathologically. The duodenum should also be evaluated and biopsied, since gastric diseases may extend to the small intestine as well. Lymphoplasmacytic infiltrates are the most common, but infiltrates may also consist of eosinophils or other inflammatory cells. Eosinophilic gastritis may reflect the presence of parasites or allergic processes. In cats, it may be part of the feline hypereosinophilic syndrome.

Management

Symptomatic treatment is initiated with antiemetics (see Chapter 2.17), and protection of the gastric mucosa (**Table 9.4**). In addition, identified underlying diseases also need to be addressed. In dogs and cats with unexplained gastritis, empirical treatment with broad-spectrum anthelminthics such as fenbendazole (50 mg/kg q.24h. for 5 days

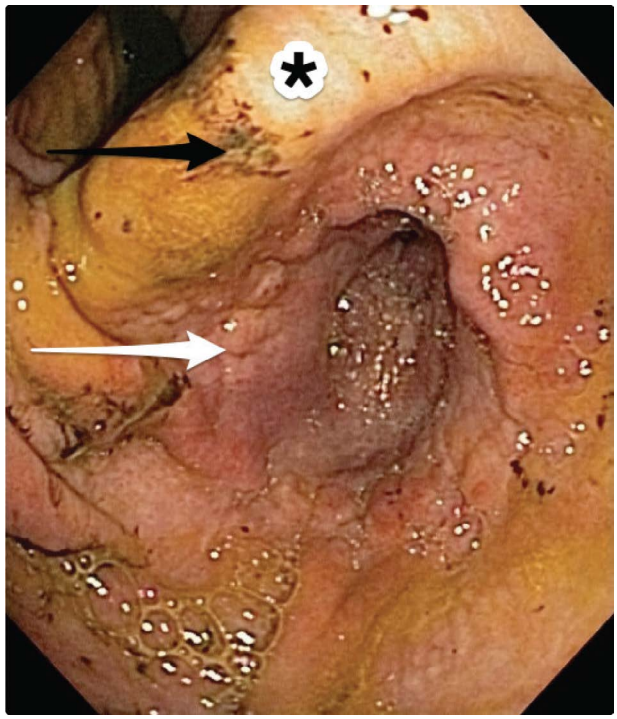


FIGURE 9.23 Gastroscopic view of a dog with chronic vomiting and hyporexia after endoscopic extraction of a plastic foreign body. The pyloric antrum can be seen below the incisura angularis (asterisk). The antral mucosa looks thickened (white arrow), and there are multiple mucosal erosions (black arrow). (*Courtesy of R. Husnik.*)

[*Ollulanus* and *Physaloptera* spp.]) or pyrantel pamoate (5–10 mg/kg [*Physaloptera* spp.]) may be warranted.

Regardless of the cause of the chronic gastritis, a sensible dietary approach is necessary. Obtaining a good dietary history is helpful. For idiopathic chronic gastritis, the recommended diets are based on novel proteins or hydrolyzed peptides. They should be easily digestible and fed in several small meals throughout

TABLE 9.4 Recommended dosages for inhibitors of gastric acid production, prostaglandin analogs, and sucralfate

Drug	Dog	Cat
Omeprazole	1.0 mg/kg p.o. q.12h.	Same
Pantoprazole	1.0 mg/kg IV q.12h.	Same
Famotidine*	1 mg/kg p.o., IV q.12h., if renal azotemia is present q.24h.	Same
Ranitidine*	1–2 mg/kg p.o., SC, IV q.12h., use low end of range if renal azotemia present	Same
Misoprostol	2–5 µg/kg p.o. q.8–12h.	Unknown
Sucralfate	0.5–1 g/dog p.o. q.8–12h.	0.25–0.5 g/cat p.o. q.8–12h.

* H2-receptor antagonists have been shown to be inferior to proton pump inhibitors in their ability to suppress gastric acid production in dogs and cats.

the day to optimize gastric emptying. Dietary management may be sufficient in mild cases with few or no systemic signs, and improvement generally occurs within 2 weeks of receiving the new diet. If this is not the case, a different diet may be tried for another 2 weeks, or immunosuppressive therapy may be initiated. In moderate and severe cases, immunosuppressive doses of glucocorticoids are often required (e.g., prednisone, 1–2 mg/kg q.24h. for 2 weeks, then slowly taper in 2-week steps to every other day or lowest effective dose over 8–12 weeks). Additional immunosuppressives may be required in refractory cases.

GI pythiosis is best managed with surgical resection of the lesion with sufficient margins. This is often difficult to achieve in the stomach. Medical treatment of unresectable pythiosis is often unrewarding (itraconazole, 10 mg/kg p.o. q.24h.; terbinafine, 5–10 mg/kg p.o. q.24h.). Anti-inflammatory doses of prednisone can also be used in the hope of decreasing local inflammation and to palliate clinical signs.

Prognosis

All identifiable causes and underlying diseases should be addressed and properly managed. Idiopathic chronic gastritis generally has a fair to good prognosis.

HELICOBACTER spp. INFECTION

Definition/Overview

Helicobacter spp. are spiral-shaped Gram-negative bacteria that can live in an acidic environment. While their association with peptic ulcer and gastric neoplasia in people has been clearly documented, their pathogenic potential in dogs and cats is less well defined. *H. pylori*, the most prevalent *Helicobacter* infecting people, does not represent a significant problem in small animals. *H. heilmannii* is the predominant species isolated from cats, while *H. bizzozeronii* and *H. salomonis* are the most common species in dogs. The bacteria colonize mucus in the gastric glands and cause local inflammation.

Clinical Presentation

The main clinical sign is chronic, intermittent vomiting.

Diagnosis

Diagnosis is based on ruling out other causes of chronic gastritis and confirming with gastroscopy, which may show gross lesions (Figure 9.24). Gastric mucosal biopsies are collected and evaluated cytologically (Figure 9.25), and histopathologically. *Helicobacter* is often observed on cytologic or histopathological slides. The current consensus is that diagnosis of clinically relevant infection requires the presence of the organisms together with histopathologic evidence of follicular lymphocytic gastritis.



FIGURE 9.24 Gastroscopic view showing the pyloric antrum of a 12-year-old male neutered Domestic Shorthair cat with a 15-month history of intermittent vomiting, hyporexia, and weight loss. There are multiple erosions associated with mucosal bleeding (brown spots). Histopathology revealed follicular lymphocytic inflammation and numerous spiral-shaped bacteria on the mucosa. The cat responded to treatment with amoxicillin, clarithromycin, and metronidazole.

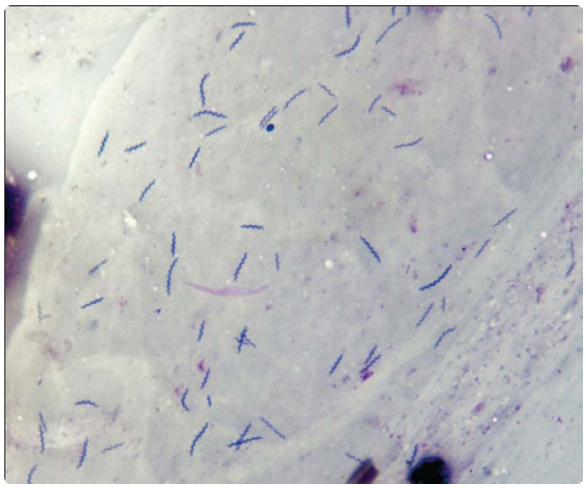


FIGURE 9.25 Cytology picture of a gastroscopic mucosal brushing showing multiple spiral-shaped bacteria in a dog. (*Courtesy of R. Husnik.*)

Management

While the pathogenic potential of *Helicobacter* spp. in dogs and cats is still subject to discussion, animals presented with clinical signs of chronic gastritis, histologic evidence of gastric inflammation, and concurrent presence of spiral-shaped bacteria in the gastric mucosa and gastritis should be treated. Eradication requires treatment with different drugs, usually consisting of one or more antimicrobial(s), an acid-reducing drug,

TABLE 9.5 Examples of oral treatment protocols used in clinical studies for eradication of *Helicobacter* spp. in dogs and cats

Antimicrobial	Antacid	Other	Comments
Metronidazole (10–15 mg/kg q.12h.) Amoxicillin (20 mg/kg q.12h.)	Famotidine (0.5 mg/kg q.12h.)		D: 2-week duration
Metronidazole (10–15 mg/kg q.12h.) Amoxicillin (20 mg/kg q.12h.)		Bismuth subsalicylate (0.22 ml/kg q.6–8h.)	D, C: 3-week duration
Amoxicillin (20 mg/kg q.12h.) Clarithromycin (7.5 mg/kg q.12h.) Metronidazole (10 mg/kg q.12h.)			C: 2-week duration

C, successful use reported in cats; D, successful use reported in dogs.

and bismuth in some protocols for a duration of 14–21 days. Examples of eradication protocols are listed in Table 9.5.

Prognosis

Prognosis is good; however, many animals may reinfect themselves in their home environment.

GASTRIC ULCERATIONS AND EROSIONS

Definition/Overview

Ulcers are mucosal lesions that extend to the muscularis mucosae and the deeper layers (submucosa, muscularis), and erosions are more superficial and limited to the lamina propria. While there are no reported numbers for the prevalence of GI ulcers in small animals, they appear to be uncommon in dogs and rare in cats.

Etiology

The main reported causes of gastric ulcer in dogs and cats are listed in Table 9.6. Long-term treatment with NSAIDs is probably the most common cause of canine GI ulcers. Administration of NSAIDs using a higher dose than that recommended by the manufacturer, or in combination with other NSAIDs or corticosteroids, significantly increases the risk of GI lesions. Dogs treated for intervertebral disc disease are also at high risk of developing ulcerative lesions in the GI mucosa. Additionally, GI ulceration may represent a complication of a variety of diseases originating in or outside the GI tract. Gastric tumors frequently ulcerate due to inadequate vascularization to maintain the integrity of the gastric mucosa. Finally, secretion of gastrin by gastrinomas and histamine by mast cell tumors may lead to excessive gastric acid production and disruption of the gastric mucosal barrier, with resulting erosions and ulcerations.

TABLE 9.6 Causes of gastrointestinal ulceration in dogs and cats

Dogs	Cats
Drugs NSAIDs 1. Accidental ingestion (acute toxicosis) 2. Chronic administration (to treat orthopedic conditions) Steroids 1. With intervertebral disc disease 2. Other	**Drugs** NSAIDs, steroids
Neoplasia Gastric carcinoma, and other gastric tumors Mast cell tumor Gastrinoma	**Neoplasia** Alimentary lymphoma, and others Systemic mastocytosis Gastrinoma
Poor perfusion of gastric mucosa Hypoadrenocorticism, shock, inadequate fluid therapy during anesthesia	**Poor perfusion of gastric mucosa** Shock, inadequate perfusion during anesthesia
Other *Helicobacter* spp. infection, inflammatory bowel disease, pancreatitis, liver disease, uremic syndrome, prolonged intensive physical activity (sled dogs), pyloric outflow obstruction, gastric dilatation–volvulus, gastric FB	**Other** Inflammatory bowel disease, hypereosinophilic syndrome, *Dieffenbachia* toxicosis, stress, gastric FB

Pathophysiology

The gastric mucosal barrier protects the gastric mucosa from the acidic environment of the gastric lumen. The hydrophobic mucous layer produced by the mucous neck cells provides a physical barrier separating the gastric epithelium from the gastric lumen and its content. It is rich in bicarbonate, which acts as a buffer against acid. Other factors involved in maintaining the mucosal barrier include the high mucosal blood flow providing nutrients, bicarbonate, and oxygen to the mucosa and eliminating acid residues, the local production of prostaglandin E2, and the rapid turnover of epithelial cells. Gastric ulcers and erosions occur in the presence of drugs or disease processes that weaken or disrupt the gastric mucosal barrier.

Clinical Presentation

In dogs, the typical presentation revolves around vomiting with or without hematemesis (Figure 9.26). Cranial abdominal pain may be present. Signs resulting from

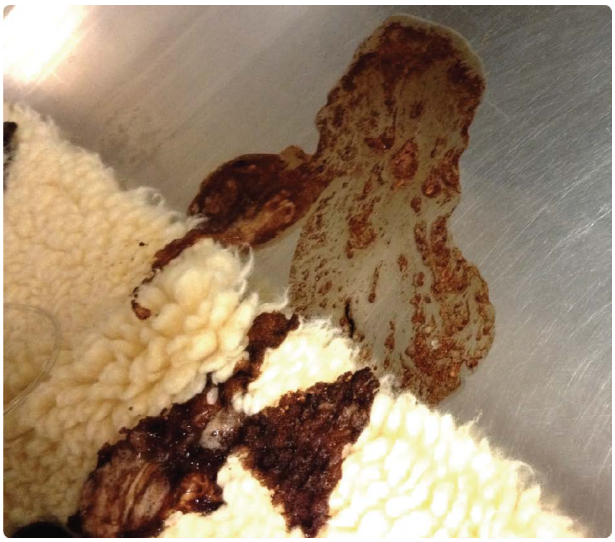


FIGURE 9.26 Bloody vomit with typical coffee-grounds appearance from a dog with a gastric ulcer due to acute NSAID toxicosis. (*Courtesy of R. Husnik.*)

fluid and possibly blood loss (dehydration, shock, anemia) may become apparent. While melena may be observed during the rectal examination (**Figure 9.27**), it is only obvious in case of significant blood loss (> 2.5–3.5 mL/kg body weight). In case of perforating ulcer, septic peritonitis usually develops with systemic inflammatory response syndrome (SIRS, sepsis).

Cats with GI ulceration may also be presented with vomiting, hematemesis, abdominal pain, and melena. However, some cats may only show vomiting with nonspecific signs such as anorexia and lethargy. GI ulcers associated with neoplasia (e.g., gastric tumor, mastocytosis) tend to have a more protracted course with weight loss and other clinical signs caused by the underlying disease.

Differential Diagnosis

Vomiting (see Chapter 2.17, **Table 2.17.2**). Severe gastric inflammation, duodenal ulcers, and acute pancreatitis may also cause hematemesis. Furthermore, mucosal bleeding associated with coagulopathies or platelet diseases may also lead to hematemesis and melena. Abdominal pain may be associated with acute pancreatitis, GI FBs, and gastroenteritis.



FIGURE 9.27 Melenic feces recovered from the rectum of a dog with gastric adenocarcinoma.

Diagnosis

In animals with suggestive evidence of GI ulceration, the diagnostic approach should focus on two objectives: (1) Confirm the presence of an ulcerative GI lesion and (2) search for an underlying disease predisposing the animal to develop GI ulcers.

A minimal database consisting of CBC, serum biochemistry, urinalysis, and abdominal imaging should be obtained. The CBC may show evidence of blood loss anemia (microcytic hypochromic anemia), which may be regenerative or nonregenerative depending on the duration of blood loss and/or changes associated with the underlying disease. Serum biochemistry may reveal an increased blood urea nitrogen (BUN) in an otherwise fasted patient (suggestive of GI bleeding) and/or abnormal results due to fluid and electrolyte loss or to an underlying disease. Abdominal radiographs are important to rule out a GI obstruction. Additionally, they may identify signs of perforation and peritonitis (e.g., peritoneal effusion with decreased serosal detail, pneumoperitoneum). Abdominal ultrasound allows a more detailed assessment of the gastric pylorus, antrum, and body and is useful to confirm the presence of free fluid or gas in the peritoneum. Moreover, a full abdominal scan allows evaluation of the other abdominal organs in the search for underlying disease. Masses detected during the physical examination (e.g., skin masses [mast cell tumors]) or during the ultrasound examination should be aspirated and evaluated cytologically.

The diagnostic examination of choice to confirm GI ulceration is endoscopy. Ulcers may be disseminated throughout the gastric mucosa (long-term use of NSAIDs in dogs) or present on the lesser curvature at the entrance of the pyloric antrum (acute NSAID toxicosis, gastric tumors) (**Figures 9.28** and **9.29**). Mucosal biopsies should be collected around the ulcer margins and in other areas and evaluated histologically. In cases of gastric neoplasia, an effort should be made to collect deep biopsies of the tissue surrounding the ulcer(s).

Management/Prevention

Supportive treatment is essential and includes correction of fluid and electrolyte deficits and administration of antiemetics as needed. If the animal is in pain, appropriate analgesia should be provided using opioid drugs. A surgical approach is required after initial stabilization of the patient in cases of perforated ulcers and associated peritonitis.

Protection of the gastric mucosa with inhibitors of acid secretion is essential. Proton pump inhibitors (PPI; e.g., omeprazole) are considered more effective than histamine type-2 receptor antagonists (H2-RA;



FIGURE 9.28 Gastroscopic view from a young Dalmatian that accidentally ingested a high dose of naproxen. A sharply delineated peptic ulcer is visible on the lesser curvature.

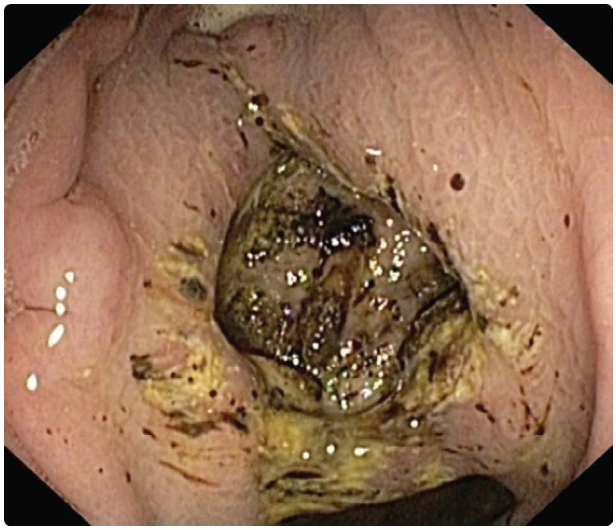


FIGURE 9.29 Gastroscopic view from an older mixed-breed dog showing an ulcerated gastric adenocarcinoma with a deep ulcerated center and raised edges. (*Courtesy of R. Husnik.*)

e.g., famotidine, ranitidine) for providing continuous acid suppression during their duration of action. Among H2-RA, famotidine is more reliably efficacious than ranitidine and cimetidine. Inhibitors of acid secretion should be administered over a prolonged period of time to dogs and cats with GI ulcers (4–6 weeks). Additionally, sucralfate is the drug of choice to coat ulcers and promote a quicker re-epithelization and healing. It is usually administered simultaneously with an H2-RA or PPI, although there is still some debate about the value of staggering oral administration of sucralfate and acid suppressants. Misoprostol is an oral prostaglandin E analog that has been used with success in dogs with NSAID toxicosis (see dosage in Table 9.4). Additionally, treatment of identified underlying conditions should be initiated as early as possible.

Dietary support for gastric ulcers should consist of an easily digestible diet that is low in fiber and fat and promotes rapid gastric emptying. Alternatively, in some patients, the preferred diet may need to be selected on the basis of identified underlying diseases (e.g., hydrolyzed diet in IBD, "renal diet" in chronic kidney disease).

Prevention of GI ulcers is recommended in patients at risk. First, simultaneous administration of steroid and NSAIDs or treatments involving combinations of NSAIDs should be avoided at all costs. In animals with severe joint pain that are unresponsive to single-agent therapy, opioids and/or gabapentin should be considered as part of the analgesic protocol. Dogs and cats with a significant burden of mast cell tumors are likely to benefit most from H2-RA therapy. In high-risk patients such as dogs with intervertebral disc disease treated with corticosteroids or NSAIDs, PPIs or H2-RA are often administered in the hope of limiting the extent of gastric mucosal lesions. Similarly, dogs receiving long-term NSAIDs chronic osteoarthritis or other orthopedic problems may benefit from preventive gastroprotective treatment, particularly once they have experienced signs of erosive/ulcerative gastritis. Misoprostol may be of benefit as well. Other risk situations include dogs receiving high immunosuppressive doses of corticosteroids to treat various immune-mediated diseases, although there is no documented benefit of preventive use of inhibitors of gastric acid production in these patients.

Prognosis

In the absence of perforation, canine GI ulcers are usually associated with a good outcome if their cause can be identified and eliminated (e.g., acute NSAID toxicosis). However, in many instances, the underlying disease may significantly compromise the prognosis (e.g., gastric neoplasia, chronic liver failure, chronic kidney disease). Cats with GI ulcers secondary to gastric lymphoma, gastrinoma, and mastocytosis appear to have a good prognosis.

Dogs with perforated gastric or duodenal ulcers that undergo surgery usually have a reasonable survival if the underlying problem can be successfully addressed. However, only 50% of dogs with nonmalignant perforated ulcers survived in a study from the UK. In cats, surgically treated perforated GI ulcers appear to have a good prognosis.

GASTRIC DILATATION AND VOLVULUS

Definition/Overview

Gastric dilatation–volvulus (GDV) is a syndrome that occurs in large to giant breed dogs and is characterized

by rotation of the stomach on its mesenteric axis followed by gaseous gastric distension.

Etiology

The precise etiology of GDV is unknown. Identified risk factors include a narrow and deep thoracic conformation, stress, and nutritional factors that ultimately lead to rapid filling of the stomach with large quantities of food or water. For instance, once-daily feeding, rapid ingestion of a meal, exercising after a meal, and eating from a raised platform all have the potential to trigger GDV.

Pathophysiology

The pylorus moves ventrally from the right to the left with a resulting rotation of 90–360 degrees and positions itself near the gastric cardia on the left side. Gas accumulates in the stomach, since neither eructation nor aboral emptying is possible. The distended stomach compresses the caudal vena cava and the portal vein, resulting in decreased venous return to the heart, decreased cardiac output, and ultimately cardiovascular collapse.

Clinical Presentation

Abdominal distension with tympany, abdominal pain, retching or vomiting (often nonproductive), hypersalivation, and acute collapse are common presenting signs. Hypovolemic and/or distributive shock may be noticeable on presentation (tachycardia, weak pulses, pale mucous membranes with abnormal capillary refill time).

Differential Diagnosis

Gastric dilatation secondary to food engorgement, mesenteric volvulus, splenic torsion, diaphragmatic tear with gastric herniation.

Diagnosis

Typical history and physical examination are suggestive; however, they do not allow differentiation between gastric dilatation and GDV. Gastric volvulus is confirmed with right lateral abdominal radiographs (Figure 9.30). However, aggressive shock treatment and attempts to deflate the stomach are often necessary before obtaining survey abdominal films.

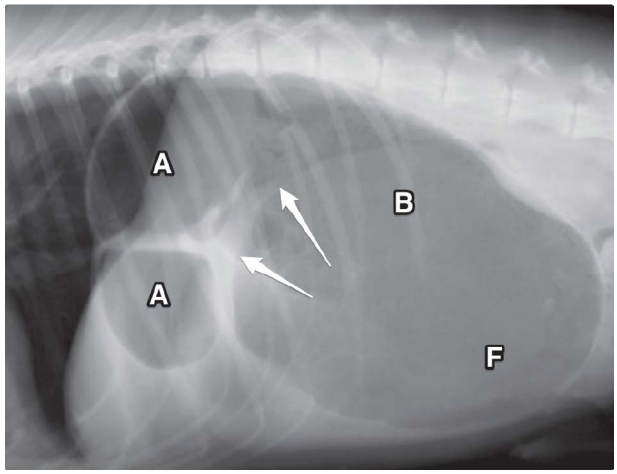


FIGURE 9.30 Right lateral abdominal radiograph of a dog with gastric dilatation–volvulus. The antrum (A) is visible in the dorsocranial aspect of the abdomen while the fundus (F) and body (B) are located more caudal. Compartmentalization of the stomach is visible (arrows). (*Courtesy of L. Gaschen.*)

Box 9.3 Procedure for passage of an orogastric tube in a dog with gastric dilatation–volvulus

- **Material:** Use largest-diameter, smooth-surfaced, flexible orogastric tube possible (e.g., greater than 9.5 mm outside diameter in large dogs). Water-soluble lubricating jelly. Canine mouth speculum (e.g., roll of 2-inch adhesive tape).
- **Sedation:** With exception of recumbent or severely affected dogs, mild sedation is usually required. One option is IV administration of butorphanol (0.2–0.4 mg/kg) with diazepam (0.2–0.5 mg/kg).
- **Preparation:** Mark the distance from the canine tooth to the last rib on the tube using piece of tape.
- **Introduction:** Cover the end of the tube with lubricating jelly and gently introduce the tube through the speculum, pharynx, and esophagus. When the level of the tape marking is reached, the tube should be at the lower esophageal sphincter. Gently rotating the tube may be required to pass the sphincter. Passage through the lower esophageal sphincter should not require force.
- **Limit:** The procedure should be aborted if the stomach cannot be intubated after a few attempts. Consider percutaneous gastric trocharization (see text).

Management

Aggressive treatment of cardiovascular collapse using two large bore catheters placed in each cephalic vein is lifesaving and needs to be initiated immediately after presentation. (See Chapter 23 for proper choice of fluids and required doses.) If surgery needs to be delayed (e.g., because of fluid resuscitation), orogastric intubation is attempted in order to decompress the stomach and lavage its content (Box 9.3). If attempts at orogastric intubation are unsuccessful, percutaneous trocharization may be performed using a 3-inch 12- to 14-gauge IV catheter that is introduced into the stomach caudally to the last rib in the left flank after the region is clipped and aseptically prepared. This usually causes some peritoneal contamination with gastric content. Ultimately, explorative celiotomy with repositioning of the stomach is followed by evaluation of gastric wall vitality (Figure 9.31). Partial gastrectomy may be required if segments of the stomach are devitalized; partial or total splenectomy

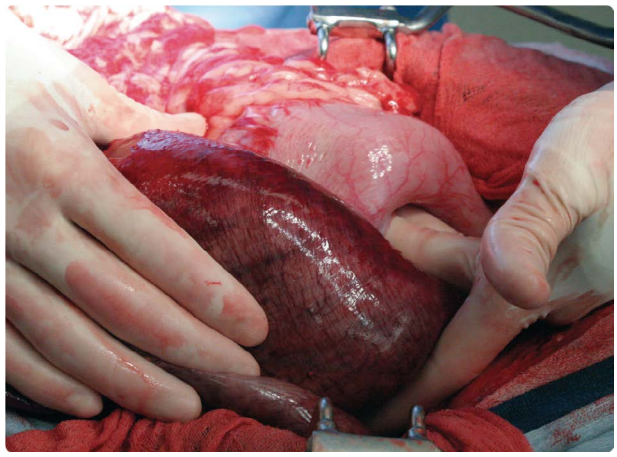


FIGURE 9.31 Exploratory celiotomy of a dog with gastric dilatation–volvulus after repositioning of the stomach. A devitalized portion of the stomach (antrum) is shown in the foreground and compared with the normally perfused body. (*Courtesy of D. Ogden.*)

may be necessary in the presence of splenic necrosis, infarction, or torsion. Gastropexy (pyloric antrum to right abdominal wall) is recommended to lower the likelihood of recurrence. Cardiac dysrhythmias commonly occur and need to be addressed if they significantly compromise cardiac output. Hypokalemia and hypomagnesemia need to be diagnosed and treated as they may complicate cardiac arrhythmias.

Prognosis

The overall mortality rate is currently between 10% and 27%. Negative prognostic factors include > 6-hour duration of clinical signs, post-fluid therapy serum lactate concentration > 6.4 mmol/L or < 4 mmol/L decrease between pre- and post-fluid lactate, and devitalized gastric wall with need for gastric resection.

GASTRIC OUTLET OBSTRUCTION

Causes of gastric outlet obstruction include gastric FBs, antral pyloric hypertrophy, and gastric neoplasia as well as gastric pythiosis.

GASTRIC FOREIGN BODY

Definition/Overview

Young animals are more likely to play with foreign objects, but ingestion of gastric FBs may occur in animals of any age. While many dogs are indiscriminate eaters at risk for any type of GI FB, cats are more likely to ingest linear FBs.

Etiology

FBs may consist of bones, toys, socks, towels, or linear material such as string or wool. Linear FBs may lodge at the pylorus and cause intestinal perforation and peritonitis. Hair balls may be a problem, especially in long-haired cats (Box 9.4).

Box 9.4 The problem of feline hairballs

While hairballs commonly occur, particularly in long-haired cats, they do not usually cause significant health problems. Typically, affected cats vomit occasionally while remaining otherwise healthy ("healthy vomiters"). The formation of hairballs may be related to the unusual fasted digestive motility pattern displayed in cats, which may make the emptying of hair material into the duodenum more difficult. This promotes gastric retention of swallowed hair and ultimately formation of a hairball.

In most cats, treatment involves administration of a petroleum laxative or dietary supplementation with a bulk laxative. Psyllium is sufficient to control the problem. Long-haired cats may benefit from regular clipping. In some cats, trichobezoars may form, cause chronic gastritis, and/or obstruct the gastric outlet and, therefore, require endoscopic or surgical extraction. Frequent vomiting of hairballs may also be an early sign of chronic enteropathies and should prompt clinicians to initiate further diagnostic tests. This is particularly true in short-haired cats, which are usually not prone to having hairballs.

Pathophysiology

Gastric outlet obstruction may cause hypokalemic metabolic alkalosis.

Clinical Presentation

History of possible FB ingestion and acute-onset vomiting in an otherwise normal animal. Anorexia and lethargy are commonly associated signs. Cranial abdominal discomfort or pain may be elicited on palpation. Dehydration and electrolyte and acid–base abnormalities are frequent complications.

Differential Diagnosis

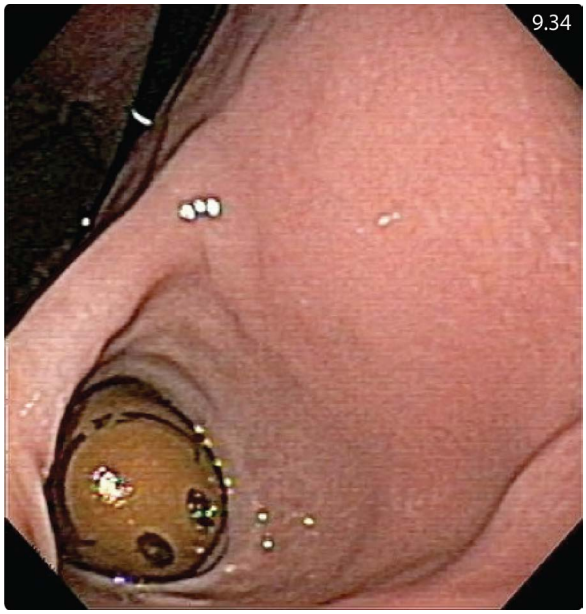
Dietary indiscretion and GI infections (e.g., parvovirus) are the most important differential diagnoses in puppies. In adult dogs, acute gastritis due to dietary indiscretion and acute pancreatitis are the top two differentials. However, any GI or systemic disease-causing acute vomiting should be considered both in dogs and cats.

Diagnosis

Diagnosis is confirmed with abdominal imaging. Survey radiographs may show a dilated stomach full of food or secretions for a prolonged period after meals. In some cases, the foreign object may be visible (Figures 9.32 and 9.33). In case of doubt, contrast radiographs may help to visualize the obstruction more accurately. Alternatively, ultrasound examination of the stomach may confirm the presence of a foreign object.







FIGURES 9.32–9.34 Eight-year-old male neutered Pekingese presented with a 10-day history of anorexia, vomiting, and lethargy. (**Figure 9.32**) Ventrodorsal abdominal radiograph. A round structure of soft tissue density is visible surrounded by gas in the pyloric antrum. (**Figure 9.33**) The foreign body is not visible in this dorsoventral view where gastric gas has accumulated in the fundus. This highlights the importance of obtaining both ventrodorsal and dorsoventral views for an optimal evaluation of the stomach. (*Radiographs courtesy of LSU SVM Diagnostic Imaging Service.*) (**Figure 9.34**) Gastroscopic view. A bouncing ball with a smiley face is visible in the pyloric antrum and could easily be extracted using an endoscopic snare.

Management

Gastric FBs need to be removed either endoscopically (Figures 9.34 and 9.35) or surgically. Foreign material that has partially passed into the duodenum (e.g., socks, towels) should be removed surgically. Fluid therapy is promptly initiated to replace deficits and stabilize the patient prior to inducing anesthesia.

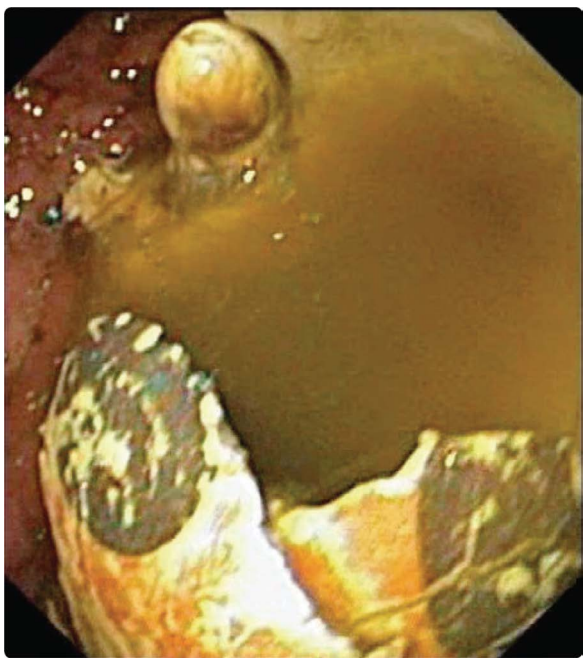


FIGURE 9.35 Gastroscopic view of a dog that had chewed and swallowed parts of a plastic soccer ball. Typical clinical signs had been present for 3 weeks.

Prognosis

Prognosis is generally good once the foreign material has been removed. It may be guarded to poor in severely debilitated animals or in cases with gastric perforation and peritonitis. Possible surgical complications include dehiscence and peritonitis.

GASTRIC ANTRAL PYLORIC HYPERTROPHY

Definition/Overview

Thickening of the antral wall may be due to hypertrophy of the mucosa, the muscularis, or both layers. Acquired pyloric antral hypertrophy is most commonly due to hyperplasia of the antral mucosa and occurs preferentially in middle-aged to older small breed dogs (e.g., Lhasa Apso, Pekingese, Maltese, and Shih Tzu). Congenital pyloric hypertrophy characterized by hyperplasia of the antral muscularis is a rare congenital disorder of brachycephalic breeds such as Boxers, Boston Terriers, and Bulldogs and has also been reported in Siamese cats.

Etiology/Pathophysiology

The exact causes and pathophysiology remain unknown. An increased frequency of GI tract lesions was reported in brachycephalic dogs, and acquired pyloric antral hypertrophy was diagnosed endoscopically in > 80% of examined dogs, although most of the dogs did not show any clinical signs. An association was suggested between the chronic inspiratory dyspnea seen in these breeds and chronic duodenogastric reflux, which may be the cause of the antral mucosal hypertrophy.

Clinical Presentation

Chronic, intermittent vomiting that worsens progressively with severity of the mucosal hypertrophy and resulting pyloric obstruction. In puppies and kittens with the congenital form, signs start after weaning. Projectile vomiting may occur.

Differential Diagnosis

Other diseases of the stomach, chronic pancreatitis, diseases originating outside the GI tract (e.g., chronic kidney disease).

Diagnosis

Survey abdominal radiographs or abdominal ultrasound may suggest delayed gastric emptying and show thickening of the antral wall. Barium contrast studies may be useful to visualize the narrowing of the pyloric passage. Diagnosis is confirmed with gastroscopy or surgical exploration and histologic evaluation of mucosal or full-thickness biopsies. Antral mucosal folds can easily be viewed on endoscopic evaluation of the stomach (Figures 9.36 and 9.37). Histopathologic examination of mucosal biopsies confirms the mucosal hyperplasia.

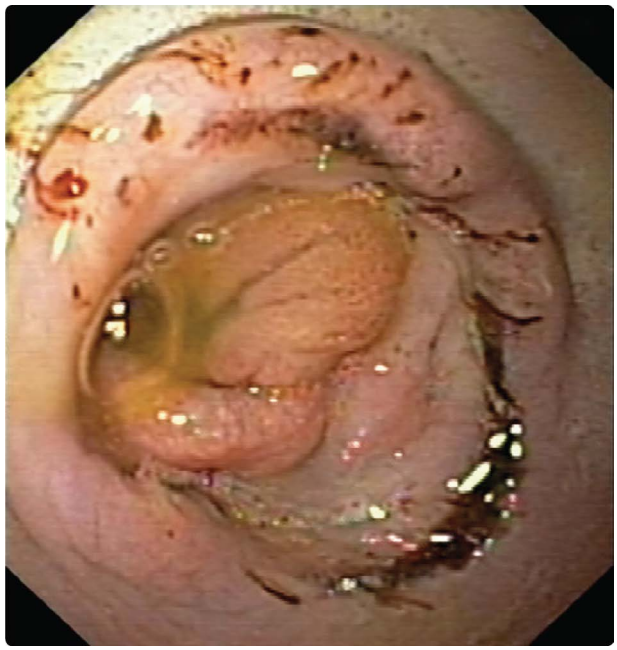


FIGURE 9.36 Gastroscopic view of the pylorus in a French Bulldog with gastric antral pyloric hypertrophy. Note the prominent mucosal folds surrounding the pylorus, with multiple erosions (bleeding) that may be associated with duodenogastric reflux. (*Courtesy of P. Lecoindre.*)

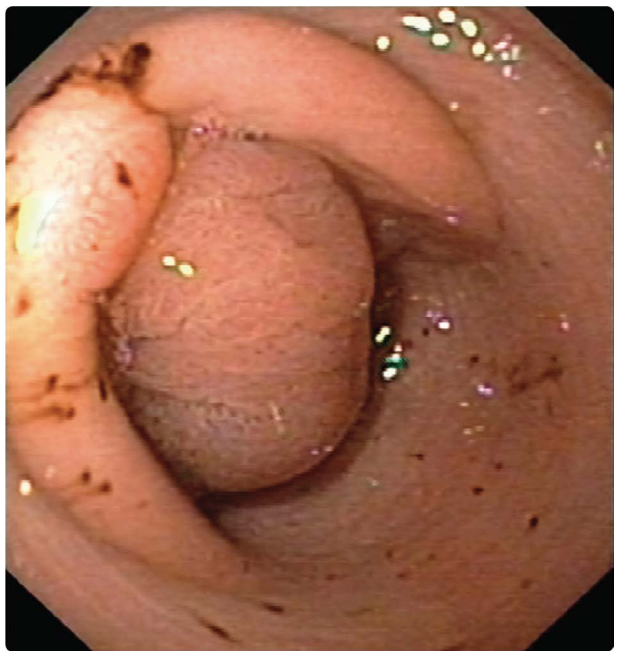


FIGURE 9.37 Gastroscopic view of the pylorus in a Boxer dog with gastric antral pyloric hypertrophy. Note the prominent mucosal fold obstructing the pylorus. There are multiple erosions (bleeding) surrounding the pylorus. (*Courtesy of P. Lecoindre.*)

Management

Treatment is surgical and consists of removing the redundant tissue and performing a Y-U pyloroplasty. Tissue specimens should be submitted for histologic confirmation. In some instances, pyloric antral resection may be required. Pyloric myotomy, while easier to perform, is usually not successful in these animals. In brachycephalic dogs, surgical correction of brachycephalic airway obstructive syndrome should be considered to address the underlying factor.

Prognosis

Surgery is curative, and the prognosis is good. Possible surgical complications include dehiscence or lack of improvement due to inappropriate surgical technique.

NONOBSTRUCTIVE GASTRIC EMPTYING DISORDERS

Definition/Overview

Motility is often the "missing link" in the complex equation of GI health in dogs and cats. The prevalence of GI motility disorders in small animals cannot be precisely documented because obtaining a definitive diagnosis is often difficult, sometimes even impossible. However, it is thought that these disorders are of significant clinical importance.

Etiology

Elucidating the origin of nonobstructive GI dysmotility is often challenging. Often, it results from diseases located outside the stomach and intestines, including abdominal inflammation (e.g., acute pancreatitis), immune-mediated diseases, and metabolic diseases. Alternatively, motility disorders may also result from primary GI disorders such as GI inflammation or neoplasia. Furthermore, diseases affecting the autonomic nervous system, such as dysautonomia, also impact GI motility. Finally, postoperative ileus has been shown to cause a significant delay in gastric emptying of up to 48 hours in dogs undergoing abdominal surgery.

Clinical Presentation

Vomiting of more or less digested food is the most common clinical sign, particularly when it occurs long after food intake (e.g., > 10–12 hours), when the stomach should be empty. Projectile vomiting may occur in the absence of a prodromal phase. Additionally, the animal may be bloated and have pain on cranial abdominal palpation and/or signs of colic. Hyporexia or anorexia, signs of nausea, increased belching, pica, and/or polydipsia may also be observed.

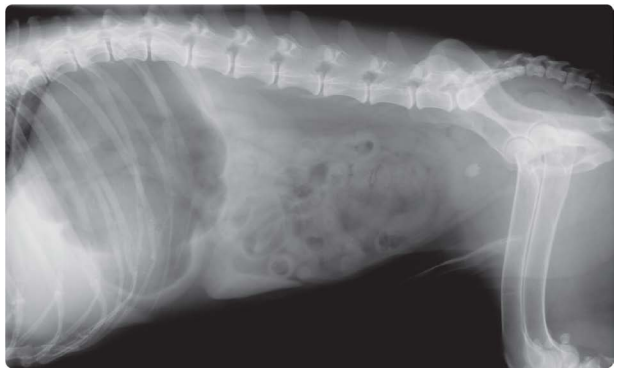


FIGURE 9.38 Right lateral abdominal radiograph of a 15-year-old male neutered Cocker Spaniel with recurrent episodes of bloat and colic. The stomach is dilated with gas, but there is no indication of gastric outlet obstruction. Note that a radiopaque cystourolith is visible.

Differential Diagnosis

Due to the relatively vague clinical signs, the list of differential diagnoses is long. It is essential to first rule out GI obstruction, which may require immediate surgical management.

Diagnosis

Since many underlying disorders may affect gastric motility, a minimal database (CBC, chemistry panel, urinalysis) plus survey abdominal radiographs are necessary to screen for underlying diseases and confirm the absence of GI obstruction (Figure 9.38). Accurate assessment of gastric emptying is difficult under practical conditions. Radionuclide scintigraphy is recognized as the current gold standard in dogs and cats but is only available at select referral centers. Radiographic studies are easily accessible in clinical veterinary practice. However, assessment of gastric emptying of liquid barium is an insensitive technique, with the exception of diagnosis of mechanical obstructions. Mixing barium with food may allow better evaluation of the solid phase of gastric emptying. Unfortunately, barium can easily dissociate from the test meal and cause the study to be unreliable. Barium-impregnated polyethylene spheres (BIPS) have been used for evaluation of GI transit times in dogs and cats. However, correlation between gastric emptying of BIPS and the gold standard has been disappointing in dogs and in cats, and the use of these spheres has been limited. Abdominal ultrasound is a promising and widely available modality for the evaluation of gastric antral motility and gastric emptying.

Management

Proper diagnosis and treatment of any underlying disease that may affect gastric motility are essential. Therapy of functional, nonobstructive disorders of gastric motility is based on dietary modification and judicious use of prokinetic drugs.

Dietary modifications designed to facilitate gastric emptying are based on knowledge of digestive

TABLE 9.7 Site of action and recommended dosage of gastrointestinal prokinetics

Name	Site of action	Dose
Metoclopramide	Pyloric antrum, duodenum (?)	0.2–0.5 mg/kg p.o., SC q.8h. CRI: 1–2 mg/kg/24h.
Cisapride	Lower esophagus (C), lower esophageal sphincter, pyloric antrum, small intestine, colon	0.1–0.5 mg/kg p.o. q.8–12h.; dose can be progressively increased up to 1 mg/kg q.8h.
Mosapride	Pyloric antrum	0.25–2 mg/kg p.o. q.12–24h. (D); currently only available in Asia
Prucalopride	Pyloric antrum, small intestine (?), colon	0.01–0.6 mg/kg p.o. q.12–24h.
Erythromycin	Lower esophageal sphincter (D), pyloric antrum, small intestine, colon	0.5–1.0 mg/kg p.o. or IV q.8h. (after dilution)

C, cat only; CRI, constant rate infusion; D, dog only.

physiology. First, gastric emptying of liquid food is faster than that of solid foods. Also, diets with high-caloric density tend to remain longer in the stomach. In addition, gastric emptying of fat is slower than that of proteins, which is slower than that of carbohydrates. Consequently, feeding a liquid or semi-liquid diet of low-caloric density, low in fat and protein should maximize gastric emptying. Finally, increased meal frequency and decreased meal size are also useful. Dietary treatment of bilious vomiting or duodenogastric reflux consists of feeding a light meal late at night. Additionally, prokinetic drugs may be beneficial in nonobstructive disorders of gastric emptying (Table 9.7).

Prognosis

Prognosis is good if the primary cause of delayed gastric emptying can be identified and corrected. Idiopathic GI dysmotility can be a challenge to manage efficiently. Dysautonomia carries a poor prognosis in cats and dogs.

GASTRIC NEOPLASIA

Definition/Overview

Stomach tumors are uncommon and typically occur in older in dogs and cats. Benign canine gastric neoplasms include adenomatous polyps and leiomyomas. Adenocarcinoma and lymphoma are the most prevalent tumor types diagnosed in the dog, followed by leiomyosarcoma and stromal tumors. Lymphoma is the most common gastric neoplasia found in cats.

Etiology

The etiology of gastric tumors has not been elucidated. Canine breeds at risk for adenocarcinoma include the Belgian Shepherd Dog, Rough Collie, and Staffordshire Bull Terrier. A predisposition in male dogs has been reported for gastric adenocarcinoma and gastric lymphoma.

Clinical Presentation

The early stages of gastric neoplasia usually remain subclinical. Hyporexia is the most common clinical sign followed by vomiting and weight loss. In advanced stages with ulceration of the gastric mucosa, hematemesis and melena may occur. Vomiting is due either to gastric outflow obstruction or to abnormal gastric motility associated with the neoplastic wall infiltration. Adenomatous polyps are usually subclinical unless they cause gastric outflow obstruction.

Differential Diagnosis

Other disease processes causing gastric outflow or small intestinal obstruction (FBs, pythiosis). Other conditions associated with hyporexia/anorexia and vomiting that originate from the GI tract or from other organ systems.

Diagnosis

A minimal database consisting of CBC, biochemistry panel, and urinalysis is recommended to evaluate the general condition of the animal and screen for possible systemic repercussions of gastric tumors such as blood loss anemia. Diagnosis is confirmed with abdominal imaging. In some instances, survey abdominal radiographs may reveal an enlarged stomach with delayed emptying (Figure 9.39). Filling defects or ulcerated areas

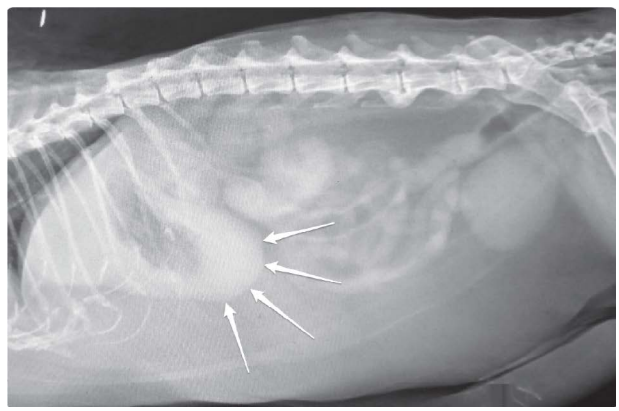


FIGURE 9.39 Twelve-year-old Domestic Shorthair cat with anorexia, weight loss, and lethargy of 4 weeks' duration. Right lateral abdominal radiograph. The cat was severely overweight. Although the cat did not eat for 2 days, the stomach is distinctly visible and partially filled with gas (arrows). The gastric wall appears thickened at the level of the pyloric antrum (although this could also be due to summation of gastric fluid and gastric wall), and the serosal contour of the stomach is somewhat irregular. (*Courtesy of C. Montgomery.*)

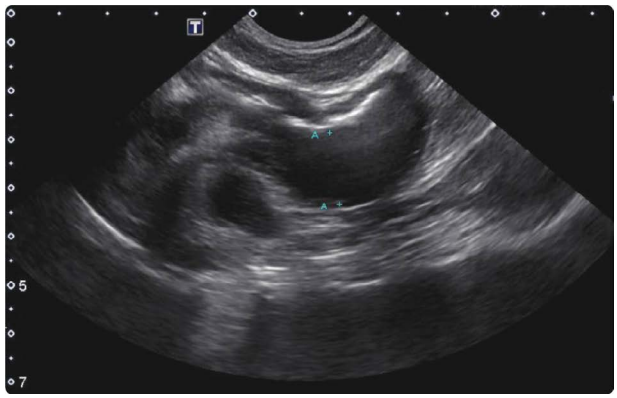


FIGURE 9.40 Abdominal ultrasound of the same cat as Figure 9.39. The gastric wall at the level of the pyloric antrum was severely thickened (14.8 mm between the two calipers).

may be detected on contrast studies. Abdominal ultrasound often shows thickening of the gastric wall (Figure 9.40). Most canine gastric adenocarcinomas are located in the antral area or on the lesser curvature, while lymphomas are often diffusely infiltrative. Enlarged lymph nodes and/or hepatic nodules suggestive of local metastases may be visible (Figure 9.41). Double lateral thoracic radiographs are useful to screen for pulmonary metastases. Cytologic evaluation of ultrasound-guided aspirates of the abnormal gastric wall may be helpful to diagnose lymphoma (Figure 9.42). Endoscopic evaluation with sampling of mucosal biopsies in and around the suspect areas (Figures 9.29 and 9.43) and histologic evaluation are useful to confirm the tumor type. While no appearance is typical for one specific tumor type, most adenocarcinomas are ulcerated. Occasionally, tumors are located in the submucosal layers (linitis plastica) and obtaining representative endoscopic biopsies may be challenging.

Management/Prognosis

By the time animals develop clinical signs and are presented to a veterinarian, the neoplastic process is often advanced and severe. Probably due to a high prevalence

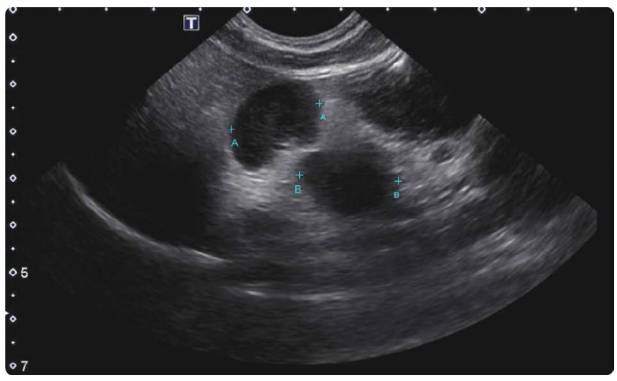


FIGURE 9.41 Abdominal ultrasound of the same cat as Figures 9.39 and 9.40. The gastric lymph nodes were very prominent (distance "a", 19.6 mm; distance "b", 21.2 mm). (*Ultrasound images courtesy of LSU SVM Diagnostic Imaging Service.*)

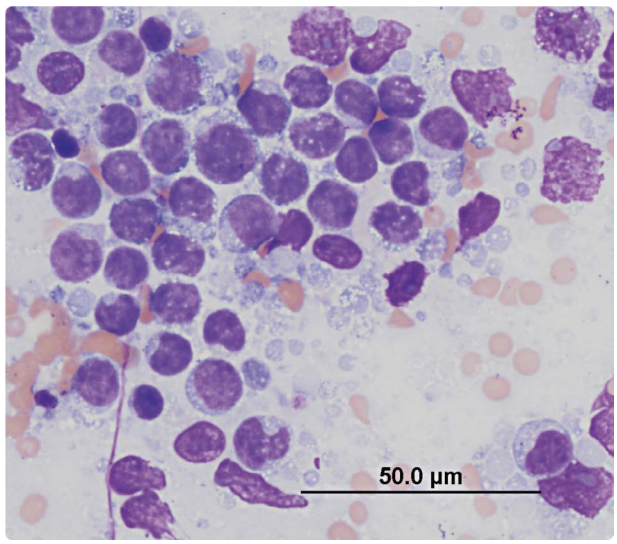


FIGURE 9.42 Cytologic evaluation of a fine-needle aspirate from the gastric wall depicted in Figures 9.39–9.41. A dense population of medium-sized lymphocytes and a few large lymphoblasts are visible, confirming the diagnosis of gastric lymphoma (50× objective). (*Courtesy of V. Le Donne.*)

of metastases at the time of diagnosis, surgical resection (antral resection and gastroduodenostomy, or Billroth type I procedure) does not significantly improve the prognosis of dogs with gastric adenocarcinomas. However, surgery may be a successful option for canine leiomyosarcomas, with a reported median survival time of 12 months. While canine gastric lymphomas usually carry a poor prognosis, feline alimentary lymphomas

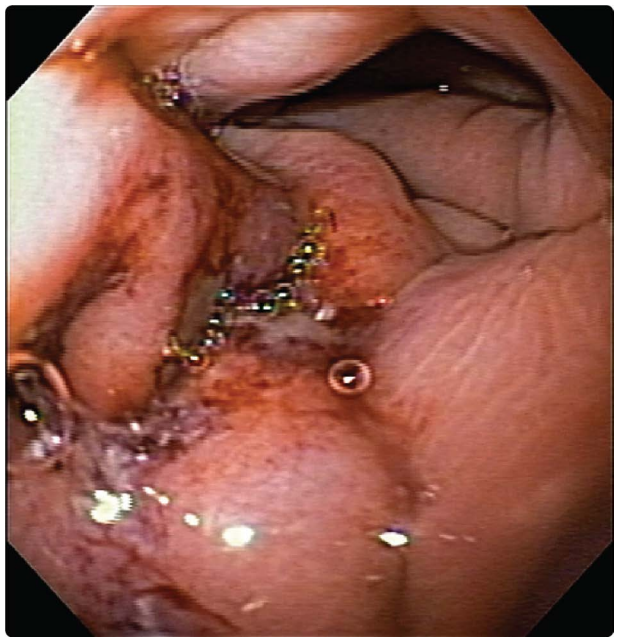


FIGURE 9.43 Close-up endoscopic view of a gastric adenocarcinoma in a 15-year-old female spayed Miniature Schnauzer. There are thickened mucosal folds surrounding an ulcerated area.

may respond to specific chemotherapy protocols. Small-cell feline alimentary lymphomas usually achieve prolonged remission with prednisolone (1–2 mg/kg p.o. daily) and chlorambucil (2 mg p.o. q.48h.) therapy. Large-cell alimentary lymphomas require more aggressive chemotherapy protocols, and their prognosis is less favorable.

PART 4: DISEASES OF THE SMALL INTESTINE

Overview

Small intestinal diseases are common in dogs and cats. The small intestine is the intestinal segment where absorption of nutrients, electrolytes, and water takes place. Small intestinal brush border enzymes are essential for activation of pancreatic enzymes and final processing of nutrients before they can be absorbed through the mucosa using active and passive diffusion mechanisms.

Small Intestinal Anatomy

The small intestine is divided into three anatomic segments: Duodenum, jejunum, and ileum. The total surface of the small intestinal mucosa is multiplied by a factor of 500 through formation of mucosal villi and presence of microvilli on the luminal surface of the enterocytes. The microscopic structure consists of mucosa, submucosa, and both the internal and external muscular layers. The mucosa consists of villi, lamina propria, and muscularis mucosae (Figure 9.44). The epithelial cells multiply in the small intestinal crypts and migrate over a few days to the tips of the small intestinal villi while they are undergoing maturation.

Normal Small Intestinal Function

Digestion and Absorption

In the small intestine, pancreatic and gastric enzymes facilitate luminal digestion, while enzymes produced by epithelial cells and located in the brush border of enterocytes are responsible for triggering the activation of pancreatic enzymes and further processing of oligo- and disaccharides, small peptides, and lipids. Carbohydrates, amino acids, and fatty acids are transported actively or passively through the epithelial barrier using transcellular and paracellular pathways. Lipids undergo complex transformations in order to be absorbed into the epithelial cells. Chylomicrons are formed in the enterocytes and diffuse into the lacteals to the thoracic duct. The intestinal barrier prevents free passage of intestinal content into the body and consists of the enterocytes with the glycocalyx that bathes their microvilli and the tight junctions that connect them on their lateral membrane.



FIGURE 9.44 Photomicrograph of the jejunal mucosal layer in a cat. (1) Jejunal crypt; (2) tip of jejunal villus; (3) lamina propria; (4) muscularis mucosae (arrow). H&E stain, 40× objective.

Importance of the Gut Microbiome

The development of molecular biology techniques for rapid sequencing has made it possible to fully map the composition of the gut microbiome. Microbial profiling based on 16S rRNA genes was the first culture-independent method used to study the composition of the gut microbiota. In addition, metabolomics provides information about the production of microbial metabolites to define the metabolic activity of the microbiome and its interactions with the host. The intestinal microbiota contains 10× more cells and 150× more genes than the host animal. It consists of bacteria (by far the most common microorganisms), archaea, viruses, fungi, and protozoa. The most common bacterial sequences in the gut typically belong to five phyla: Firmicutes, fusobacteria, bacteroidetes, proteobacteria, and actinobacteria. The exact composition varies along the digestive tract depending on the prevailing microenvironment and the physiological function of the individual intestinal segments. For example, the small intestine is home to a mixture of aerobic and facultative anaerobic bacteria, while the large intestine is almost entirely populated by anaerobes.

The intestinal microbiome contributes to numerous metabolic functions, protects against pathogens, and promotes the development of the immune system. It thus directly or indirectly influences numerous physiological processes in the host animal. The intestinal microbial community is involved in various metabolic and physiological activities including breaking down otherwise indigestible complex carbohydrates, providing energy

sources to support the integrity of the intestinal epithelium, educating the immune system, protecting against colonization with pathogens and producing metabolites such as short-chain fatty acids, secondary bile acids, and vitamins. The gut microbiota plays an essential role in the health of the gut and other organs such as the liver and even the brain. As a result, any imbalance in intestinal microbiota (intestinal dysbiosis) can have an adverse effect on the general health of the host.

Small Intestinal Motility

Three physiologic motility patterns are described in the small intestine: Peristaltic waves (aboral movement of chyme over long intestinal segments), stationary contractions (leading to intestinal segmentation), and clusters of contraction (mixing and aboral movement of chyme over short segments). Diarrhea usually is associated with the occurrence of pathologic giant aboral contractions.

ACUTE ENTERITIS

Overview

Acute enteritis occurs frequently in dogs and cats and can be a sign of many diseases affecting the small intestine primarily or secondarily. The approach to diarrhea is explained in Chapter 2.3 (**Table 2.3.1** lists the characteristics of small and large bowel diarrhea; **Table 2.3.2** lists the various causes of acute diarrhea). This chapter provides further details on common causes of acute enteritis. Overall, viral and parasitic causes of enteritis are more commonly diagnosed in puppies and kittens, while dietary indiscretion can occur at all ages; finally, acute hemorrhagic diarrhea syndrome (AHDS) affects middle-aged to older dogs.

VIRAL ENTERITIS

CANINE PARVOVIRAL ENTERITIS

Overview

The etiology, pathogenesis, diagnosis, and prevention of canine parvovirus infection are also discussed in Chapter 21. The virus targets rapidly dividing cells such as small intestinal crypt cells (**Figures 9.45** and **9.46**). The associated damage eventually greatly diminishes the absorptive capacity of the small intestine and compromises the intestinal barrier. The risk of bacterial translocation, bacteremia, and sepsis is greatly enhanced by the concurrent neutropenia.

Clinical Presentation

The following breeds are at higher risk of infection: Rottweiler, Dobermann, Labrador Retriever, American Staffordshire Terrier, German Shepherd Dog, and Alaskan Malamute. The most severe cases occur in

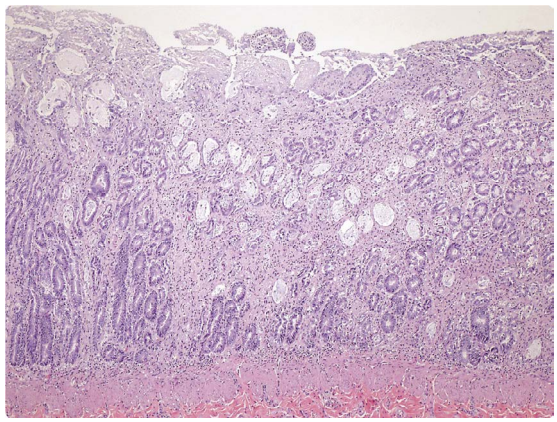


FIGURE 9.45 Six-month-old dog with parvovirus infection. Photomicrograph of the jejunal mucosa. There is severe villous atrophy with necrotic crypts (see **Figure 9.46**). Hematoxylin and eosin (H&E) stain, 40x objective. (*Courtesy of N. Wakamatsu.*)

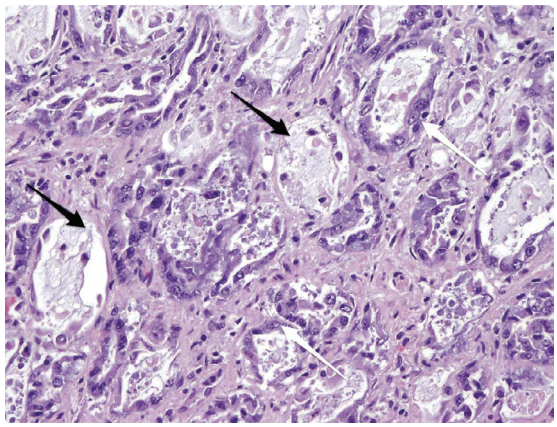


FIGURE 9.46 Photomicrograph of the jejunal crypts (same dog as **Figure 9.45**). Several crypts lack epithelial lining (black arrows) and are filled with necrotic material, while others show evidence of epithelial regeneration (white arrows). (*Courtesy of N. Wakamatsu.*)

puppies between the ages of 4 and 12 weeks, at the time when maternal immunity fades away. However, parvovirus infection is prevalent in dogs until 6 months of age. Anorexia and vomiting are often the first clinical signs observed. They are followed a few hours later by foul smelling, often bloody diarrhea (see **Figure 2.3.7**). Without treatment, puppies rapidly dehydrate. Fever is generally associated with secondary bacterial infection.

Intense vomiting and diarrhea may cause metabolic acidosis that often responds well to IV fluid therapy with crystalloids and generally does not require administration of sodium bicarbonate. Hypokalemia results from GI loss and may contribute to the occurrence of small intestinal intussusception. In severe cases, life-threatening complications, including sepsis and disseminated intravascular coagulation, may occur.

Differential Diagnosis

In puppies or in young dogs presented for acute vomiting, the differential diagnosis must include GI FB and

intestinal intussusception, which should be ruled out with abdominal radiographs. "Garbage can gut" and severe infestation with intestinal parasites may also cause hemorrhagic gastroenteritis.

Diagnosis

A preliminary diagnosis of parvovirus infection is made in the presence of acute hemorrhagic gastroenteritis in a young dog that is not adequately vaccinated. The probable presence of a highly contagious disease justifies drastic measures to prevent the spread of the infection in the veterinary hospital (isolation of the sick dog, thorough disinfection). Confirmation of diagnosis requires fecal testing for parvoviral antigen using a cage-side test. The antigen test may be positive during the viral shedding period, which lasts for 10–12 days after infection. However, the result may be falsely negative as viral shedding may wax and wane. Also, the test can give a false-positive result in dogs that have been recently vaccinated with a modified live vaccine. In such cases, fecal PCR may be useful to differentiate vaccine and wild-type virus. Neutropenia is a typical finding in dogs with parvovirus infection; however, it is not always present at the time of the initial veterinary visit. Detection of other laboratory changes may be useful to set up an adequate treatment plan. Electrolyte abnormalities, especially hypokalemia, should be corrected. Panhypoproteinemia (characterized by simultaneous presence of hypoalbuminemia and hypoglobulinemia) is due to intestinal protein loss. Depending on the severity of the problem, there may be a need for colloids (e.g., plasma) to support oncotic pressure.

Management

Aggressive treatment is required and consists of rapid correction of fluid deficits and electrolyte imbalances. Crystalloids are used in adequate amounts with added electrolyte solutions as needed. However, a recent study has suggested good success in treating dogs with parvovirus infection on an outpatient basis (**Box 9.5**).

It is essential to stop the vomiting as quickly as possible. A variety of antiemetic agents are available (see Chapter 2.17, **Table 2.17.1**). A combination of antiemetic drugs with different modes of action is sometimes required to obtain the desired result. Recent research has shown the benefits of early feeding in very small amounts; dogs that received early nutrition after they stopped vomiting had a lower mortality and a faster weight gain during recovery.

Because of the risk of secondary bacterial infection, parenteral administration of broad-spectrum antibiotics such as amoxicillin and clavulanic acid (12.5–20 mg/kg IV q.12h.) is recommended. Parenteral aminoglycosides (with risk of nephrotoxicity) or fluoroquinolones (e.g., enrofloxacin 10 mg/kg q.24h. off-label in growing dogs) may be added to improve efficacy against Gram-negative bacteria. The value of fecal microbiota transplantation (FMT) was highlighted in a recent study where puppies with parvovirus infection that received daily FMT in addition to conventional treatment had faster resolution of diarrhea and shorter hospitalization times than those that did not.

Box 9.5 Practical tip: Outpatient treatment of canine parvovirus infection

An outpatient treatment for dogs with parvoviral enteritis was evaluated in a recent study. After initial in-hospital stabilization with IV fluids, the outpatient treatment consisted of:
- SC administration of isotonic fluids (30 mL/kg q.6h. after replacement of fluid deficits)
- Enteral nutrition (commercial recovery diet approx. 1–1.2 kcal/kg q.6h. syringe-fed PO)
- Daily SC injections of maropitant (1 mg/kg)
- One SC injection of cefovecin (8 mg/kg), a proprietary long-acting third-generation cephalosporin

The 80% survival rate compared favorably with the 90% recovery rate in hospitalized parvovirus patients treated with IV fluids. Also, there was no difference in time to recovery between the hospitalized and the outpatient group. This study shows that an outpatient protocol may be a reasonable alternative option for owners who cannot afford the costly hospitalization for puppies and young dogs infected with parvovirus. However, adequate supportive care and monitoring remain essential to maximize the chances of a rapid recovery.

Source: Venn EC, Preisner K, Boscan P, et al. (2017). Evaluation of an outpatient protocol in the treatment of canine parvoviral enteritis. *J Vet Emer Crit Care* 27(1):52–65.

Disinfection of contaminated surfaces is essential to prevent spread of infection. Disinfectants with demonstrated efficacy against parvovirus include sodium hypochlorite, aldehydes, and oxidizing agents. A 1:30 dilution of commercially available bleach is efficacious after 10 contact minutes. However, bleach is a mucosal irritant and may damage metals, rubber, plastic, and cement. It is inactivated by light; thus, it is preferable to prepare solutions immediately before their use. It is also inactivated in the presence of organic material such as mud or feces. Oxidizing solutions such as hydrogen peroxide (Virox, Accel) and potassium peroxymonosulfate (Virkon, Trifectant) claim extremely high efficacy within minutes with minimal corrosive effect.

Prognosis

Dogs with mild-to-moderate disease generally have a good prognosis if appropriate treatment is initiated early. In severe cases, the prognosis is fair because complications are more common, and therapy is more intensive. Overall, quick diagnosis and early and aggressive treatment optimize therapeutic success.

OTHER VIRAL INTESTINAL INFECTIONS

Feline panleukopenia and canine and feline coronavirus infections are discussed in detail in Chapter 21.

BACTERIAL ENTERITIS

Overview

Rarely, dogs and cats may develop bacterial enteritis. Responsible pathogenic agents include *Campylobacter*, *Clostridium perfringens*, *Clostridium difficile*, and *Salmonella* spp., as well as specific strains of *Escherichia coli*. However, these same bacteria can also be isolated in the feces of healthy dogs and cats, and it is believed that they are often opportunistic agents. Overall, the exact role of bacterial enteropathogens in dogs and cats with enteritis remains controversial. In some instances, they may present a risk of zoonotic infection for people at risk after contact with shedding dogs and cats that often do not show any sign of disease. These facts have contributed to an unclear situation that renders diagnostic and therapeutic decisions difficult. If these bacteria are not the source of the animal's problems, use of antibiotics is not recommended because it may lead to development of resistant strains, which in the long term may have repercussions on public health. Additional research is necessary to define the role of enteropathogens more clearly in canine and feline intestinal diseases.

SALMONELLOSIS

Etiology

Salmonella is rod-shaped facultative anaerobic Gram-negative bacteria of the Enterobacteriaceae family. The majority of *Salmonella* relevant to veterinary medicine are serovar *S. enterica* sub species *enterica*.

Pathophysiology

Salmonella are enteroinvasive bacteria that may induce acute mucosal inflammation resulting in enterocolitis, mucosal sloughing, and secretory diarrhea. While most *Salmonella* infections remain localized to the GI tract, bacterial translocation and septicemia may occur and cause severe systemic complications. Generally, healthy adult carnivores are resistant to salmonellosis. Consumption of raw-meat-based diets is a risk factor for *Salmonella* infection in dogs and cats. The prevalence of healthy carriers is highest in shelters.

In people, salmonellosis is characterized by diarrhea, fever, and abdominal cramps, often mild to moderate in severity and followed by spontaneous recovery. The most common infection pathway is through ingestion of contaminated food, in particular chicken eggs and egg-based products, but also pork and chicken meat or contaminated vegetables. Even though dogs and cats are only rarely implicated in outbreaks of human salmonellosis, isolated foci have been associated with visits to a veterinary hospital. This is why excellent hygiene is recommended around dogs and cats shedding *Salmonella*, particularly if sensitive subjects such as very young children, elderly people, and immunocompromised patients may be exposed.

Clinical Presentation

Fever, lethargy, and anorexia often start 3–5 days post infection or onset of immune suppression. They may be followed by vomiting and often bloody small and/or large bowel diarrhea and abdominal pain, weight loss may ensue. In case of bacterial translocation, signs of sepsis and involvement of other organs. The clinical course is usually acute to subacute.

Differential Diagnosis

Other causes of acute enteritis and/or colitis such as parvovirus infection (in puppies), parasite infestation with hookworms, whipworms, *Giardia, Cryptosporidium*, or *Tritrichomonas* (cats), other bacterial infections, dietary indiscretion, AHDS.

Diagnosis

Fecal isolation and serotyping of *Salmonella*, PCR. CBC may show changes suggestive of systemic inflammation, and biochemistry profile may indicate involvement of other organs.

Management

Treatment consists of administration of antimicrobial drugs based on documented sensitivity of the isolated strain.

Prognosis

Animals recovering from clinical salmonellosis may become healthy *Salmonella* carriers for weeks after the clinical signs have subsided. This may be due to persistence of *Salmonella* in the lymph nodes. *Salmonella* may survive for long periods in the environment.

PARASITIC ENTERITIS

The Companion Animal Parasite Council (CAPC) and the European Scientific Counsel Companion Animal Parasites (ESCCAP) maintain very informative and freely accessible websites on intestinal parasitoses of small animals that should be consulted for additional information on the parasites listed here and on other GI parasites (www.capcvet.org; www.esccap.org).

HOOKWORMS

Etiology

Hookworms are common in tropical and subtropical areas (*Ancylostoma caninum*—dog; *A. tubaeforme*—cat) and warm coastal regions (*A. braziliense*—dog, cat) but also in cooler climates (*Uncinaria stenocephala*—dog). Adult hookworms live in the small intestine and produce eggs that are shed with the host's feces and develop to third-stage larvae (L3), which are infectious.

Dogs and cats infect themselves by ingesting L3 (direct fecal–oral transmission, ingestion of infected paratenic hosts such as flies, cockroaches, and dung beetles), or through penetration of the skin by L3. In dogs, puppies can be infested by nursing an affected bitch (transmammary infection). Some larvae undergo arrested development in muscle and can be reactivated during stressful events and migrate to the intestine.

Pathophysiology

Adult hookworms ingest the host's blood and cause intestinal inflammation (Figure 9.47).

Clinical Presentation

The clinical signs consist mainly of small bowel diarrhea. Blood loss anemia can be life threatening in puppies (Figure 9.48). Hyporexia, weight loss, poor hair coat, and pica may also be observed. In dogs that were infected percutaneously, pruriginous skin lesions may occur at the points of entry, particularly in the interdigital spaces.

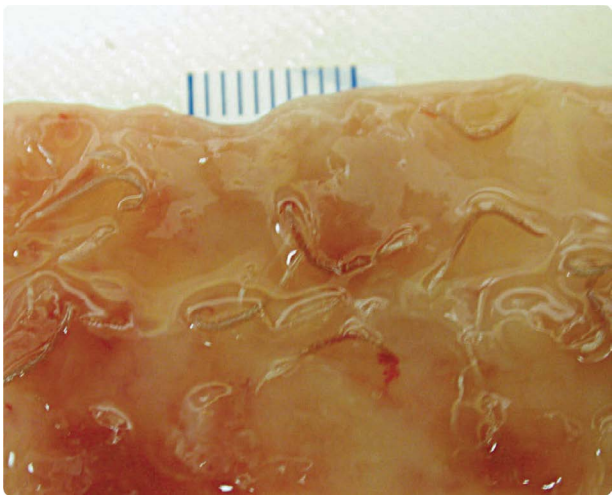


FIGURE 9.47 Postmortem view of hookworms causing damage to a dog's small bowel mucosa.



FIGURE 9.48 Pale oral mucous membranes in a 12-week-old mixed-breed puppy with massive hookworm infestation.

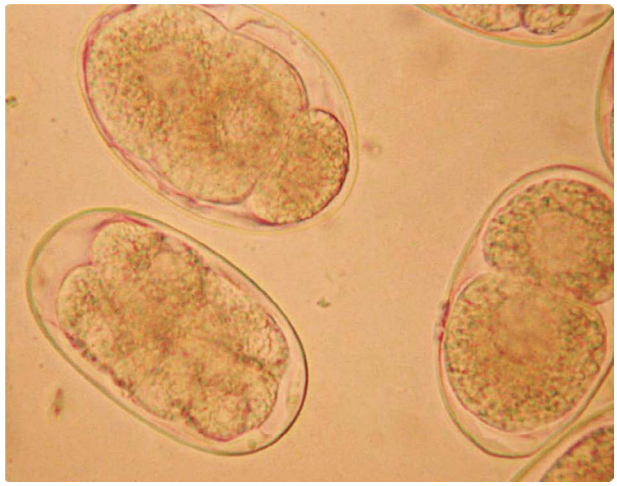


FIGURE 9.49 Photomicrograph of an *Ancylostoma caninum* ova. (*Courtesy of E. Greiner.*)

Differential Diagnosis

Other causes of acute enteritis. Acute blood loss anemia in puppies may also be caused by heavy flea infestation, which may occur concurrently to hookworm infestation in stray puppies and kittens from tropical and subtropical areas.

Diagnosis

Fecal flotation and visualization of the parasite ova (Figure 9.49).

Management/Prevention

Treatment with pyrantel pamoate (5–10 mg/kg p.o., repeat after 7–10 days) is approved for all hookworm species. Fenbendazole (50 mg/kg p.o. q.24h. for 3 consecutive days) is also efficient. The efficacy of macrocyclic lactones such as moxidectin, milbemycin oxime, and ivermectin differs between species. Alarmingly, multidrug resistance of *A. caninum* has been reported to occur in U.S. greyhounds. Supportive treatment as required: For example, anemic puppies and kittens often require blood transfusion (whole blood or packed red blood cells).

Detailed preventive treatment protocols can be found on the CAPC and ESCCAP websites.

Public Health Consideration

Cutaneous larva migrans can occur when hookworm larvae penetrate human skin and result in a pruriginous but self-limiting dermatitis ("creeping eruption").

Prognosis

Good to excellent.

ROUNDWORMS

Etiology

Ascarids that may infest small animals include *Toxascaris leonina* (dogs and cats), *Toxocara canis* (dog), and *Toxocara cati* (cat). Additionally, *Baylisascaris procyonis* (the raccoon roundworm) may also occasionally infest dogs in North America. Adult roundworms live in the small intestine (Figure 9.50) and produce eggs that are shed in the feces. Larvae are released upon ingestion of embryonated eggs and migrate to the liver and lungs. Pulmonary lesions can induce clinical signs in puppies. Larvae then undergo tracheal migration and eventually infest the small intestine, or somatic migration, with formation of cysts in tissues with possible reactivation in stressful situations.

Pathophysiology

Adult roundworms cause enteritis, particularly in puppies and kittens.

Clinical Presentation

Puppies and kittens: Vomiting, small intestinal diarrhea, poor general health, and development of a pot-belly are common. Heavy infestation can result in small intestinal obstruction or intussusception. It can also cause pulmonary signs such as coughing and tachypnea. **Adult dogs and cats:** Infestation is less common and less likely to cause clinical signs.

Differential Diagnosis

In puppies and kittens, other causes of acute enteritis; intestinal FBs if the roundworms cause bowel obstruction.

Diagnosis

Fecal flotation and visualization of the parasite ova (Figure 9.51).

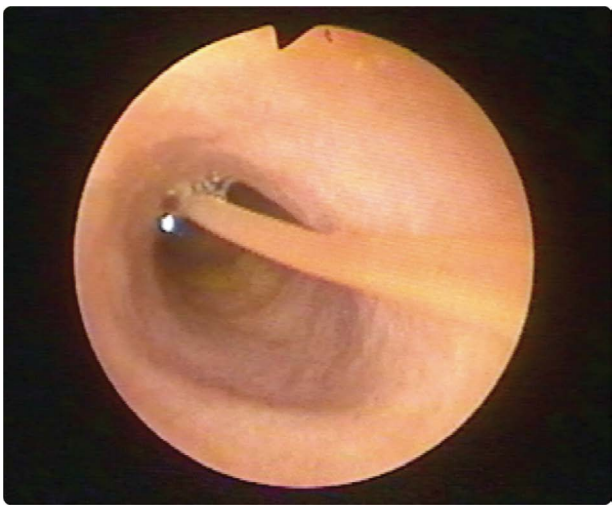


FIGURE 9.50 Endoscopic view of an adult roundworm in the duodenum of a cat. (*Courtesy of R. Husnik.*)



FIGURE 9.51 Photomicrograph of a *Toxocara canis* egg. (*Courtesy of E. Greiner.*)

Management/Prevention

Piperazine, pyrantel pamoate, fenbendazole, and selected macrocyclic lactones (e.g., milbemycin oxime, moxidectin) should be given to eliminate roundworms. Supportive treatment should be administered as required.

Detailed preventive treatment protocols can be found on the CAPC and ESCCAP websites.

Public Health Consideration

In people, ingestion of embryonated eggs from *Toxocara* spp. may lead to larva migrans and cause pulmonary and hepatic disease, retinitis, and neurologic disease. *Toxocara* larva migrans can have a devastating outcome in people.

Prognosis

Excellent.

ISOSPORA spp.

Etiology

Dog—*Isosporacanis, I. ohiensis, I. neorivolta, I. burrowsi.* Cat—*I. felis, I. rivolta.* Sporulated oocysts are ingested (directly or via paratenic hosts) and further develop in the small intestinal enterocytes (enteroepithelial cycle).

Pathophysiology

Isospora spp. replicate in the small intestine and may induce villus atrophy, lacteal dilation, and hyperplasia of the lymphatic follicles in Peyer's patches.

Clinical Presentation

Clinical signs generally only occur in puppies and kittens and may consist of vomiting, watery diarrhea, abdominal pain, and dysorexia. Dehydration and death can occur in severe cases.

Differential Diagnosis

Other causes of acute enteritis in puppies and kittens.

Diagnosis

Isospora spp. oocysts are usually large and easy to detect on microscopic examination of supernatant fluid after fecal flotation.

Management

While the disease is generally self-limiting, treatment may be required in clinical situations. The poorly absorbed sulfa drug sulfadimethoxine (50–60 mg/kg p.o. q.24h. for 5–20 days) is the only approved anticoccidial drug for dogs and cats in the United States and the United Kingdom. Other antiprotozoal drugs, such as ponazuril (20 mg/kg p.o. q.24h. for 1–3 days), are frequently administered off-label to dogs and cats after adequate compounding. In breeding facilities and shelters, proper cleaning of the environment (prompt elimination of feces before oocysts sporulate, steam cleaning of contaminated surfaces), treatment of dams prior to parturition, and preventive anticoccidial treatment of all puppies and kittens may be required.

Prognosis

Excellent.

DIETARY INDISCRETION

Definition/Overview

Dietary indiscretion is probably the most common cause of acute gastroenteritis in dogs. Overall, puppies and young dogs are more commonly affected than older dogs. Some canine breeds such as Retrievers are known to be prone to dietary indiscretion. Cats are more discriminant eaters, and dietary indiscretion is rarely diagnosed in this species.

Etiology

Ingestion of unusual food such as food prepared for human consumption, garbage that may contain food in various stages of decomposition, or any other food not usually part of the affected dog or cat's diet.

Pathophysiology

Toxins from rotting food cause small intestinal mucosal irritation and may cause osmotic and secretory diarrhea. Unusual food, such as food prepared for human consumption, cannot be properly digested and absorbed and thus can cause osmotic diarrhea.

Clinical Presentation

Acute diarrhea (with or without vomiting) is the most common presentation. Lethargy, hyporexia, dehydration, electrolyte imbalances, and abdominal discomfort are common accompanying signs.

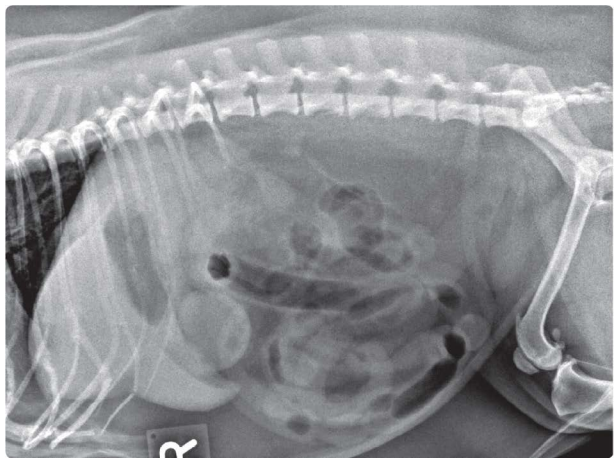


FIGURE 9.52 Right lateral abdominal radiograph from an adult mixed-breed dog with dietary indiscretion and functional ileus. Generalized distension of small intestinal loops is present. (*Courtesy of L. Gaschen.*)

Differential Diagnosis

Other causes of acute gastroenteritis/enteritis such as parasite infestation and viral or bacterial enteritis. In vomiting animals, intestinal obstruction should be ruled out with appropriate abdominal imaging (Figure 9.52). In puppies with possible exposure and questionable immune status, parvovirus infection should be ruled out prior to hospitalization.

Diagnosis

History and presentation are often very suggestive.

Management

Supportive, with administration of fluids (IV, SC, or p.o. depending on the severity of clinical signs), and antiemetics in vomiting or nauseous animals. A 12- to 24-hour fast is implemented (small puppies may require parenteral glucose solution during fasting to avoid hypoglycemia), followed by offering small meals consisting of commercial or home-made, easily digestible diet for 3–5 days and progressive return to a balanced diet after that. Probiotics may be useful (Box 9.6). In dogs with severe diarrhea and abdominal discomfort, loperamide (0.1–0.2 mg/kg p.o. q.8h.) or diphenoxylate (0.1 mg/kg p.o. q.8h.) may be indicated for 24–72 hours, although this is only rarely necessary. Dogs that live in multistory high-rise buildings might also be candidates for antidiarrheal drugs because of the difficult logistics for bringing them outdoors for defecation.

Prognosis

Good to excellent in most cases. Recurrences are common in dogs prone to eating offending foods.

Box 9.6 Practical tip: Use of probiotics in acute or chronic enteritis

- Probiotics are living microorganisms that may modulate intestinal immune function, promote epithelial cell homeostasis, exert neuromodulatory effects, block the effects of pathogenic bacteria, and have nutritional benefits.
- Probiotics designed for use in dogs and cats and manufactured by reputable pharmaceutical or pet food companies are preferred, as over-the-counter products have been shown not to be as reliable. Some products contain one bacterial strain while others include several strains. Also, concentrations of colony-forming units (CFU) vary from 1×10^8 to 1.1×10^{11} CFU per sachet or capsule.
- Very little data is available to support clinically appreciable beneficial effects of probiotics on the GI tract of dogs and cats. Various probiotics have been shown to shorten the duration of acute diarrhea in shelter cats, decrease the time to first normal feces in dogs with acute enteritis, and accelerate improvement of clinical score and recovery of the fecal microbiome in dogs with AHDS. Additionally, a recent pilot study suggested a beneficial effect of probiotics in dogs with lymphoma receiving standard chemotherapy. In an open study of dogs with IBD, a multistrain highly concentrated probiotic administered for 60 days appeared to be as efficient as a combination of prednisone and metronidazole. They were found to increase tight-junction protein expression in another study, suggesting that they may support quicker normalization of mucosal permeability.
- There is a lack of data evaluating optimal treatment duration. The author administers probiotics daily for 2–4 weeks to animals with acute enteritis and for months in dogs and cats with chronic enteritis if positive effects are seen in the first 2–4 weeks.

ACUTE HEMORRHAGIC DIARRHEA SYNDROME

Definition/Overview

Acute hemorrhagic diarrhea syndrome (AHDS) is the name currently used to describe the canine syndrome known in the past as hemorrhagic gastroenteritis (HGE). It has been shown that affected dogs do not have any gastric inflammation. The syndrome can affect dogs of all breeds and all ages, although middle-aged dogs of small and toy breeds seem to be predisposed.

Etiology and Pathophysiology

The etiology of AHDS is not fully understood. *Clostridium perfringens* and its recently discovered pore-forming toxin Net F is present in the feces of many dogs with AHDS and thought to play a key role in the pathogenesis. However, other yet unidentified factors may play a role as well. It is unclear if the clostridial proliferation observed in the duodenum is a cause or a consequence of the disease. AHDS has severe repercussions on species diversity of the intestinal microbiota and causes acute dysbiosis. However, recovery of the microbiome is quick after the affected dogs improve clinically following appropriate treatment.



FIGURE 9.53 Hemorrhagic diarrhea from a dog with acute hemorrhagic diarrhea syndrome.

Clinical Presentation

Acute-onset bloody diarrhea (Figure 9.53), possibly with vomiting and anorexia. Affected dogs are usually very dehydrated and in various stages of hypovolemic shock. Lethargy and abdominal pain are also common.

Differential Diagnosis

Parvovirus infection, bacterial infections, salmon poisoning disease, severe parasite infestations, dietary indiscretion, intestinal volvulus or intussusception, acute pancreatitis, acute liver or kidney disease, hypoadrenocorticism, sepsis, immune-mediated thrombocytopenia, and anticoagulant rodenticide and other toxicoses.

Diagnosis

Initially, affected dogs typically have a high packed cell volume (PCV; sometimes above 65%) and a normal or low serum concentration of total solids (or total proteins, albumin, or globulins). White blood cell counts may be normal, high, or low depending on the severity of disease. Mild thrombocytopenia is common.

Other serum biochemistry changes may include prerenal azotemia, increased liver enzymes, hypoglycemia, and electrolyte abnormalities. Metabolic acidosis is often present. Abdominal radiographs usually show an enteritis pattern with fluid- and gas-filled small intestinal loops.

Management

Aggressive fluid therapy. IV boluses of isotonic crystalloid solutions (10–20 mL/kg) should be given to treat hypovolemic shock if present. Perfusion and cardiovascular status should be reassessed every 15 minutes and further boluses administered as required until normal blood pressure is restored. Fluid deficits should be replaced over a 6- to 12-hour period with crystalloid solutions, adding the maintenance requirements and estimated ongoing losses due to continuing diarrhea. Electrolyte deficits such as hypokalemia should also be corrected. Other treatments include antiemetics and possibly gastric antacids if decreased perfusion of the gastric mucosa is suspected (see Table 9.4). The PCV generally normalizes in response to aggressive fluid therapy, and the serum protein concentration usually drops to levels indicative of hypoproteinemia (transient), with both low serum albumin and globulin concentrations (Figure 9.54).

Systemic use of antibiotics should be avoided in the treatment of AHDS. When endpoints such as time to resolution of diarrhea and length of hospital stay were compared between dogs given amoxicillin and clavulanic acid and those receiving placebo, affected dogs did not benefit from antibiotics. Intravenous broad-spectrum antibiotics should be reserved for severe cases with existing or impending sepsis (Box 9.7). A highly concentrated multistrain probiotic improved recovery of clinical and laboratory parameters in dogs with AHDS (Box 9.6).

Affected dogs should be fasted for 12–24 hours and then offered small quantities of easily digestible food frequently (boiled chicken and rice, adequate commercial prescription diets).

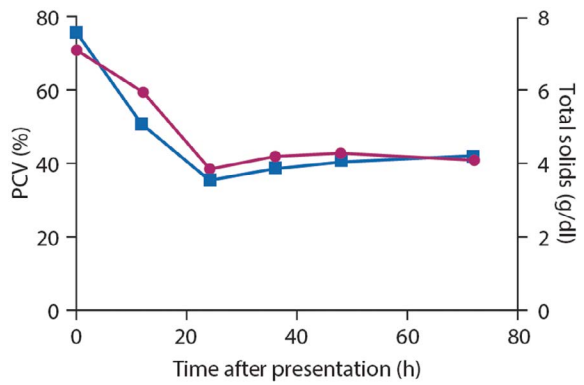


FIGURE 9.54 Evolution of PCV (red line) and total solids (blue line) with treatment in a 6-year-old Miniature Schnauzer dog with acute hemorrhagic diarrhea syndrome. The initial PCV was 70% (reference range 35–55). The total solids plummeted from 7.5 to 3.5 g/dL within 24 hours with aggressive fluid therapy (reference range 5.8–7.5).

Box 9.7 Indications for antibiotic use in dogs with AHDS

- Systemic signs of illness that persist after rehydration, pain management, and symptomatic treatment, for example:
  - Depressed mental status
  - *Tachycardia:* Heart rate > 120/min small-breed dogs, > 100/min large-breed dogs
  - *Tachypnea:* Respiratory rate > 30/min
  - *Hypotension:* Mean arterial pressure < 80 mmHg
  - Evidence of bowel mucosa in the diarrhea
- Signs of systemic inflammation at presentation, for example:
  - Rectal temperature > 39.5°C or 103.1°F
  - WBC < 4,000 or > 25,000/µL
  - Band neutrophils > 2,500/µL
- Presence of an immunocompromising underlying disease, for example:
  - Immunosuppressive treatment
  - Neutropenia
- High probability of ineffective clearance of bacteria by the liver, for example:
  - Portosystemic shunt flow
  - Liver dysfunction

Modified from Unterer S, Busch K: Acute hemorrhagic diarrhea syndrome in dogs. (2021): *Vet Clin North Am Small Anim Pract* 51: 79–92.

Prognosis

Good when dogs are presented early in the course of the disease. Most dogs can be discharged following after a median of 3 days of fluid therapy (range 1–7 days). Serious complications may include disseminated intravascular coagulation, sepsis, and aspiration pneumonia in vomiting animals. AHDS may be fatal if the emergent needs of the patient are addressed too late.

INTESTINAL OBSTRUCTION

Etiology

Small intestinal obstruction most often results from FBs such as peach pits, corncobs, toys, and fishhooks in dogs and linear foreign bodies in cats. Other differential diagnoses for intestinal obstruction include intussusception and neoplasia. Intussusceptions (Figure 9.55) are seen mostly in young animals, particularly in conjunction with severe acute enteritis, such as parvovirus infection or ascarid infestation but can also be seen in cases of chronic diarrhea, such as IBD and intestinal neoplasia. Intestinal volvulus (torsion) is a rare disorder in dogs that involves intestinal rotation at the root of the mesentery, with complete occlusion of the cranial mesenteric artery (Figure 9.56). This results in bowel necrosis, release of toxins, and life-threatening hypovolemic and septic shock. Most cases



FIGURE 9.55 An ileocolic intussusception was diagnosed and surgically removed from a 1-year-old male Beagle with chronic diarrhea. Shown is the cecum that was prolapsed into the ascending colon. (*Courtesy of A. Grooters and K. Saile.*)

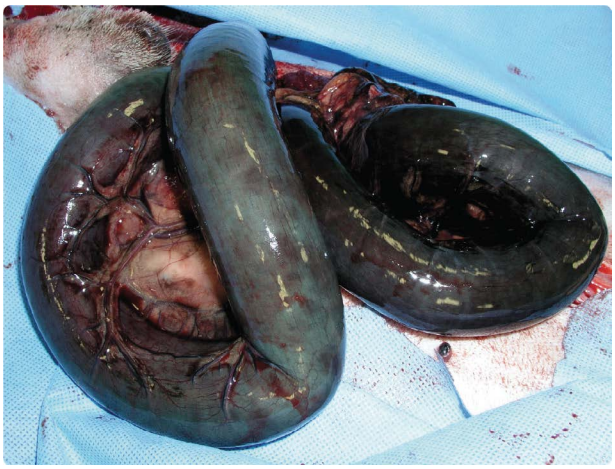


FIGURE 9.56 Intestinal volvulus in a dog. The small bowel loops are dilated with a hemorrhagic, necrotic wall. (*Courtesy of R. Husnik.*)

have been reported in adult, medium-to-large breed male dogs.

Pathophysiology

Small intestinal obstruction generally causes an accumulation of intestinal content, fluid, or gas in the loops located craniad to the site of obstruction. Intussusceptions are thought to occur as a complication of abnormal intestinal motility associated with enteritis or with abnormal intestinal masses.

Clinical Presentation

Clinical findings are related to the site, severity, and cause of the obstruction. Complete upper intestinal obstruction results in severe vomiting associated with fluid loss and dehydration and possible hypovolemic shock. Partial obstructions often present with an insidious onset of vomiting and intermittent chronic diarrhea.

Differential Diagnosis

Dietary indiscretion or other causes of acute gastroenteritis and acute pancreatitis are the top differentials.

Diagnosis

The history is sometimes helpful for raising suspicion of a FB. A thorough physical examination is important in all cases, including inspection of the base of the tongue for linear foreign bodies, especially in cats (see Chapter 2.17, **Figure 2.17.4**). Abdominal palpation may reveal discomfort or pain, and an FB or intussusception may be identifiable. Abdominal radiographs are essential to document or rule out obstruction (**Box 9.8**). Signs of intestinal obstruction are readily recognizable (**Figures 9.57–9.61**). In severe cases, signs of bowel

Box 9.8 Practical tip: Antiemetics may mask the signs of gastrointestinal foreign bodies

Several effective antiemetics are currently available to veterinarians:
- Maropitant (1 mg/kg IV or SC q.24h.)
- Metoclopramide, which can be administered as a CRI to dogs and cats receiving IV fluids (1–2 mg/kg q.24h.)
- Ondansetron (0.5–1 mg/kg IV or SC q.12h.)

These antiemetics may suppress vomiting in patients with gastric or small intestinal foreign bodies and thus delay proper treatment involving foreign body retrieval via exploratory celiotomy or endoscopy (for gastric foreign bodies only). Delayed treatment may make it necessary to resect intestinal tissue (when enterotomy would have been sufficient with early intervention) or even increase the risk of perforation. Consequently, abdominal radiographs should be performed as soon as possible in dogs and cats with history and clinical signs compatible with a GI foreign body in order to rule out obstruction.

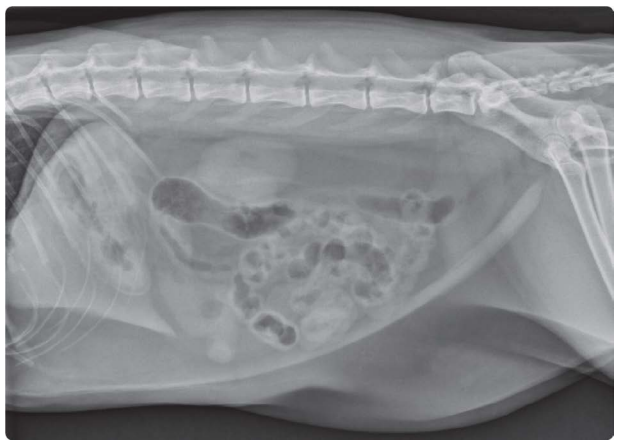


FIGURE 9.57 Cat with a linear foreign body. Right lateral abdominal radiograph. All small intestinal loops are located centrally, diffusely plicated, and corrugated in appearance. There are multiple, rounded, comma-shaped, and paisley-shaped gas opacities of varying size throughout the small bowel.



FIGURE 9.58 Ventrodorsal radiograph of the same cat as Figure 9.57. The arrow points to a caudally displaced small bowel loop that displays a plicated appearance with content of mixed soft tissue and gas density. (*Courtesy of L. Gaschen.*)

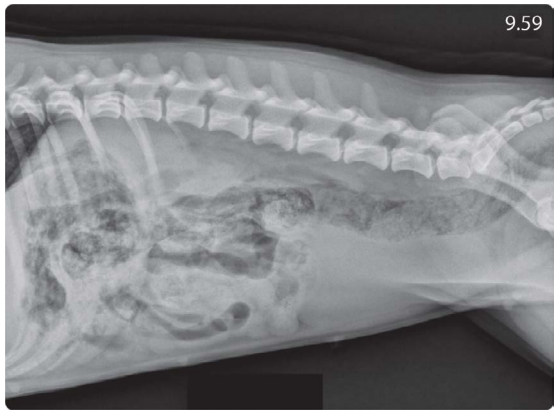
perforation, such as decreased serosal detail and free abdominal gas, may be present as well. Additionally, abdominal ultrasound may help confirm the diagnosis of intussusceptions and masses. A minimum database consisting of CBC, biochemistry panel, and urinalysis may help characterize the fluid and electrolyte losses and document inflammation or sepsis in complicated cases.

Management

Treatment of intestinal obstruction involves surgical removal of the cause of the obstruction (Figure 9.61). Broad-spectrum antibiotics should be given IV to patients with signs of intestinal perforation (e.g., amoxicillin 20 mg/kg q.8h., enrofloxacin 10 mg/kg q.24h., and metronidazole 10–15 mg/kg q.12h.).

Prognosis

In the absence of complications such as intestinal perforation, the prognosis after surgical extraction of a FB is excellent. The risk of suture dehiscence at the enterotomy or enterectomy site is higher in the presence of peritonitis (i.e., perforation). There is a risk of recurrence for intussusceptions unless the underlying disease is controlled. For intestinal volvulus, the prognosis is usually grave.







FIGURES 9.59–9.61 A 2-year-old female Jack Russell Terrier presented with a 4-day history of vomiting. (Figure 9.59) Right abdominal radiograph. The serosal detail is decreased throughout the abdomen. The stomach, small intestines, and colon contain a large amount of material with heterogeneous soft tissue and gas density. (Figure 9.60) Ventrodorsal radiograph of the same dog. (*Courtesy of LSU SVM Diagnostic Imaging Service.*) (Figure 9.61) Grass is extracted through a midjejunal enterotomy. Large amounts of grass were present throughout the gastrointestinal tract and were impacting the small intestine. (*Courtesy of A. Grooters and K. Saile.*)

CHRONIC ENTERITIS

PARASITIC ENTERITIS

CANINE SCHISTOSOMIASIS

Etiology

Heterobilharzia americana is the agent of canine schistosomiasis, an uncommon disease endemic in the Southeast United States and areas bordering the Gulf of Mexico. Raccoons are the parasite's reservoir host. Freshwater snails are obligatory intermediate hosts.

Pathophysiology

Percutaneous infection occurs through free-swimming cercariae. After migration, adult *Heterobilharzia* produce ova in the terminal branches of the mesenteric veins. The ova are shed through the intestinal mucosa in the feces. Granulomatous inflammation can be found in the intestinal submucosa (Figure 9.62) and in other organs as well.

Clinical Presentation

Acute-to-chronic mixed small and large bowel diarrhea. Hyporexia/anorexia, weight loss, often cachexia, lethargy, melena, and/or hematochezia are common.

Differential Diagnosis

Includes IBD (including protein-losing enteropathy [PLE]), severe parasitic enteritis, intestinal neoplasia.

Diagnosis

Blood work may reveal anemia, hypoalbuminemia, hyperglobulinemia, and eosinophilia. Hypercalcemia is present in 11%–50% of affected dogs and may be associated with polyuria/polydipsia and/or azotemia. Abdominal radiographs and ultrasound may show evidence of mineralization of the small intestinal wall, particularly in the submucosal layer. Diagnosis is confirmed with saline sedimentation of feces or a commercially available fecal PCR.

Management

Praziquantel (25 mg/kg q.8h. for 2–3 days), possibly in combination with fenbendazole (50 mg/kg q.24h. for 10 days).

Prognosis

Depends on the severity of lesions at presentation. In retrospective studies, the survival rate 6 or more months after diagnosis was between 55% and 73.5%.

GIARDIASIS

Definition/Overview

Studies concerning the prevalence of giardiasis in the canine and feline populations report rates of 5%–10% in healthy pets and pets presented for veterinary care. The prevalence is greatest in patients that live in high-density group housing, especially when recommended disinfecting protocols are not carried out optimally. In such cases, *Giardia* cysts can easily survive in the environment and continuously infect new animals or reinfect animals after they have been treated.

Etiology

Giardia duodenalis is a flagellated protozoan that exists in two forms: A motile trophozoite of piriform to ellipsoidal shape (Figure 9.63) and a cyst form that is highly resistant in the environment. Cysts are absorbed with contaminated

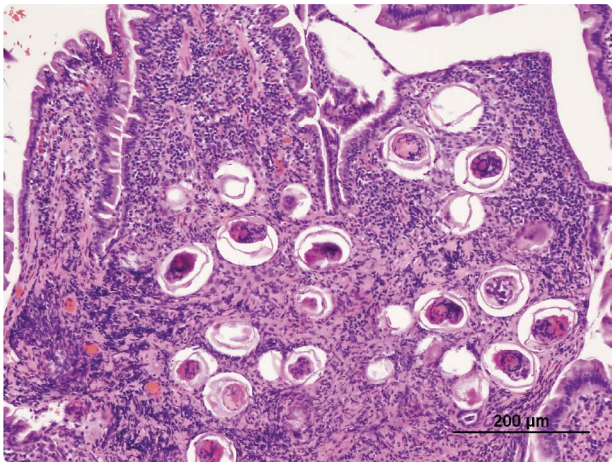


FIGURE 9.62 Photomicrograph of a duodenal mucosal sample from a dog with canine schistosomiasis. There are numerous eggs present in the mucosa that are associated with granulomatous inflammation. (*Courtesy of M. Im Hof.*)

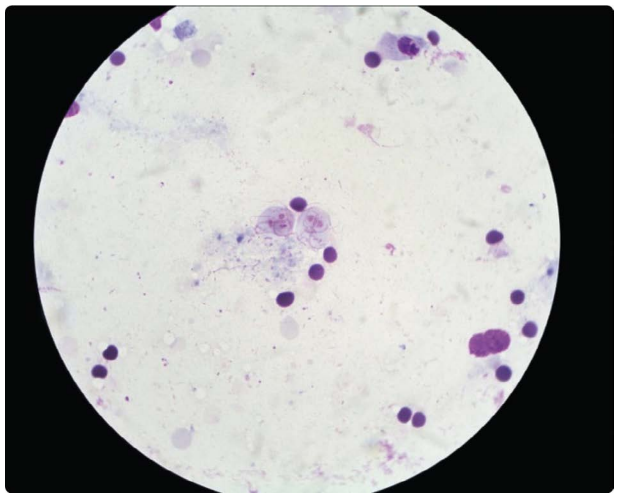


FIGURE 9.63 Photomicrograph of a fecal smear from a dog with *Giardia* infection. Two trophozoites are visible in the middle of the picture. Wright–Giemsa stain. (*Courtesy of R. Husnik.*)

food or water and release trophozoites into the small intestinal lumen. Trophozoites multiply by cell division and become encysted. *Giardia* cysts have four nuclei and a thin envelope. Under favorable conditions, they can persist for 3 weeks or even longer in the environment.

Giardia isolates are further divided into several different genotypes or assemblages with specific host ranges. The zoonotic potential of canine and feline giardiasis is very low. Consumption of water contaminated with *Giardia* cysts is the main origin of infections in people.

Pathophysiology

Trophozoites are found in highest concentration in the duodenum. They attach to the mucosal epithelium and cause disease by affecting epithelial permeability.

Clinical Presentation

Diarrhea with watery feces and admixed mucus. In severe and chronic infections, malabsorption and weight loss may occur and the animal may be in poor general condition. Importantly, many infected dogs and cats do not show clinical signs.

Differential Diagnosis

Other causes of chronic, intermittent diarrhea and malabsorption, such as other parasite infections, chronic enteropathies, exocrine pancreatic insufficiency, and possibly alimentary lymphoma.

Diagnosis

Several diagnostic tests are available for the diagnosis of *Giardia* infections in dogs and cats (Table 9.8 and Figure 9.63). Confirmation of diagnosis can be complicated by the fact that cysts are shed intermittently.

TABLE 9.8 Diagnostic tests for *Giardia* in the feces of dogs and cats

Diagnostic test	Target	Sensitivity
Flotation with zinc sulfate or sugar centrifugation	Cysts	– Intermediate, operator dependent – Can be increased from 70% to 90% if three samples collected at 2- to 3-day intervals are examined
IFA or ELISA	Specific antigens	– Intermediate to good – Diagnostic accuracy of cage-side ELISA test is equivalent to that of antigen tests run in the laboratory
PCR	DNA sequences	– Intermediate to high – Only recommended for determination of specific assemblage

DNA, deoxyribonucleic acid; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assays; PCR, polymerase chain reaction.

Management

The goal of treatment is to stop diarrhea and attempts to fully eliminate *Giardia* infection may not be successful. In dogs, metronidazole (25–30 mg/kg p.o. q.12h. for 5–8 days) and fenbendazole (50 mg/kg p.o. q.24h. for 5 days) are most used and appear to be equally efficacious. In cats, metronidazole benzoate (25 mg/kg p.o. q.12h. for 7 days) is well tolerated and eliminates cyst shedding within 7–10 days of treatment. Fenbendazole can also be used at the same dose as in dogs, although its efficacy may be inferior. Other drugs, including tinidazole (44 mg/kg p.o. q.24h. for 3 days), can also be used in cats.

An increased rate of resistance of *Giardia* spp. to metronidazole and other antigiardial agents has been reported in human patients. However, no published data concerning drug resistance of canine or feline giardiasis are currently available.

Dogs kept in group housing should be removed from their runs, shampooed, and rinsed with quaternary ammonium-based disinfectants. The runs should be cleaned and disinfected before reuse. Quaternary ammonium containing disinfectants have shown an excellent efficacy for inactivating *Giardia* cysts in a short period of time.

Prognosis

Good.

FUNGAL AND OOMYCETAL ENTERITIS

HISTOPLASMOSIS

Etiology

Histoplasma capsulatum is a dimorphic saprophytic fungus that can be found in temperate and subtropical climates. Most cases of canine or feline histoplasmosis described in the literature come from the Americas, particularly from the Ohio, Missouri, and Mississippi River Valleys. Other endemic regions include Mexico and South American areas.

Pathophysiology

Infection occurs predominantly infected by inhalation of microconidia (mycelium) that transform into yeast and infect macrophages in the lungs. The infection can remain local (respiratory tract). If it propagates, it generally also involves the GI tract. Sporting and working dogs are at increased risk.

Clinical Presentation

GI signs include chronic small or large bowel diarrhea. Weight loss and poor body condition score are common. Affected animals are sometimes presented with PLE. Other organ systems may be infected and cause additional clinical signs.

Differential Diagnosis

Other causes of chronic diarrhea and weight loss such as parasite infections, IBD, and alimentary lymphoma.

Diagnosis

The most reliable diagnosis consists in identifying the organism on cytologic smears from fine-needle aspirates of lymph nodes, from rectal scrapings (Figure 9.64), or on histologic analysis of intestinal biopsies. Alternately, urine antigen tests have a reasonable sensitivity, although there is cross-reactivity with other systemic fungi such as *Blastomyces*.

Management

First-line treatment includes itraconazole (10 mg/kg once daily) and must be continued for at least 6 months. Lesion resolution (as evidenced with clinical and imaging examinations) should guide the decision to discontinue treatment.

Prognosis

Intestinal histoplasmosis carries a fair to good prognosis, which is negatively affected by multisystemic extent and increasing severity of the disease.

PYTHIOSIS

Etiology

Pythium insidiosum is a eukaryotic microorganism from the class Oomycota found in subtropical climates (such as the southeast and Gulf of Mexico regions of the United States) and sporadically in other areas. It causes severe, progressive GI disease. It affects particularly large breed male dogs, probably because of their increased risk of environmental exposure. High infection rates occur where dogs are exposed to small bodies of water which is favored by the organism.

Pathophysiology

Motile *Pythium* zoospores are attracted to and invade damaged GI mucosa. The disease is characterized by transmural inflammation that may affect one or more of the following sites: Stomach, gastric antrum, small intestine, colon, and rectum (rarely the esophagus) (Figures 9.15 and 9.65). Local lymph nodes are often reactively enlarged.

Clinical Presentation

Young, large breed dogs with access to the outdoors and swimming areas are most commonly affected. History commonly indicates a progressive illness. Vomiting, diarrhea, and weight loss (Figure 9.66) are also commonly observed, with possible hyporexia. In advanced cases, clinical features are suggestive of obstruction of the proximal GI tract, with vomiting and a palpable intestinal mass. Poor body condition is frequently present. Interestingly, lethargy and other signs of systemic illness are observed only in severe cases as a consequence of complete GI obstruction or GI perforation.

Differential Diagnosis

Intestinal FB, histoplasmosis, parasitic enteritis, IBD, small intestinal neoplasia.

Diagnosis

Peripheral eosinophilia, anemia, hypoalbuminemia, and hyperglobulinemia may be present. Abdominal

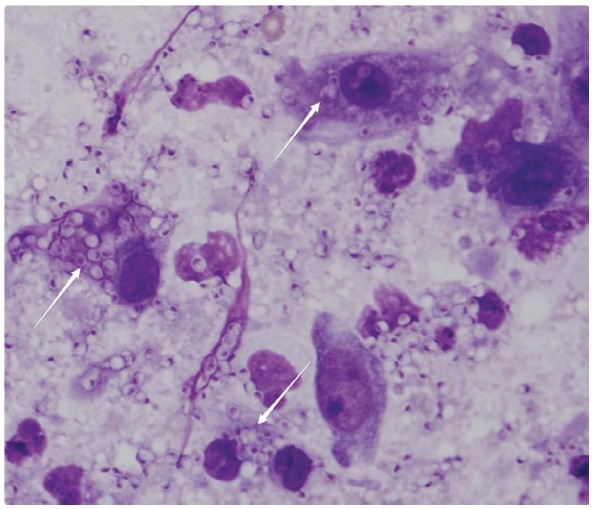


FIGURE 9.64 Photomicrograph of a fine-needle aspirate of a mesenteric lymph node from a dog with intestinal histoplasmosis. The arrows point to macrophages filled with yeast forms of *H. capsulatum*. Wright–Giemsa stain. (*Courtesy of S. Gaunt.*)

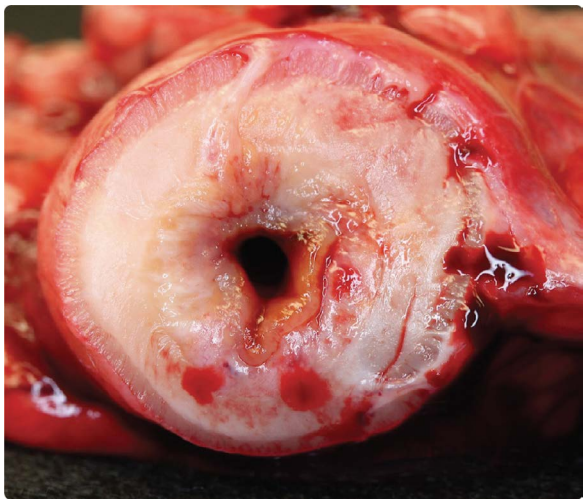


FIGURE 9.65 Cross-section of a resected jejunal segment from a 2-year-old mixed-breed dog with intestinal pythiosis. The wall is severely thickened, and the normal structure is not recognizable. The severe narrowing of the jejunal lumen caused partial intestinal obstruction. (*Courtesy of A. Grooters.*)

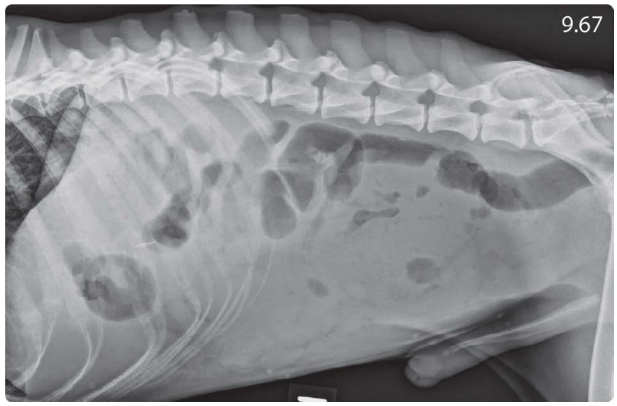


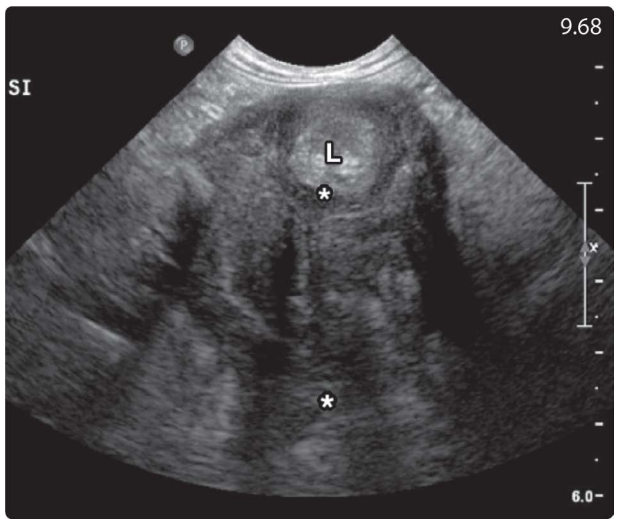
FIGURE 9.66 Two-year-old female spayed Boxer dog with a progressive history of chronic, intermittent vomiting. The dog has lost weight and is in poor body condition. Gastric antral pythiosis was diagnosed. (*Courtesy of K. Ryan.*)

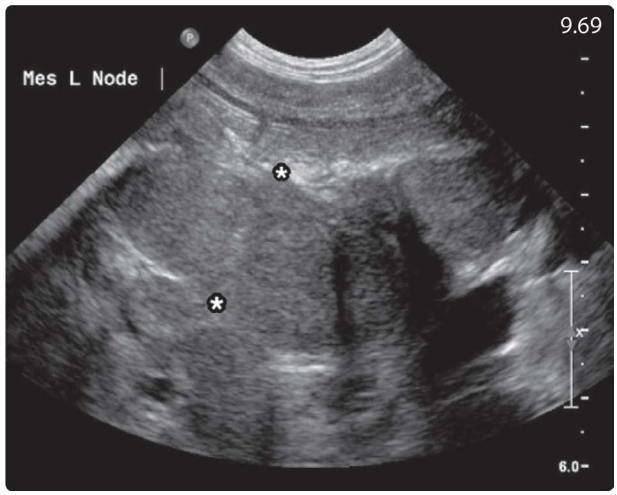
imaging: Radiographs may reveal an abdominal mass with or without obstructive pattern (Figure 9.67); ultrasound helps locate the affected segment, which is characterized by transmural thickening with disappearance of the normal small intestinal wall structure (Figure 9.68) and lymph node enlargement (Figure 9.69). Ultrasound-guided fine-needle aspirates can be performed. An ELISA test for detection of serum antibodies is available (locations can be found on the web). Histopathologic diagnosis is granulomatous enteritis affecting mostly the submucosa and muscularis layers (Figure 9.70). Oomycetal organisms may be detected with special stains (Figure 9.71) or with immunohistochemistry. Fresh infected tissue may also be cultured to confirm the diagnosis.

Management

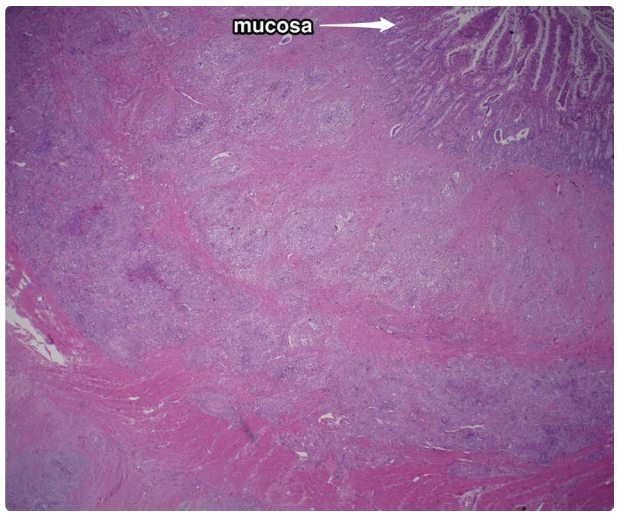
Aggressive surgical resection of the lesion with 5 cm clean tissue margins on both sides is the preferred treatment for GI pythiosis. Enlarged abdominal lymph nodes should be biopsied, but their resection is not absolutely essential since they are rarely infected. Except in cases where total resection with 5 cm clean margins could be performed (usually midjejunal masses), medical treatment with a combination of itraconazole (10 mg/kg p.o. q.24h.) and terbinafine (5–10 mg/kg p.o. q.24h.) is recommended. Prednisone (1 mg/kg p.o. q.24h.) can also be used to decrease local inflammation and to palliate clinical signs in the short term. ELISA serology should be performed at the time of diagnosis and 3 months postoperatively, and medical treatment can be discontinued if the titer decreases by greater than 50%.

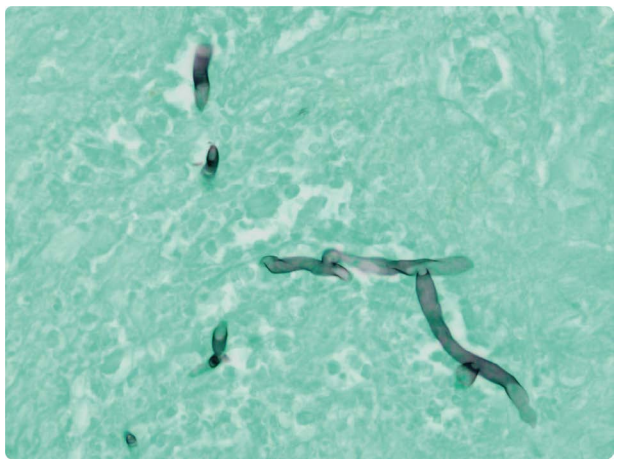






FIGURES 9.67–9.69 Two-year-old male Catahoula Cur with intestinal pythiosis. **(Figure 9.67)** Left lateral abdominal radiograph. There is an ill-defined central abdominal soft tissue mass that displaces the intestines dorsally and ventrally. **(Figure 9.68)** Abdominal ultrasound. The cross-section of this small intestinal segment reveals a markedly eccentrically thickened wall (~3 cm) with abnormal layering (between asterisks). L, intestinal lumen. **(Figure 9.69)** Abdominal ultrasound. Note the much enlarged mesenteric lymph node (between asterisks). The measured size was 2.2 × 6.4 cm. (*Courtesy of LSU SVM Diagnostic Imaging Service.*)





FIGURES 9.70 and 9.71 Dog with pythiosis affecting the jejunum. **(Figure 9.70)** Low-magnification photomicrograph of the intestinal wall. The mucosa is visible at the top right of the image (arrow); the deeper structures (submucosa, muscularis) are obliterated by granulomatous and eosinophilic inflammation. H&E stain. **(Figure 9.71)** High-magnification photomicrograph of an intestinal lesion. Infectious organisms with morphology suggestive of *P. insidiosum* are nonspecifically stained. Grocott methenamine silver stain. (*Courtesy of LSU SVM Pathology Service.*)

Prognosis

Poor, except if complete surgical resection of the GI lesion is possible. Recurrence is common unless full resection with clean margins could be achieved. The disease is fatal if untreated.

CHRONIC CANINE ENTEROPATHY

Definition/Overview

The general term "chronic enteropathy" (CE) is used frequently to describe dogs and cats with chronic intestinal diseases of unknown origin. Diet-responsive CE (DRCE), idiopathic gut dysbiosis (also called antibiotic-responsive diarrhea), and inflammatory bowel disease (IBD) are different forms of chronic enteropathy. They may form a continuum, with diet responsive diarrhea (DRD) being the mild form of CE and IBD requiring immunosuppressive treatment representing the severe form of the disease.

Etiology

Based on research in rodent models, people, dogs, and cats, IBD results from a combination of factors that include dysregulation of the immune system and its interactions with intestinal microbiota and/or dietary components, severe changes in the gut microbiota affecting its richness, diversity, and the abundance of various bacterial taxa, and compromised integrity of the intestinal mucosal barrier.

Specific forms of CE have been recognized as occurring more frequently in several canine breeds. For instance, in the Southeast UK, Weimaraners, Rottweilers, German Shepherd Dogs, Border Collies, and Boxers were at increased risk of developing IBD. Examples of established breed associations include lymphangiectasia and duodenal crypt inflammation with protein-losing enteropathy (PLE) in Yorkshire Terriers, PLE also in Border Collie, German Shepherd Dog, and Rottweiler, PLE and protein-losing nephropathy in Soft-Coated Wheaten Terriers, and cobalamin deficiency in Shar Peis. German Shepherd Dogs have a high prevalence of idiopathic intestinal dysbiosis and IBD.

Pathophysiology

Recognition of commensal intestinal microbiota by the innate immune system is altered. Toll-like receptors (TLRs) are pattern-recognition receptors located on immune and epithelial cells that mediate the interactions between intestinal microbiota and the host. Polymorphisms in various TLRs have been identified in the intestinal mucosa of dogs with CE, which may trigger an inflammatory response. In addition, significant changes in the gut microbiota were detected. In dogs and people, IBD reduces the diversity of the intestinal microbiome. Furthermore, in dogs with IBD, the bacterial taxa *Firmicutes* (including the *Clostridiales*), *Bacteroidetes*, and *Fusobacteria* are diminished, and *Proteobacteria* (including *Enterobacteriaceae*) are increased. It is not clear whether these changes are the origin of the intestinal inflammation or if they reflect the altered environment in the chronically inflamed gut, or both. Intestinal dysbiosis is accompanied by changes in the gut metabolome. For instance, *Clostridium hiranonis* is a bacteria involved in transformation of primary into secondary fecal unconjugated bile acids (FUBA). These have numerous important functions locally and act as signaling molecules to remote organs. Abundance of *C. hiranonis* and concentration of secondary FUBA are decreased in dogs with IBD, and this has consequences both within and beyond the GI tract. Similarly, *Faecalibacterium* is associated with production of

short-chain fatty acids that are used as a source of energy by colonic epithelial cells and are decreased in the presence of intestinal inflammation.

Clinical Presentation

Chronic or chronic, intermittent diarrhea of more than 3 weeks' duration. Mild CE may cause intermittent clinical signs, whereas progressive and severe clinical signs are common in severe IBD. Poor body condition with poor hair coat is frequent with severe disease. Dehydration is possible. Thickened small intestinal loops may occasionally be palpated. Animals may show pain or discomfort on abdominal palpation. Ascites, hydrothorax, and peripheral edema may occur in cases of significant protein loss (e.g., PLE). Clinical activity scoring systems have been validated for use in the dog: CIBDAI (Canine Inflammatory Bowel Disease Activity Index) and CCECAI (Canine Chronic enteropathy Clinical Activity Index) (Table 9.9). Clinical activity scoring is useful for documenting the severity of clinical signs at presentation and for accurate evaluation of clinical response to treatment.

Differential Diagnosis

General differentials include chronic intestinal FB, intestinal parasitoses, fungal enteritis, bacterial enteritis, and diseases originating outside the GI tract such as chronic kidney disease, chronic liver disease, chronic pancreatitis, exocrine pancreatic insufficiency, and atypical hypoadrenocorticism.

Diagnosis

Diagnosis of CE consists of an elimination process to rule out other diseases of known etiology that may cause similar clinical signs: Fecal flotation and a *Giardia* antigen test should be performed in all dogs. Alternatively, empiric parasiticide treatment can be administered (e.g., fenbendazole, 50 mg/kg q.24h. for 3–5 days). Subsequently, the diagnostic process is different for dogs with mild clinical signs and no evidence of complications such as hypoproteinemia and for dogs that are more severely affected.

Mildly affected dogs can undergo a treatment trial with a novel protein or hydrolyzed peptide diet without further diagnostics (see Management), while severely affected dogs should be evaluated more thoroughly with collection of a minimal database, including CBC, serum biochemistry, and urinalysis. Presence of hypoalbuminemia, often accompanied by hypoglobulinemia, suggests PLE, particularly if other causes can be ruled out. Sensitivity of abdominal ultrasound is intermediate, and scans may be normal or show focal or diffuse loss of wall layering, presence of mucosal striations or spicules, wall thickening, and enlarged and/or hypoechoic mesenteric lymph nodes. If lesions are present, localization to a specific intestinal segment may be helpful (Figures 9.72 and 9.73).

Upper GI endoscopy and exploratory celiotomy are both good procedures for collecting intestinal mucosal biopsy samples, and each offers different advantages and drawbacks. Observation of severe mucosal lesions during duodenoscopy is a negative prognostic factor.

Procurement of biopsy samples may be useful to further evaluate disease severity. Biopsy specimens of adequate quality and quantity are required for accurate interpretation by pathologists. The most important justification for histology is to rule out a neoplastic infiltrate. However, it is also useful to evaluate the magnitude of intestinal mucosal inflammation based on the severity and type of the infiltrate and the severity of the architectural mucosal changes, although histopathological and clinical severity of disease correlate poorly overall. There

TABLE 9.9 Clinical activity indices used in dogs with chronic enteropathies

CIBDAI[1]	CCECAI[2]
A: Attitude/activity 0 = normal 1 = slightly decreased 2 = moderately decreased 3 = severely decreased **B: Appetite** 0 = normal 1 = slightly decreased 2 = moderately decreased 3 = severely decreased **C: Vomiting** 0 = no vomiting 1 = mild (1 episode/week) 2 = moderate (2–3 episodes/week) 3 = severe (>3 episodes/week) **D: Stool consistency** 0 = normal 1 = slightly soft feces 2 = very soft feces 3 = watery diarrhea **E: Stool frequency** 0 = normal 1 = slightly increased (2–3 times daily) or fecal blood, mucus, or both 2 = moderately increased (4–5 times daily) 3 = severely increased (>5 times daily) **F: Weight loss** 0 = none 1 = mild (<5% body weight) 2 = moderate (5–10% body weight) 3 = severe (>10% body weight) **Evaluation of scores** CIBDAI 0–3: No clinical significance CIBDAI 4–5: Mild IBD CIBDAI 6–8: Moderate IBD CIBDAI 9 and above: Severe IBD	**A + B + C + D + E + F + G: Serum albumin concentration** 0 = >20 g/L or 2.0 g/dL 1 = 15–19.9 g/L or 1.5–2.0 g/dL 2 = 12–14.9 g/L or 1.2–1.4 g/dL 3 = <12 g/L or <1.2 g/dL **H: Ascites and peripheral edema** 0 = none 1 = mild ascites or peripheral edema 2 = moderate amount of ascites or peripheral edema 3 = severe ascites/pleural effusion and peripheral edema **I: Pruritus** 0 = no pruritus 1 = occasional episodes of itching 2 = regular episodes of itching that stop when the dog is asleep 3 = dog regularly wakes up because of itching **Evaluation of scores** CCECAI 0–3: No clinical significance CCECAI 4–5: Mild enteropathy CCECAI 6–8: Moderate enteropathy CCECAI 9–11: Severe enteropathy CCECAI 12 and above: Very severe enteropathy

1 Jergens AE, Schreiner CA, Frank DE, et al. (2003). A scoring index for disease activity in canine inflammatory bowel disease. *J Vet Intern Med* 17(3): 291–297.

2 Allenspach K, Wieland B, Gröne A, et al. (2007). Chronic enteropathies in dogs: Evaluation of risk factors for negative outcome. *J Vet Int Med* 21: 700–708.



FIGURE 9.72 Abdominal ultrasound of a dog with inflammatory bowel disease, crypt disease, and protein-losing enteropathy. The normal layers of the intestinal wall are not recognizable in this oblique section of a small intestinal loop. Hyperechogenic striations are present and run from the lumen to the serosa. There is free abdominal fluid. (*Courtesy of LSU SVM Diagnostic Imaging Service.*)

are now established scoring systems that take both architectural and inflammatory mucosal changes into account. Inflammatory infiltration may be of varying severity and consist of lymphocytes and plasma cells (lymphoplasmacytic enteritis), eosinophils, neutrophils or macrophages, or combinations thereof (Box 9.9). Examples of small intestinal mucosal architectural changes include villus stunting and/or fusion (Figure 9.74), surface epithelial injury, crypt distension (Figure 9.75), lacteal dilation (Figure 9.76), and mucosal fibrosis. It is noteworthy that in animals responding to treatment, histopathologic

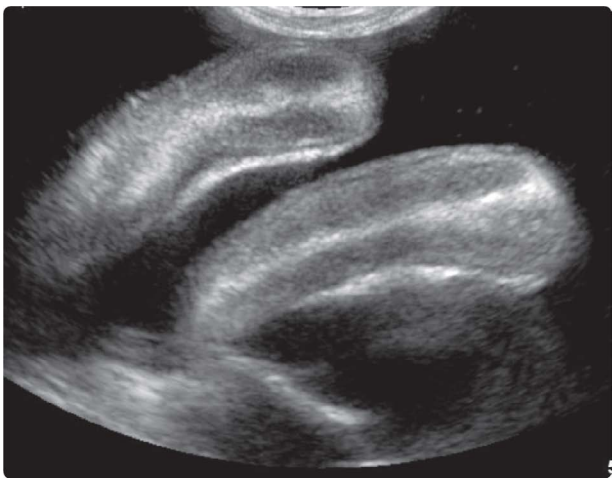


FIGURE 9.73 Abdominal ultrasound of another dog with severe inflammatory bowel disease and protein-losing enteropathy. The normal layers of the intestinal wall are obliterated by an irregular hyperechogenic pattern. There is free abdominal fluid. (*Courtesy of LSU SVM Diagnostic Imaging Service.*)

Box 9.9 Further considerations with different types of intestinal infiltrates

Lymphoplasmacytic enteritis: Most common type of inflammatory infiltrate, nonspecific. A mild-to-moderate lymphoplasmacytic mucosal infiltrate may be present in the absence of clinical signs.

Eosinophilic enteritis: Rule out parasitic enteritis or allergic causes and in cats eosinophilic syndrome. Idiopathic eosinophilic enteritis may occur in dogs and cats. While it usually responds well to steroids in dogs, this disorder is often steroid resistant in cats.

Neutrophilic (or suppurative) enteritis: Bacterial infectious component cannot be ruled out, and treatment with broad-spectrum antibiotic should be considered alone or in association with immunosuppressive drugs.

Granulomatous enteritis: Rule out fungal enteritis. Idiopathic transmural granulomatous enteritis usually carries a poor prognosis. See also granulomatous colitis below.

lesions do not seem to improve in correlation with clinical signs. This finding suggests that CE can be controlled clinically but not healed.

Management

In most instances, the goal of treatment is to manage the clinical signs. Full recovery is possible in mild cases.

The standard approach for a dog with mild-to-moderate chronic recurrent diarrhea of unknown origin without systemic repercussions is to initiate a food trial with a novel protein or hydrolyzed peptide diet. In numerous studies from locations around the world, between one-half and two-thirds of dogs with signs of CE responded to this simple dietary approach within 10–14 days. Because DRCE is so common, a second

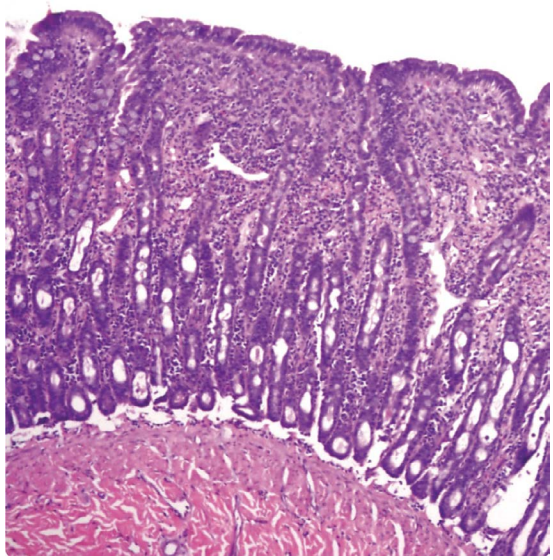


FIGURE 9.74 Photomicrograph of the duodenal mucosa of a 10-year-old female spayed Domestic Shorthair cat with chronic inflammatory bowel disease. There is marked blunting and fusion of the intestinal villi (compared with **Figure 9.44**), and a moderate lymphoplasmacytic infiltrate. H&E stain.

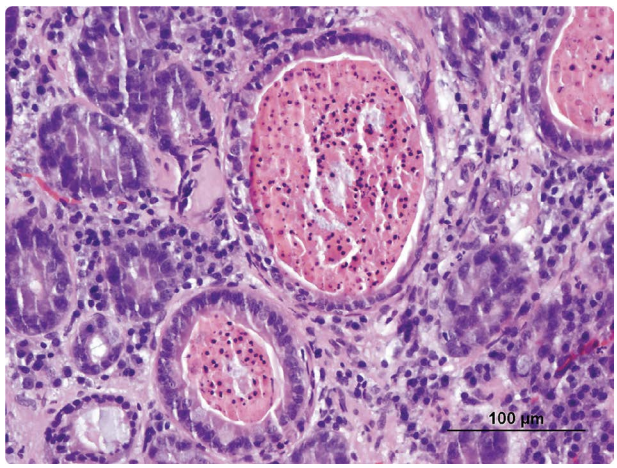


FIGURE 9.75 Photomicrograph of the duodenal mucosa of a dog with protein-losing enteropathy. Two intestinal crypts are markedly distended and filled with necrotic material. The diagnosis was moderate lymphocytic plasmacytic duodenitis with severe crypt lesions. H&E stain.

food trial with another novel protein or hydrolyzed peptide diet should be considered for dogs who do not respond to the first trial.

Although there is only little evidence supporting their beneficial effects in dogs with CE, probiotics, particularly the high-dose multistrain products, are often included in the treatment plan (Box 9.6).

While dysbiosis occurs in most dogs with IBD, a subset of young large breed dogs with CE (particularly but not exclusively German Shepherd Dogs) respond to prolonged treatment with antimicrobials such as tylosin (20 mg/kg p.o. q.12h.) or metronidazole (10–15 mg/kg p.o. q.12h.). This may result from an inability of these dogs' immune systems to interact adequately with their intestinal microbiota. Clinical experience accumulated over the past decades indicates that prolonged treatment (4–8 weeks) is necessary, and that relapses are common.

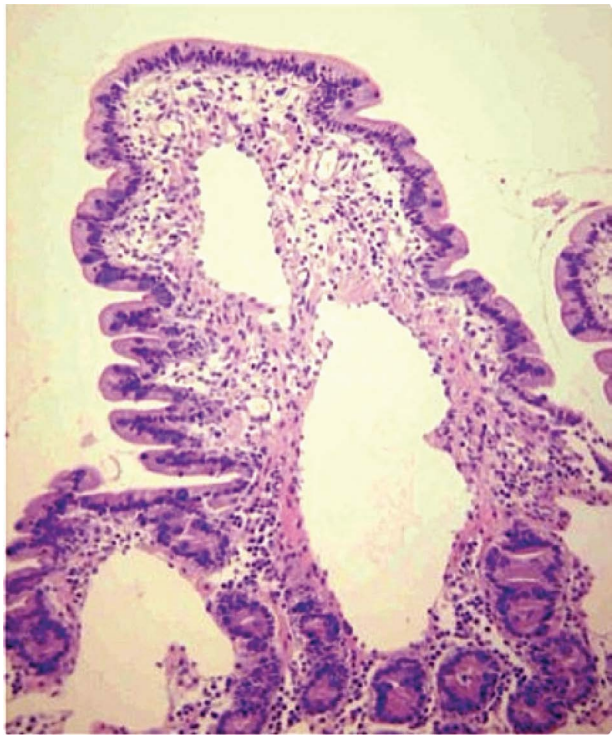


FIGURE 9.76 Photomicrograph of the duodenal mucosa of a Yorkshire Terrier with protein-losing enteropathy. The villus is markedly distended, and dilated lacteals partially filled with eosinophilic material are visible. The diagnosis was moderate idiopathic lymphangiectasia. H&E stain.

In refractory cases, and in dogs with severe disease and evidence of systemic involvement, a more thorough workup with acquisition of a minimal database should be initiated (see Diagnosis).

In dogs with histopathologic evidence of IBD, immunosuppressive doses of prednisone or prednisolone (Table 9.10) are generally the mainstay of initial treatment.

TABLE 9.10 Dosage of oral immunosuppressive drugs used in the treatment of inflammatory bowel disease in small animals

Drug	Canine dose	Feline dose	Side effects
Prednisone, prednisolone	– 1–2 mg/kg q.12–24h. – For dogs > 25 kg, 50–60 mg/m^2 body surface area per day is recommended with a maximum daily dose is 80 mg per dog	– Prednisolone preferred – Same dose as canine	– In dogs, they include polyuria/polydipsia, panting, alopecia, pot-bellied appearance, calcinosis cutis – Rare in cats, may cause diabetes mellitus
Budesonide	– 3 mg/m^2 q.24h.	– 1 mg per cat q.24h.	– Same as above
Azathioprine	– Initially 2 mg/kg q.24h. for 3 weeks, then 1–2 mg/kg q.48h. – Up to 3 weeks of treatment may be necessary for the drug to reach maximal effect	– Do not use in cats	– Hepatotoxicity, pancreatitis, rarely bone marrow suppression
Chlorambucil	– Initially 4–6 mg/m^2 q.24h. for the first 7–21 days, then the dose can be decreased by 25%–33% or the dosage interval increased to every 2–3 days	– 2 mg per cat 3 times weekly	– Rarely bone marrow suppression
Cyclosporine	– 5 mg/kg q.12–24h.	– Same as canine	– Vomiting, nausea, gingival hyperplasia

Initially, very high doses (e.g., 2 mg/kg q.12h.) are recommended for a few days, followed by a regular immunosuppressive dose (2 mg/kg per day in 1 dose or divided into 2 doses). Dietary treatment consists of hydrolyzed peptide or novel protein diet, which has been shown to be superior to easily digestible low-fat diet for long-term maintenance of remission in moderate-to-severe canine IBD. A recheck is scheduled after 1–2 weeks to reassess the situation. In cases showing good response, the dose of prednisone should be maintained for another 2 weeks, then slowly decreased in 2- to 4-week steps.

Treatment failure should prompt the clinician to review the diagnosis and ascertain that no mistakes or erroneous assumptions were made in the diagnostic process. Refractory IBD patients must be examined thoroughly to detect intercurrent diseases that may be contributing to treatment failure. For instance, a significant proportion of dogs with IBD (particularly those with PLE) may develop hypocobalaminemia because of severe involvement of the distal small intestine. Cobalamin deficiency may cause a delayed response or lack of response to adequately designed immunosuppressive treatment. Serum cobalamin concentration should be determined. Supplementation is essential in these animals and can occur either subcutaneously or orally (Table 9.11). Relatively frequently, dogs with moderate-to-severe IBD require treatment with a combination of immunosuppressive agents (Table 9.10). In cases with unacceptable corticosteroid side effects, another immunosuppressive drug should be added to allow decreasing the prednisone dose. Alternatively, budesonide can be used. Budesonide is a glucocorticoid that undergoes high first-pass hepatic metabolism after intestinal absorption but still affects the pituitary–adrenal axis. Budesonide may cause fewer side effects than prednisone. It has been used in large breed dogs, which tend to be more prone to severe polyuria and polydipsia. There is no documented benefit in using the controlled release formulation compared with the generic substance.

TABLE 9.11 Treatment protocol for hypocobalaminemic dogs and cats with chronic enteropathy

Species	Weight	SC dose	Oral dose
Cats	Any weight	250 µg	250 µg
Dogs	< 4.5 kg	250 µg	250 µg
	4.5–9 kg	400 µg	250 µg
	9–18 kg	600 µg	500 µg
	18–27 kg	800 µg	1,000 µg
	27–36 kg	1,000 µg	1,000 µg
	36–45 kg	1,200 µg	1,000 µg
	> 45 kg	1,500 µg	1,000 µg

Schedule

Subcutaneous administration: Administer once weekly dose for 6 weeks, then one dose 30 days later. Recheck serum cobalamin 30 days after the last injection.

Oral administration: Administer once daily for 12 weeks and recheck serum cobalamin 1week after discontinuation of treatment.

Serum cobalamin at recheck

- Above the reference range and the underlying process has been successfully managed, discontinue cobalamin injections or oral therapy.
- Within the reference range, continue monthly injections or daily oral administration.
- Below the reference range, reassess the patient and continue supplementation.

Texas A&M University GI Laboratory website (http://vetmed.tamu.edu/gilab), with permission.

Prognosis

Good in mild cases that respond to dietary trials. Return to a less expensive commercial food may be possible after 2–3 months of dietary treatment; however, some dogs require life-long administration of an elimination diet. A UK study showed that only a quarter of dogs with DRCE required any additional treatment (e.g., antibiotics or immunosuppressives) 1 year after diagnosis. In contrast, the prognosis is guarded to poor in dogs requiring immunosuppression.

PROTEIN-LOSING ENTEROPATHY

Definition/Overview

Intestinal protein loss is a sign of failure of digestive function that may result from severe acute inflammation, acute blood loss, chronic inflammatory or neoplastic lesions, or from a disruption of chyle absorption and intestinal lymph flow.

Etiology/Pathophysiology

Primary intestinal lymphangiectasia occurs preferentially in Yorkshire Terriers, Shar Peis, Maltese, Norwegian Lundehunds, and Rottweilers. The pathogenesis of primary intestinal lymphangiectasia is still poorly understood. It results from obstruction to the flow of lymph in the intestinal wall. Secondary intestinal lymphangiectasia is commonly associated with significant intestinal mucosal inflammation (e.g., IBD) and neoplasia (alimentary lymphoma).

IBD may also directly cause PLE. The inflammatory process located in the GI mucosa may lead to protein loss both by preventing absorption of nutrients and by compromising the integrity of the intestinal mucosal barrier, leading to exudation of proteins into the intestinal lumen. PLE of Soft-coated Wheaten Terriers is a specific form of IBD affecting this breed worldwide. In approximately 50% of these dogs, PLE and protein-losing nephropathy (PLN) occur concurrently, and the pathogenesis includes a hypersensitivity component.

Crypt dilation and necrosis have been frequently associated with PLE. Dogs with small intestinal crypt abscesses have significant hypoalbuminemia and ultrasound changes of their intestinal mucosa, and their clinical presentation is generally severe.



FIGURE 9.77 Four-year-old male neutered Maltipoo with severe chronic inflammatory bowel disease and protein-losing enteropathy. The dog is cachectic and has a pot-bellied abdomen (ascites).

Clinical Presentation

Chronic, intermittent small intestinal diarrhea with possible vomiting is a common presentation. In severe cases, hyporexia/anorexia and malnutrition with evidence of malabsorption and weight loss may be observed (Figure 9.77). Importantly, significant intestinal protein loss and hypoalbuminemia may also occur without obvious diarrheic episodes. In the presence of severe hypoalbuminemia (serum albumin < 2.0 g/dL, often ≤ 1.5 g/dL), the main complaint may relate to significantly decreased oncotic pressure causing cavitary effusion (Figure 9.78) and subcutaneous edema (Figure 9.79).

Differential Diagnosis

Hypoalbuminemia and associated signs may also occur with liver failure, PLN, third spacing of proteins (vasculitis), or cutaneous loss.



FIGURE 9.78 Ten-year-old female spayed English Bulldog with chronic inflammatory bowel disease and protein-losing enteropathy. The abdomen is severely distended due to ascites. The dog also had pleural effusion.

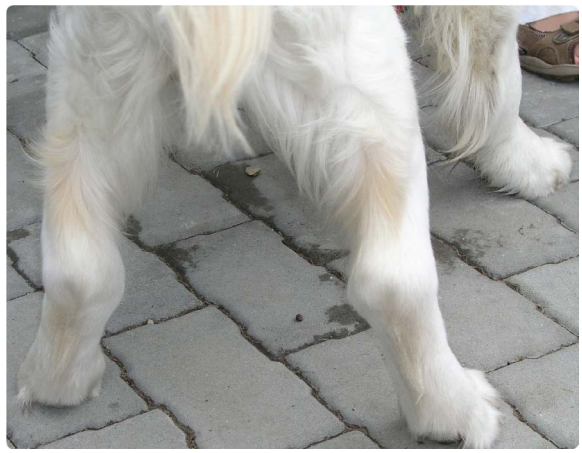


FIGURE 9.79 One-year-old male Montagne des Pyrenees with inflammatory bowel disease and protein-losing enteropathy. There is subcutaneous edema around both hocks. (*Courtesy of R. Husnik.*)

Diagnosis

First, the origin of the protein loss should be established by ruling out other processes. Generally, PLE is associated with panhypoproteinemia due to nonselective protein loss, but exceptions may occur. Other common abnormalities of dogs with PLE include hypocholesterolemia, hypocalcemia (total and ionized), hypomagnesemia, and lymphopenia.

Once the GI tract has been confirmed as the site of protein loss, further workup should include abdominal ultrasound, a technique with acceptable sensitivity that often helps assess the severity and anatomic distribution of intestinal lesions. Hyperechogenic mucosal striations are frequently observed in dogs with PLE and appear to be quite specific (Figure 9.71).

Once this initial database has been obtained, two options for diagnosis confirmation and management of the dog should be considered (Figure 9.80). In some instances, dogs with severe hypoalbuminemia are poor anesthetic candidates, and it is sometimes preferable to avoid taking excessive risks and postpone or cancel endoscopy or surgery. Additionally, many dogs with PLE have bicavitary effusion, and thoracic radiographs are recommended as a screening tool for the presence of thoracic effusion, which may represent an additional anesthetic risk. If endoscopy is performed, it may reveal a broad range of changes of varying severity (Figures 9.81 and 9.82). The diagnosis of the cause of PLE requires histopathologic analysis of intestinal biopsies (Figures 9.74 and 9.75).

Management

Dogs with PLE are in a catabolic state, and adequate nutrition is essential. Recent studies have highlighted that an important proportion of PLE dogs completely or partially responded to a 2-week dietary trial with a homemade ultralow-fat diet (ULFD). Examples of homemade ULFD include boiled, baked, or microwaved skinless chicken or turkey breast (one part) and peeled

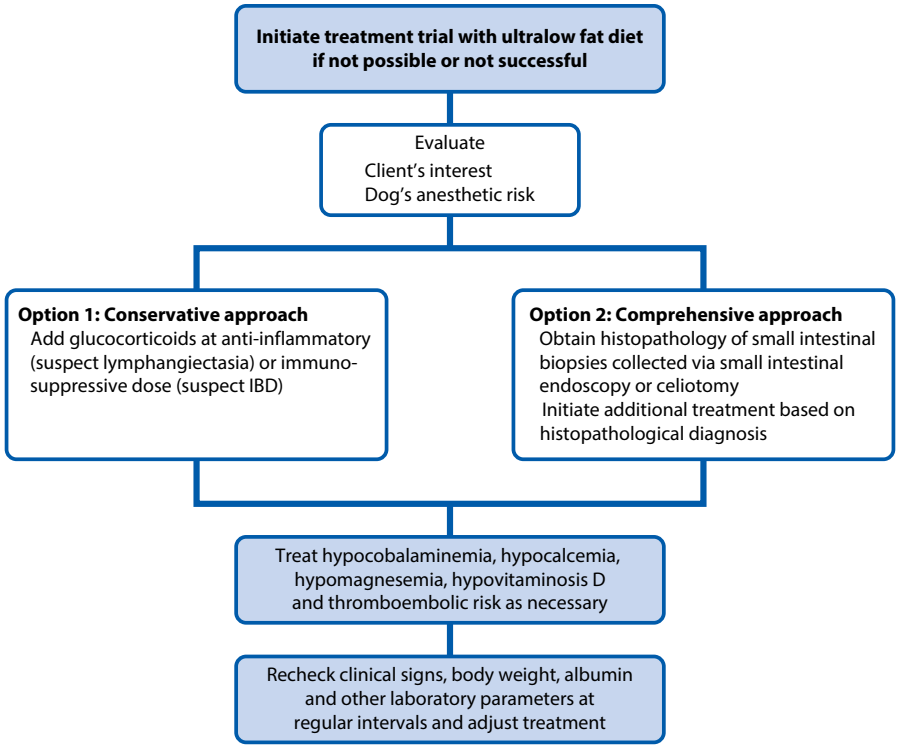


FIGURE 9.80 Recommendations for diagnostic confirmation and management of PLE in dogs.

white potatoes or boiled rice (two parts). The diet has a total caloric content of approximately 93–98 kcal/100 g (potato) or 123–128 kcal/100 g (rice). Its fat content of 0.35 g/100 kcal while conventional commercial low-fat diets have 2 g fat/100 kcal. While the diet is not balanced for long-term nutrition, it is palatable. Dogs that complete the trial successfully can progressively be switched to a commercial low-fat diet. Alternately, veterinarians can enroll the help of a board-certified small animal nutritionist to design an optimal dietary approach. In dogs with PLE associated with underlying IBD, a progressive switch to a diet consisting of hydrolyzed or novel proteins could be considered after the initial ULFD trial. In a recent study from Japan, dogs responding to this initial dietary approach were a little younger and had lower clinical scores (Table 9.9) than those that didn't. Their median survival was also markedly longer.

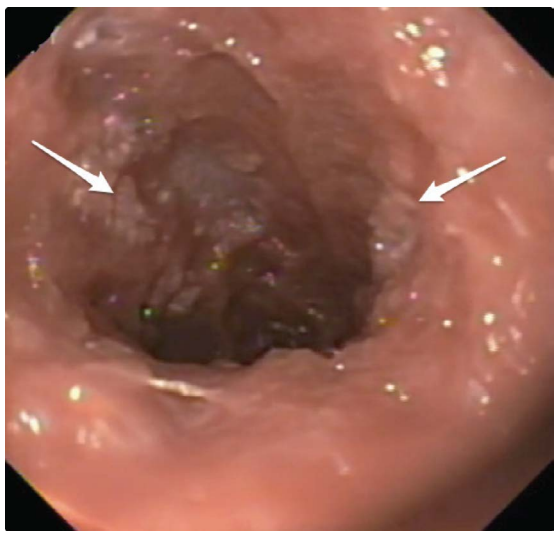


FIGURE 9.81 Endoscopic picture from the duodenum of the same dog as in **Figure 9.72**. The surface of the intestinal mucosa is very irregular and abnormal, and patches of recognizable villi are visible (arrows).



FIGURE 9.82 Endoscopic view of the duodenum of a 5-year-old Yorkshire Terrier. There are numerous multifocal white spots in the mucosa that represent dilated villi filled with chyme. The histopathologic diagnosis was idiopathic lymphangiectasia.

In dogs with primary intestinal lymphangiectasia that do not or only partially respond to the ULFD trial, anti-inflammatory glucocorticoid therapy (e.g., prednisone, 1 mg/kg per day) should be initiated. The main desired effect is to decrease the inflammation associated with lipogranulomas secondary to chyle leakage and, therefore, help restore an adequate flow in the intestinal lymphatics. In some dogs, anti-inflammatory treatment can be slowly weaned off over 2–3 months or longer. Dietary nonresponders with severe IBD and PLE should be treated with immunosuppressives (Table 9.10).

Complications

Low serum cobalamin concentrations are commonly found in dogs with PLE, especially in the presence of underlying IBD, and may delay proper healing of intestinal inflammation. Treatment is described earlier (Table 9.11).

The decrease in serum total calcium is associated with severe hypoalbuminemia, and serum ionized calcium should be measured. Ionized hypocalcemia occurs secondary to low 25-hydroxyvitamin D level which is presumably secondary to decreased ability to absorb fat in dogs with PLE. Hypovitaminosis D negatively impacts the immune system and is a negative prognostic factor. Although PLE dogs rarely experience clinical signs of hypocalcemia, those with moderately to severely decreased ionized calcium concentrations (< 2.5 mg/dL or < 1 mmol/L) should receive oral calcium carbonate supplementation (25 mg/kg p.o. q.8–12h.). Dogs with documented hypovitaminosis D should be given vitamin D supplementation. Concurrent hypomagnesemia may compromise the success of treatment and should be corrected if present (oral Mg supplementation with 1–2 mEq/kg daily).

Recent studies have revealed the high prevalence of hypercoagulability in dogs with PLE, which increases the risk of potentially fatal thromboembolic events. Hypercoagulability does not appear to resolve after successful treatment of PLE. However, clinical signs of thromboembolic disease are rare. Administration of low doses of aspirin (0.5–1 mg/kg per day) and/or clopidogrel (1–5 mg/kg per day) may be considered in order to prevent thrombosis, but this approach is controversial among specialists.

Prognosis

Generally, moderate-to-severe hypoalbuminemia (serum albumin < 2 g/dL), hypocobalaminemia and hypovitaminosis D are associated with a less favorable outcome. A few studies show a high mortality among Yorkshire Terriers with idiopathic intestinal lymphangiectasia (50%–60%). In the author's practice, these dogs often respond well to the initial dietary approach alone or with anti-inflammatory doses of glucocorticoids. A CECCAI below 8 offers an 83% sensitivity and 89% specificity of predicting clinical response to ULFD. Additionally, presence of crypt abscesses in the small intestine was associated with significantly shorter survival.

CHRONIC FELINE ENTEROPATHY

Definition/Overview

While the etiology and pathophysiology are thought to be similar to canine CE, the clinical presentation and approach of cats with CE is somewhat different. The terms CE and IBD are often used interchangeably in cats to describe chronic intestinal inflammation of unknown origin.

Clinical Presentation

The most commonly observed clinical signs are vomiting, anorexia, diarrhea, and weight loss (Figure 9.83). However, some cats may have a normal to increased appetite, and many cats, unlike dogs, will not have diarrhea at presentation. Other cats will be presented for hyporexia/anorexia and weight loss. The signs are often waxing and waning, and the owners may seek veterinary attention only late in the course of disease. Abnormal findings on physical examination of cats with CE include loss of body condition, dehydration, palpation of thickened bowel loops, and/or abdominal pain.

Differential Diagnosis

Particularly in the absence of specific signs, diseases originating outside the digestive tract such as hyperthyroidism, diabetes mellitus, chronic kidney disease, and heartworm disease, but also, liver disease and pancreatitis may share the same clinical presentation. Alimentary lymphoma, particularly diffusely infiltrative low-grade alimentary lymphoma (LGAL), is often very difficult to differentiate from IBD.

Diagnosis

The clinical signs may be very nonspecific, and the first step is to rule out diseases that may present with a similar clinical picture. A minimal database of CBC, chemistry profile, serum thyroxin concentration, and abdominal imaging (particularly ultrasound, Figure 9.114) is recommended. Serum cobalamin concentrations should be evaluated, as many cats with CE are hypocobalaminemic



FIGURE 9.83 Fourteen-year-old male neutered Domestic Longhair cat with chronic diarrhea and occasional vomiting. The cat was lethargic, cachectic, and his hair coat was in poor condition. Inflammatory bowel disease and alimentary lymphoma were among the top differentials.

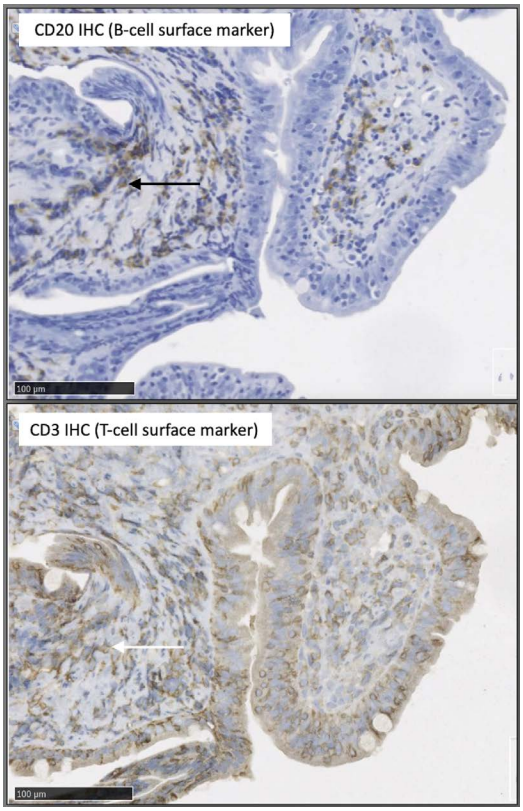


FIGURE 9.84 Photomicrograph of mucosal intestinal biopsies from a cat with IBD. There are CD20 (top, black arrow) and CD3 positive (bottom, white arrow) lymphocytes in the lamina propria showing the presence of a mixed population of B and T lymphocytes in the same areas of these sequential slices. This is typical of inflammation. Biopsies from a cat with LGAL would only show CD3 positive cells.

and require supplementation. Confirmation of diagnosis is based on histologic evaluation of intestinal biopsies collected using endoscopy or celiotomy. Differentiation between CE and low-grade alimentary lymphoma is challenging and often requires immunohistochemistry for lymphocytic surface markers (Figure 9.84). PCR for T-cell receptor rearrangement (PARR) performed on intestinal biopsies may also be helpful although false negatives and positives may occur.

Management

As is the case in dogs, a high proportion of cats with CE, particularly those with mild-to-moderate disease, may respond to an appropriate diet change (e.g., novel protein or hydrolyzed peptides). Some cats with dysbiosis may respond to concentrated probiotics or to antimicrobials (e.g., metronidazole, 10–15 mg/kg p.o. q.12h., although its therapeutic margin in cats is narrow).

Immunosuppressive therapy is the mainstay of IBD treatment. It is best initiated when histologic evidence of intestinal mucosal infiltration is available but could also be the final option of the empirical treatment sequence. Prednisolone (2–4 mg/kg p.o. q.24h. or divided into 2 daily doses) is administered for 2 weeks. If successful, once the clinical signs have been controlled for 2 weeks or longer, the dose is reduced by 25% every 2 weeks. The final goal is to maintain the cat on the lowest effective dose or even to consider discontinuation of steroid treatment if feasible. If the owner is unable to pill the cat, methylprednisolone acetate can be given (10 mg/kg SC q.2–4 weeks and tapered to q.4–8 weeks). However, repository steroids may cause more side effects and do not appear to be very successful in the author's experience. Failure to respond to treatment may indicate refractory IBD or lymphoma. Treatment of hypocobalaminemia, if present, with parenteral or oral cobalamin supplementation is necessary (Table 9.11). Refractory cases are usually treated with chlorambucil or cyclosporine (Table 9.10). Chlorambucil (2 mg per cat p.o. every other day [in cats > 4 kg body weight] or every 3 days [in cats < 4 kg body weight] and then tapered to the lowest effective dose) is generally used in combination with prednisolone. A CBC should be checked every 2–4 weeks for signs of myelosuppression. Although there are no published studies on cyclosporine use in cats with IBD, the dose generally recommended is approximately 5 mg/kg once daily (25 mg per cat).

Prognosis

In one study, the 3-year survival of cats with IBD was 77%. Many cats treated with diet change and prednisone have a positive response to treatment, although clinical signs may not completely resolve. Cats with severe histologic lesions or eosinophilic inflammation may be more difficult to manage. Feline IBD is a disease that is managed but rarely cured.

PARALYTIC ILEUS

Etiology

Primary nonobstructive disorders of intestinal motility are rare. Secondary alterations in motility of the small intestine occur with many diseases. Enteritis is associated with abnormal intestinal motility patterns that resolve with successful treatment of the inflammation. Intestinal hypomotility and ileus may occur after abdominal surgery (postoperative ileus [POI]) or during ischemic or inflammatory conditions affecting abdominal organs, such as peritonitis, pancreatitis, or parvovirus infection. Hyperthyroidism in cats may also alter intestinal transit time and cause diarrhea.

Pathophysiology

POI is thought to be due to inhibition of neural pathways and release of proinflammatory mediators and corticotrophin-releasing factor. They may be complicated by the use of opiates for analgesia.

Clinical Presentation

Vomiting (including silent vomiting without abdominal contraction), bloated abdomen, abdominal discomfort

or pain, and/or signs of colic. Hyporexia/anorexia, nausea, increased belching, pica, and/or polydipsia may also be observed.

Differential Diagnosis

Differential diagnoses are numerous. Small intestinal obstruction can result in a very similar presentation, and all necessary steps must be taken to rule it out. Autonomic neuropathy (dysautonomia) is a rare disease but should also be considered in the appropriate clinical setting.

Diagnosis

Clinical signs, abdominal radiographs often show dilated small intestinal segments in the absence of an obstructive pattern (see Figure 9.52). Precise evaluation of small intestinal motility is difficult under clinical conditions.

Management

Proper diagnosis and treatment of any underlying disease that might affect gastric motility is an essential premise. Therapy of functional, nonobstructive disorders of gastric motility is based on dietary modification and judicious use of prokinetic drugs. Dietary management is attempted at first: Small amounts of a low-fat, low-protein diet given at frequent intervals can help reduce the symptoms of delayed gastric emptying. Medical therapy can be attempted if dietary management alone is unsuccessful (Table 9.7).

Prognosis

Generally good if the problem is secondary to an underlying disease that can be treated successfully. Idiopathic disorders of small intestinal motility often represent a therapeutic challenge.

MALIGNANT SMALL INTESTINAL NEOPLASIA

Etiology

In dogs, small intestinal tumors occur relatively frequently (1%–8% of all canine cancers). Epithelial tumors include adenocarcinoma, mucinous adenocarcinoma, ring cell carcinoma, and undifferentiated carcinoma and represent 29% of all small intestinal tumors, as does lymphoma. Furthermore, 23% of small bowel neoplasms are leiomyosarcoma. These tumors may metastasize to mesenteric lymph nodes, liver, peritoneum, and lungs (adenocarcinoma metastasis rate is ~50%). Although low-grade alimentary lymphoma(LGAL) occurs much less frequently in dogs than in cats, it is a relevant differential diagnosis in dogs with CE and PLE.

In cats, small intestinal tumors are also relatively common (6%–13.5% of all feline cancers) and consist mostly of alimentary lymphoma (74%) and adenocarcinoma (17%). Siamese cats appear to be predisposed. Depending on the source, between one-third and three-quarters of all feline lymphomas are localized in the GI tract. Two main forms are recognized: LGAL, which causes a diffuse infiltration of the intestinal wall and consists of T cells, and high-grade alimentary lymphoma (HGAL), which causes focal or segmental disease and consists of B cells.

Pathophysiology

The cause of intestinal neoplasia in dogs and cats is unknown. An association between alimentary lymphoma and chronic inflammation (IBD) has been hypothesized in cats.

Clinical Presentation

Clinical signs develop late in the course of disease. They include chronic progressive vomiting, small bowel diarrhea, hyporexia/anorexia, hematochezia, and melena. An abdominal mass is palpable in 50% of cases with a discrete neoplasm. In diffusely infiltrative tumors, thickening of the small intestinal wall may also be palpable. Enlarged abdominal lymph nodes may also be detected. Clinical features of cats with LGAL are often identical to those of cats with IBD (Figure 9.83).

Differential Diagnosis

For occlusive tumors, intestinal FB, granulomatous disease (e.g., pythiosis), other causes of vomiting such as pancreatitis, metabolic disease (e.g., chronic kidney disease). Feline IBD is the top differential diagnosis for cats with LGAL.

Diagnosis

As stated previously, it may be very difficult to differentiate cats with moderate-to-severe IBD from those with LGAL. Collection of intestinal biopsies of adequate size for histopathologic interpretation is essential but does not guarantee that a final diagnosis will be reached. Both endoscopy and surgery allow collection of quality diagnostic samples. Multiple mucosal biopsies can be obtained endoscopically from the duodenum and ileum, while several full-thickness biopsies can be sampled surgically from the various sections of the small intestine. Special immunohistochemistry stains evaluating lymphocytic surface antigens (Figure 9.84) and to some extent PCR for antigen receptor rearrangement (PARR) can be of further help in attempting to confirm a diagnosis of LGAL.

CBC may reveal anemia (chronic disease or blood loss), serum chemistry may show hypoalbuminemia and increased liver enzymes. An obstructive pattern may be seen on abdominal radiographs; thoracic films may reveal metastases. Abdominal ultrasound is the most sensitive imaging method. It allows evaluation of localization, size, and extent of the mass and can be used to guide fine-needle aspiration for cytologic evaluation.

Management

In the absence of distant metastases, surgical resection with appropriate margins is the treatment of choice for most small intestinal tumors, with the exception of feline LGAL.

LGAL can be treated efficiently with a combination of prednisolone and chlorambucil (Table 9.10). Between 55% and 76% of cats achieve complete remission with a median survival time (MST) of 14–36 months. As is the case for CE, serum cobalamin concentration should be monitored, and supplementation started as necessary (Table 9.11). Chemotherapy for HGAL is best initiated after the mass has been resected. The CHOP protocol, consisting of prednisolone, vincristine, cyclophosphamide, and doxorubicin, is preferred. The rate of complete remission is 38%–87%, with an MST of 8 months.

Prognosis

Canine adenocarcinoma carries a good prognosis with > 2-year survival documented in the absence of metastases and with clean margins and an MST of 15 months. In cases with metastasis, the MST is usually significantly shorter (3 months). In cats, survival ranges from 5 to 13 months. The benefit of postsurgical chemotherapy has not been scientifically evaluated. MST for canine leiomyosarcoma with or without metastasis ranges from 9 to 22 months.

PART 5: DISEASES OF THE LARGE INTESTINE

Overview

Inflammatory diseases of the colon are frequently encountered in dogs and are less common in cats. In many instances, acute nonspecific colitis is self-limiting. Chronic colitis is often associated with a long, sometimes waxing and waning clinical course and specific treatments. Constipation is an uncommon clinical sign usually encountered in older animals and affects cats more frequently than dogs.

Anatomy and Physiology of the Large Intestine

The large intestine consists of six segments: Cecum (a short blind pouch), ascending colon, transverse colon, descending colon, rectum, and anus. The ileocolic valve and its sphincter separate the distal small intestine and the large intestine (Figure 9.85). The microscopic structure of the large intestine resembles that of the small intestine. However, the large intestinal mucosa does not form villi, the epithelial cells have fewer microvilli on their apical surface than enterocytes, and numerous goblet cells are interspersed in the epithelial layer (Figure 9.86). The colon has two main functions: Water absorption, which takes place in the proximal colon, and storage and elimination of feces. Colonic motility includes a few patterns with different functions: Stationary contractions mix the content and indirectly promote water absorption and peristaltic contractions move the feces aborally over small distances. Eventually, giant contractions precede defecation and move feces over longer segments. The gastrocolic reflex is mediated by enteric nerves and enhances colonic motility after a meal, leading to defecation.

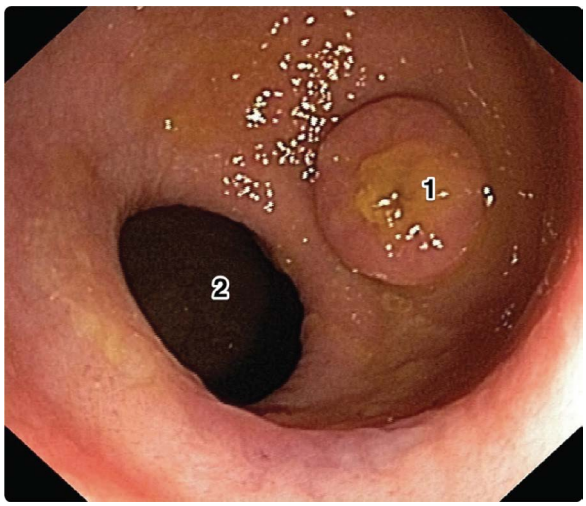


FIGURE 9.85 Endoscopic view from the ascending colon of a dog. The ileocolic junction (1) and the entrance to the cecum (2) are visible. (*Courtesy of R. Husnik.*)

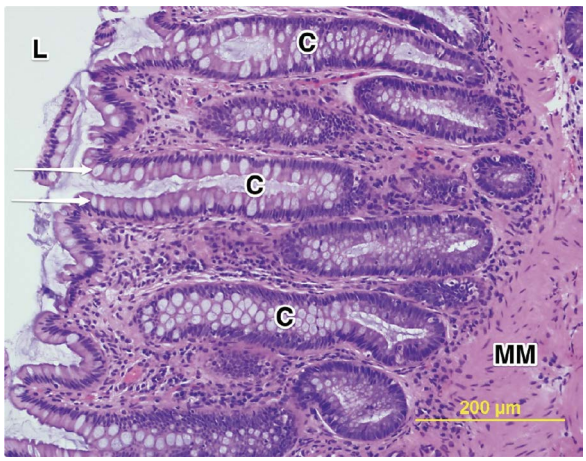


FIGURE 9.86 Photomicrograph of the canine colonic mucosa. The arrows point to a few of the numerous goblet cells. Mucus can be observed on the surface of the epithelium and in the colonic crypts. There is mild expansion of the lamina propria, with lymphoplasmacytic inflammation. C, colonic crypts; L, lumen; MM, muscularis mucosae.

ACUTE COLITIS

PARASITIC COLITIS (WHIPWORMS)

Definition/Overview

As stated earlier, the CAPC maintains a very informative and freely accessible website on intestinal parasites

of small animals, and this should be consulted for additional information (www.capcvet.org).

Etiology

Trichuris vulpis is a common cause of large bowel diarrhea in dogs. Whipworm infestation in cats is rare and caused by *T. campanula* and *T. serrata*. The infection mode is fecal–oral. Eggs develop into larvae in the small intestine, and larvae ultimately migrate to the cecum and colon, where they develop to adult worms.

Pathophysiology

Adult whipworms feed on cecal and colonic epithelial cells. Severe typhlitis and colitis may occur with heavy infestations; however, many dogs infested with few whipworms do not show clinical signs.

Clinical Presentation

Acute or chronic large bowel diarrhea that may occur in dogs of all ages. Severely affected animals may present with lethargy, hyporexia, and dehydration. Abdominal discomfort or abdominal pain due to accumulation of gas in the large intestinal lumen may also be present. Rarely, whipworm infested dogs may show hyperkalemia and hyponatremia, which is suggestive of hypoadrenocorticism, even though their adrenal glands are fully functional.

Differential Diagnosis

Other causes of acute colitis (dietary, idiopathic) or chronic colitis (IBD, granulomatous colitis). In the presence of hyperkalemia and hyponatremia, hypoadrenocorticism.

Diagnosis

Fecal flotation allows identification of the bipolar operculated eggs (Figure 9.87). However, fecal shedding of ova may only occur intermittently, particularly if immature worms are involved. Therefore, repeated fecal examinations usually increase the diagnostic yield. Alternatively, empirical treatment may be initiated with a broad-spectrum anthelminthic. Further diagnostic testing is generally not required with the exception of severely dehydrated dogs and animals with pre-existing conditions. In dogs with recurrent episodes of acute diarrhea, a more detailed workup may be indicated.



FIGURE 9.87 *T. vulpis* egg. The egg is lemon-shaped with a plug (operculum) at each pole. (*Courtesy of B. Delcambre.*)

Management

Fenbendazole (50 mg/kg per day for 3 days) or febantel (25 mg/kg once) are the anthelminthic drugs of choice. Because immature adults and larval stages are less sensitive to the drugs, treatment should be repeated 3 weeks later and again after 3 months. Milbemycin oxime and moxidectin used monthly to prevent heartworm infection are also useful for prevention and treatment of whipworm infestations. Whipworm ova are resistant to unfavorable environmental conditions and may represent a problem in shelter situations.

ACUTE IDIOPATHIC COLITIS

Etiology

Unknown. Some form of dietary indiscretion is usually present.

Pathophysiology

Colonic inflammation is associated with decreased nonpropulsive motility and excessive propulsive motility that results in diarrhea with frequent defecation of feces of decreased consistency.

Clinical Presentation

Large bowel diarrhea with all typical components including hematochezia (Figure 2.3.3), mucoid feces (Figure 2.3.6), and tenesmus (Figure 9.88), as listed in Table 2.3.1. Acute nonspecific colitis may occur in dogs of any age.

Diagnosis

Elimination of known causes of acute colitis such as whipworm infestation.



FIGURE 9.88 Tenesmus in a 2-year-old Boxer with chronic colitis. When walked, the dog immediately attempted to defecate. It remained in this position for more than 2 minutes and produced only a small quantity of liquid feces.

Management

The disease is usually self-limiting. Mild cases may not require any treatment. Moderate cases respond well to symptomatic treatment that includes dietary manipulations with a 12- to 24-hour fasting period. An easily digestible low residue diet should be fed for 3-5 days (small meals several times daily), with progressive return to a good-quality commercial diet over the following 3–5 days. Systematic use of antimicrobials in cases of acute nonspecific colitis is not recommended because increases in the resistance of *C. perfringens* to metronidazole have been reported and are concerning. Metronidazole has been commonly used in the treatment of acute colitis because of its effects on the intestinal microbiota, its properties as a modulator of inflammation, and its spectrum against anaerobic infections. The use of probiotics provides a good alternative to antimicrobials (Box 9.6).

In cases with clinical evidence of dehydration, IV fluids should be administered using balanced isotonic crystalloid solutions at appropriate rates to rapidly replace fluid deficits and provide maintenance requirements. In dogs with severe acute colitis and consistent abdominal pain, analgesic treatment should be considered.

Prognosis

Good to excellent. The disease is generally self-limiting, or it responds well to symptomatic treatment.

CHRONIC COLITIS

FUNGAL AND OOMYCETAL COLITIS

Overview

Animals infected with histoplasmosis may show signs of large bowel diarrhea. Rectal scraping or fine-needle aspiration of enlarged abdominal lymph nodes may be diagnostic and reveal large numbers of fungal organisms phagocytized by macrophages (see Figure 9.64). Pythiosis is caused by an oomycetal organism and may occasionally diffusely infiltrate the colonic and rectal wall and cause severe clinical signs. The prognosis is generally poor.

Further details about histoplasmosis and pythiosis can be found in Part 4: Diseases of the Small Intestine.

PARASITIC COLITIS

WHIPWORMS

See Acute Colitis.

TRICHOMONIASIS

Etiology

Tritrichomonas blagburni, also named *T. foetus*, is a protozoal organism associated with chronic, recurring feline colitis in large multicat households. Most affected cats come from shelters or belong to breeders, and it is suspected that environmental stress plays a role in their susceptibility to the infection. Coinfections with *Giardia* are common. *T. blagburni* is not very resistant in the environment and direct fecal–oral contact is required for transmission (e.g., multicat litterbox).

Pathophysiology

T. blagburni live in the cecum, descending colon, and ileum and may cause lymphoplasmacytic and/or neutrophilic inflammation of the mucosa with secondary architectural changes.

Clinical Presentation

The disease affects young cats, with onset between birth and 2 years of age. Seventy-five percent or more of affected cats are younger than 1 year of age at the time of diagnosis. Affected cats either live or have lived in a large multicat household. Typical clinical signs include waxing and waning large bowel diarrhea, which may contain mucus and blood. The feces are soft and malodorous (Figure 9.89). Secondary anal inflammation may be observed.

Differential Diagnosis

In shelter or other large multicat household situations, other infectious diseases such as infestation with *Giardia* or *Cryptosporidium* (see Chronic Enteritis), alone or in combination, may also occur. However, these protozoa more often cause small intestinal or mixed diarrhea. In spite of the young age of cats with suspect *T. blagburni* infections, CE should also be considered (DRD, IBD).

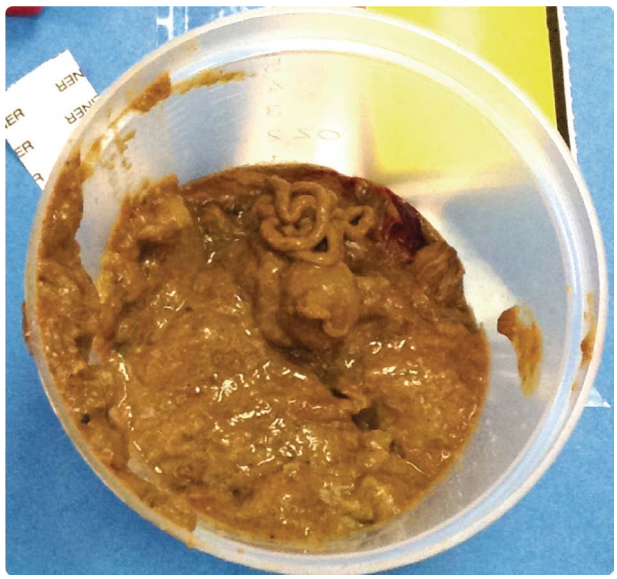


FIGURE 9.89 Soft and malodorous diarrhea from a cat with *T. blagburni* infection. (*Courtesy of M.K. Tolbert.*)

Diagnosis

Three methods are available for detection of *T. blagburni* in the feces. Direct analysis of fresh feces after dilution with saline is an insensitive method (14%) but may yield a positive result in diarrheic feces of severely affected cats (Figure 9.90). Feces are best sampled by flushing the colon with saline and should be analyzed within 2 hours. Under the microscope, *T. blagburni* trophozoites may be misdiagnosed as *Giardia*; however, they have a characteristic forward motion that contrasts with the "falling leaf" motion of *Giardia* trophozoites. Another method is to inject a small amount of fresh feces into a special culture medium (In Pouch TF-Feline) and evaluate the medium under the microscope at daily intervals for the presence of *T. blagburni* trophozoites. The sensitivity of culture is intermediate (55%). Fecal PCR is the most sensitive method to detect *T. blagburni*, particularly when samples are collected using a fecal loop. Recommendations to increase the yield of fecal PCR can be found at www.JodyGookin.com.

Management

Treatment of *T. blagburni* infection in cats is problematic as fenbendazole and metronidazole, as well as many other drugs, are ineffective. In a recent study, ronidazole (30 mg/kg p.o. q.24h. for 2 weeks) was effective at resolving clinical signs in 23 of 27 cats, with most cats becoming PCR negative. Only three cats developed side effects consisting mostly of lethargy, vomiting, and lack of appetite that resolved after discontinuation of the drug. Ronidazole neurotoxicity has been reported within 3–9 days after initiation of treatment and resolved after discontinuation of the drug. Therefore, ronidazole should be administered only after a definitive diagnosis has been made and only at the dosage listed earlier. Natural resistance of *T. blagburni* to ronidazole has been demonstrated in up to 21% of cats. Ronidazole is not approved for use in cats and must be compounded in capsules.

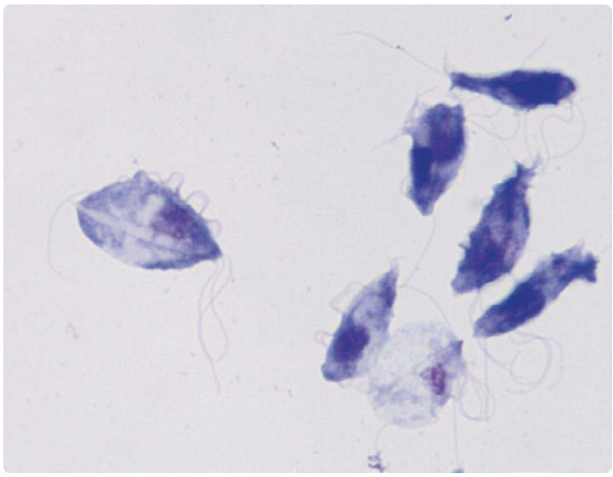


FIGURE 9.90 Microphotograph of stained *T. blagburni* trophozoites. (*Courtesy of M.K. Tolbert.*)

Prognosis

Spontaneous resolution of *T. blagburni* infection usually occurs within 2 years of onset. However, many cats may remain silent carriers and be able to infect other cats. Ronidazole treatment is most efficacious in animals relocated to single-cat households, as the risk for reinfection is low.

CHRONIC IDIOPATHIC COLITIS

DIET-RESPONSIVE CHRONIC COLITIS

Overview

In a study of 70 dogs with chronic diarrhea, 39 (56%) responded to an elimination trial with a novel protein diet. Of those, 27 (69%) exclusively showed large bowel diarrhea while nine (23%) had mixed large and small bowel signs. Similarly, in another study, 27 (49%) of 55 cats with chronic intestinal disease were diet responsive, while 16 (29%) were diagnosed as food sensitive. Two-thirds of the feline group had abnormal findings on colonic or rectal histopathology.

Based on these data, an elimination trial with hydrolyzed peptide or novel protein diets chosen on the basis of the animal's dietary history should be initiated in all dogs with mild-to-moderate chronic idiopathic colitis. Clinical signs generally abate within 10–14 days of treatment.

INFLAMMATORY BOWEL DISEASE

Etiology/Pathophysiology

The etiology and pathophysiology of IBD are described in Part 4 (Diseases of the Small Intestine, Chronic Enteropathy). While it appears that IBD most often affects the small intestine or both small and large intestine concurrently (especially in cats), colonic IBD is a recognized disease. Synonyms include lymphoplasmacytic colitis, eosinophilic colitis.

Differential Diagnosis

Whipworms, diet-responsive colitis, possibly colorectal neoplasia. In cats with compatible signalment and history, *T. blagburni* infection.

Diagnosis

The diagnostic approach must be comprehensive to rule out all other known causes of colitis (Figure 2.3.8). While a treatment trial with sulfasalazine or olsalazine may be appropriate in dogs with suspect colonic IBD, colonoscopy with collection and histologic evaluation of mucosal biopsies is recommended prior to initiating immunosuppressive treatment. This will confirm the presence and assess the severity of colonic inflammation (Figures 9.91 and 9.92) and rule out other diseases such as granulomatous colitis or neoplasia (e.g., lymphoma, especially in cats). Colonoscopy

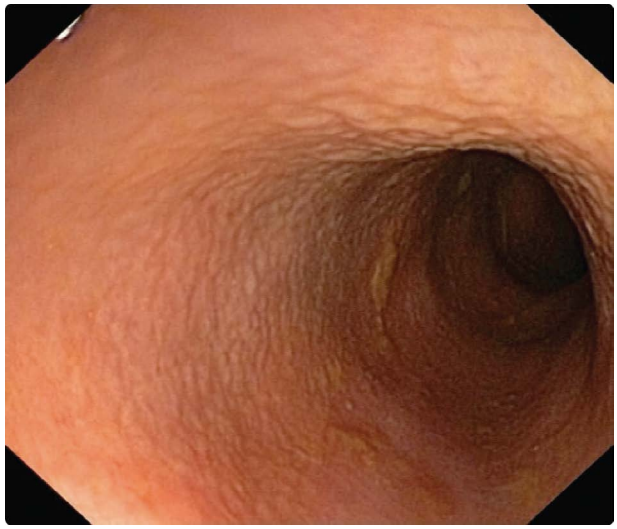


FIGURE 9.91 Colonoscopy view of a dog with chronic large bowel diarrhea. The inability to see submucosal vessels indicates thickening of the mucosa. The mucosal surface is irregular with a cobblestone pattern. The histopathologic diagnosis was severe lymphoplasmacytic colitis. (*Courtesy of R. Husnik.*)

requires appropriate preparation with prolonged fasting (24–48 hours), administration of osmotic laxative polyethylene glycol solution, and possibly enemas. A full examination of the rectum, colon, and cecum is only possible using flexible endoscopes under general anesthesia.

Management

In dogs with suspect colonic IBD, an anti-inflammatory treatment trial with sulfasalazine may be attempted (10–30 mg/kg [maximum 1 g total dose] p.o. q.8h. for 4–6 weeks). Sulfasalazine liberates 5-aminosalycilic acid in the colon and is widely used in the treatment of dogs with colitis. After successful completion of the initial treatment regimen, it is best to slowly decrease the dose in stages of 10–14 days. Monitoring tear production regularly during treatment is essential as keratoconjunctivitis sicca is a common complication. Olsalazine (5–15 mg/kg q.8–12h.) may be used in dogs that do not tolerate sulfasalazine. In addition, dietary fiber supplementation is often helpful (see Box 9.10). In cats with colonic IBD and in dogs with confirmed colonic IBD refractory to sulfasalazine or olsalazine, immunosuppressive prednisone should be initiated (Table 9.10).

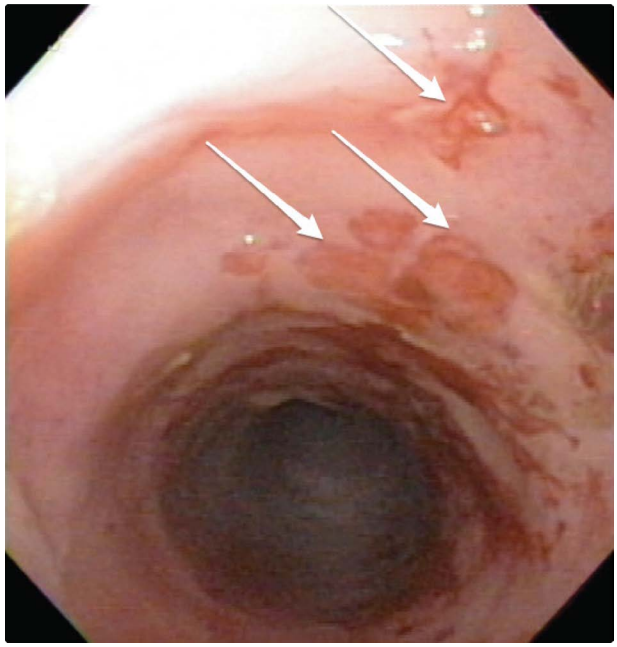


FIGURE 9.92 Colonoscopy picture of a 6-year-old cat with chronic large bowel diarrhea and hematochezia. There are numerous mucosal ulcerations (arrows). The histopathologic diagnosis was severe, ulcerative lymphoplasmacytic colitis. The cat improved when fed a novel protein diet and treated with immunosuppressive doses of prednisolone.

Box 9.10 Fiber supplementation in dogs with colitis and chronic idiopathic large bowel diarrhea

Overall, dietary fibers enhance the structure and function of the intestinal epithelium and also have beneficial effects on colonic motility. As a trade-off, they may have a negative impact on nutrient digestibility depending on the specific fiber type. Soluble fibers are fermented to short-chain fatty acids (SCFAs) by the colonic microbiota. SCFAs are an essential source of energy for colonic epithelial cells.

- Psyllium is a soluble fiber derived from the seed of *Plantago ovata*. It has great water-holding capacities and forms gels in water, two properties that can contribute to improvement of fecal consistency. Psyllium was very efficient when added to a highly digestible diet in the treatment of chronic idiopathic colitis. The initial daily dosage is 0.5 tablespoon (T) for toy breeds, 1 T for small dogs, 2 T for medium dogs, and 3 T for large dogs. The fiber supplement should be administered with each meal in two divided doses, and the dose increased to effect. Psyllium is included as an ingredient in a few commercial prescription diets.
- Canned pumpkin is another source of soluble fiber. It is administered with an initial dosage comparable to that of psyllium, and the dose is adapted to effect.

Other sources of SCFAs include fructooligosaccharides and beet pulp, which are included in some commercial diets.

Prognosis

Prognosis for IBD is generally better when only the colon is affected. However, one retrospective study of dogs with IBD did not find any association between localization of disease and outcome. Nevertheless, clinical studies demonstrated that many dogs and cats with colitis respond completely to dietary modification and/or, for dogs only, to sulfasalazine treatment.

GRANULOMATOUS COLITIS

Definition/Overview

Granulomatous colitis (GC) is a form of IBD that occurs most frequently in young Boxer dogs or, infrequently, in other breeds such as Mastiffs, Alaskan Malamutes, French Bulldogs, and English Bulldogs.

Etiology

Adherent-invasive *E. coli* that adhere to and invade intestinal epithelial cells and have been identified as the cause of GC. These bacteria are taken up by endosomes and persist in the macrophages instead of being cleared. A genetic predisposition for GC is suspected due to the preponderance of cases in young Boxer dogs. Preliminary results from genetic studies in Boxers with GC and healthy controls point to a defective clearance of *E. coli* in macrophages.

Clinical Presentation

The onset of disease generally occurs before 2 years of age. Clinical signs include severe chronic large intestinal inflammation with diarrhea, hematochezia, increased frequency of defecation, tenesmus, and presence of excessive mucus in the feces. Although physical examination is most frequently unremarkable, weight loss and inappetence can be seen in severe cases (Figure 9.93).

Diagnosis

Signalment, history, and clinical signs are usually very suggestive. While it is tempting to initiate a treatment trial in these dogs, a comprehensive diagnostic workup including endoscopic biopsies is the recommended approach.

Colonoscopy typically reveals sites of severe colonic hemorrhage and ulcerations interspersed with stretches of normal-appearing mucosa. Histology may show severe infiltration with neutrophils, macrophages, lymphocytes, plasma cells, and mast cells. Accumulation of large macrophages staining strongly positive with periodic acid Schiff (PAS) in their cytoplasm is pathognomonic for GC (Figure 9.94). Confirmation of the presence of *E. coli* using fluorescent in situ hybridization (FISH) analysis on formalin-fixed biopsies is now recommended as part of the detailed diagnostic workup of dogs with suspect histiocytic ulcerative colitis (HUC; Figure 9.95).



FIGURE 9.93 An 18-month-old Boxer with granulomatous colitis and chronic intermittent large bowel diarrhea, episodes of anorexia, and weight loss.

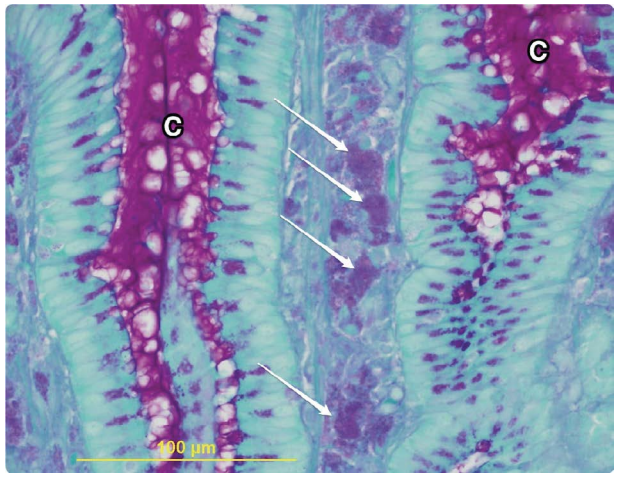


FIGURE 9.94 Photomicrograph from a colonic biopsy from a Boxer with granulomatous colitis. There are numerous, purple-stained macrophages in the lamina propria (arrows point to four such cells). It is thought that the PAS-positive intracellular material represents accumulation of *E. coli*. C, colonic crypts; PAS, periodic acid Schiff stain.

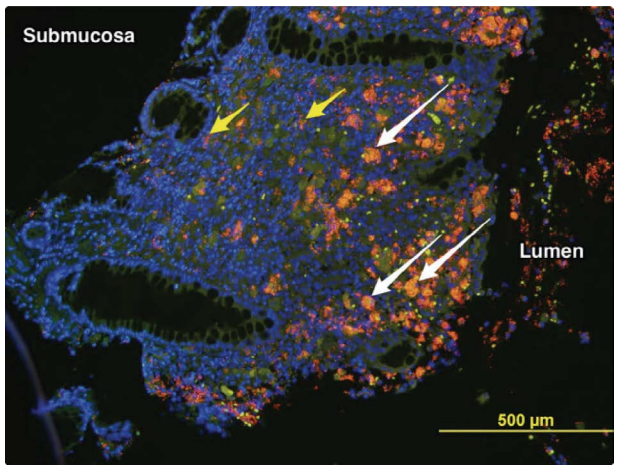


FIGURE 9.95 Photomicrograph of a colonic biopsy from a dog with granulomatous colitis (fluorescent in situ hybridization or FISH). Long white arrows show some of the macrophages filled with *E. coli* while short yellow arrows show examples of clusters of *E. coli* within the mucosa. *E. coli*-Cy3 probe stains *E. coli* in red orange; 4′, 6-diamidino-2-phenylindole (DAPI) stains nuclei in blue. (*Courtesy of K. Simpson.*)

Management

Treatment of the disease consists of enrofloxacin at 10–20 mg/kg p.o. q.24h. for 4–6 weeks. Most affected dogs respond within 10–14 days of initiating therapy. While several dogs were reportedly disease-free after the drug had been discontinued, there is increasing evidence that GC may relapse after treatment. Recent reports suggest that up to 43% of dogs with GC/HUC develop enrofloxacin resistance early in the disease process and may be refractory to treatment if they are treated empirically. Therefore, it is prudent to send colonic biopsies for culture and sensitivity before starting treatment and

tailor the choice of antibiotics to the specific sensitivity profile of the cultured *E. coli*.

Prognosis

The long-term prognosis is guarded to poor.

COLORECTAL OBSTRUCTION

Etiology/Pathophysiology

Luminal colonic or rectal obstruction may result from a FB or from the presence of hardened feces such as may be the case in constipated or obstipated patients. Alternatively, benign rectal strictures may occur in response to significant trauma of the rectal or distal colonic mucosa (e.g., FB, anorectal surgery). Fibrosis and cellular proliferation are responsible for narrowing of the lumen. Neoplastic masses arising from the colonic wall may also cause an obstruction to the passage of feces in the distal colon and rectum. They may cause malignant strictures. Finally, space-occupying lesions occurring in neighboring organs such as the prostate or sublumbar lymph nodes (**Figure 9.104**) may also compromise passage of feces through the distal large bowel.

Clinical Presentation

Dyschezia, tenesmus (**Figure 9.96**), passage of ribbon like feces (**Figure 9.97**), and hematochezia are frequently observed in association with partial or total colorectal obstruction. Severe retention of feces may lead to systemic repercussions such as hyporexia, lethargy, and vomiting.

Differential Diagnosis

Primary colonic dysmotility, perineal hernia, anal sacculitis, and pseudocoprostasis may all cause dyschezia.

Diagnosis

In animals with a suggestive presentation, abdominal palpation and digital rectal examination often allow confirmation of the presence of partial or total obstruction of the distal large bowel. Sedation may be required for a thorough rectal examination, particularly in animals who are in pain. Radiographs and ultrasound of the abdomen and pelvic canal may be useful to detect a radiopaque FB and/or evaluate the severity of fecal retention and examine the surrounding structures. Endoscopic evaluation can be performed using a rigid proctoscope or a flexible endoscope. This allows visualization of the rectum and distal colon and collection of mucosal biopsies if a neoplastic process is suspected.

Management

Most FBs can be dislodged using repeated warm water enemas with added water-soluble gel. Digital dilation of mild rectal strictures may be successful, although several procedures at intervals of 1 week are generally required. Balloon dilation usually has a higher success rate. In severe cases or cases refractory to dilatory procedures, surgical removal is required (rectal pull-through if possible or other procedure). The treatment of obstructive neoplasia relies on surgical excision if feasible.



FIGURE 9.96 Severe tenesmus and dyschezia in a 4-year-old Husky with constipation due to a rectal stricture. The anus was scarred and extremely painful to palpation. The dog vocalized loudly each time it tried to defecate. Eventually, defecation ceased, presumably because it was too painful. Attempts at surgical correction, including anal resection, were unsuccessful, and the dog was euthanized. (*Courtesy of C. Burrows.*)

Prognosis

FB, benign polyp –good to excellent. Stricture, other neoplasia –guarded to poor. Anorectal surgery may lead to fecal incontinence or recurrence of stricture.



FIGURE 9.97 This 13-year-old Dachshund was presented with the complaint of tenesmus and "narrow stools." The dog strained hard to defecate and passed pencil-thin feces. Rectal examination revealed a stricture. Biopsy revealed scar tissue, and the dog responded well to balloon dilation and sulfasalazine. (*Courtesy of C. Burrows.*)

FUNCTIONAL LARGE BOWEL DISORDERS

CHRONIC IDIOPATHIC LARGE BOWEL DIARRHEA

Definition/Overview

Chronic idiopathic large bowel diarrhea (CILBD) affects dogs and is characterized by recurrent large bowel diarrhea in the absence of histopathologic evidence of inflammation. It appears to be comparable to irritable bowel syndrome with diarrhea (IBS-D), a disease that is relatively common in people.

Etiology/Pathophysiology

The etiology of CILBD is unknown. In people, IBS is associated with visceral hypersensitivity, and patients have enhanced perception of visceral events such as contractions and gas throughout their GI tract. Stress, diet, and intestinal and colonic microbiota are all thought to play a role in the pathogenesis. Approximately 40% of dogs with CILBD have abnormal personality traits and/or are exposed to environmental stress factors (e.g., working dogs, boarding). Associated behavioral issues may include separation anxiety, submissive urination, noise sensitivity, aggression, or nervous, high-strung dogs. Environmental factors may range from presence of visitors in the household and construction in the house to traveling and moving.

Clinical Presentation

Dogs of all ages may be affected (median age 6 years old) and exhibit chronic intermittent large bowel diarrhea. Excessive mucus in the feces, hematochezia, increased number of daily defecations, and/or tenesmus are common. Appetite may be decreased during diarrheic episodes, and abdominal pain may be present. Vomiting may occur as well.

Differential Diagnosis

Whipworm infestation, diet-responsive colitis, colonic IBD, granulomatous colitis (in Boxer dogs and Bulldogs), colonic neoplasia.

Diagnosis

CILBD is a diagnosis by exclusion, and all other causes of chronic, intermittent large bowel diarrhea must be ruled out (Figure 2.3.8). Diagnostic criteria for CILBD include chronic or chronic recurring large bowel diarrhea of at least 4 weeks' duration, absence of or only minimal abnormal findings on physical examination and blood work, no other identifiable cause of diarrhea, and lack (or only minimal) changes observed during colonoscopy with unremarkable histopathologic evaluation of the colonic mucosa. Predisposing environmental factors or behavioral issues may be present.

Management

Between 63% and 96% of dogs with CILBD respond to fiber supplementation alone (Box 9.9). In fiber-refractory dogs, a full behavioral assessment should be performed, and behavior-modifying drugs prescribed as appropriate. In one study, approximately 60% of dogs requiring drug treatment responded, while 40% did not.

Prognosis

Prognosis is good considering the high response rate to fiber supplementation.

CONSTIPATION

Definition/Overview

Constipation is characterized by infrequent or difficult evacuation of feces. Obstipation is the result of recurrent, intractable constipation. Constipation and obstipation may culminate in the syndrome of megacolon. In the cat, constipation is a relatively frequent problem, while obstipation and megacolon are less common. Constipation and associated problems occur less frequently in the dog.

Etiology

Primary constipation is due to abnormal colonic motility. Neuromuscular dysfunction may occur in animals with lumbosacral disease or in cats with idiopathic megacolon. Dehydration, hypokalemia, and hypocalcemia may all negatively impact colonic motility. Inactivity and obesity may also cause prolonged large bowel transit time. Furthermore, use of opiates and anticholinergics may also lead to constipation.

Secondary constipation is more common and is associated with processes that impair the transit and evacuation of colonic content, such as mechanical obstruction of the colon or rectum. Obstructions can be intraluminal (e.g., fecal impaction, FB, stricture), intramural (neoplasia), or extramural (e.g., narrowing of the pelvic canal, space-occupying lesions impinging on the descending colon or rectum).

Clinical Presentation

Typical clinical signs include reduced, absent, or painful defecation, which may be progressive. Other clinical signs associated with a primary underlying disease might be present, such as those associated with hypothyroidism, which is more common in dogs. The onset of distal bowel signs may be insidious, and animals may be presented late when the problem is severe. Dyschezia may be observed (Figure 9.96). Chronic constipation/obstipation may have systemic repercussions such as anorexia, lethargy, weight loss, and vomiting.

Differential Diagnosis

Diseases of the anorectum such as perineal hernia and anal sacculitis may cause painful defecation. Pseudocoprostasis can be caused by matted hair around the anus, which occasionally occurs in dogs and cats with long hair. Importantly, some cat owners may not be able to differentiate stranguria and dyschezia, and lower urinary tract diseases should always be ruled out.

Diagnosis

A detailed physical examination is required. This may reveal varying degrees of dehydration, weight loss, and abdominal pain. Rectal palpation should be performed and may reveal pelvic canal abnormalities, a rectal FB, a stricture, or presence of a perineal hernia.

A thorough screening of animals presented with recurrent constipation is recommended to identify obstructions and underlying diseases and assess the systemic repercussions of the problem. A minimal database consisting of CBC, biochemistry panel, and urinalysis should be obtained in all cats presented for constipation to rule out metabolic causes and underlying chronic diseases such as chronic kidney disease. Abdominal radiographs help characterize the severity of colonic impaction (**Figures 9.98** and **9.99**) and identify predisposing factors such as intraluminal radiopaque foreign material, intraluminal or extraluminal mass lesions, pelvic fractures, and spinal abnormalities. Extraluminal mass lesions may be further evaluated by abdominal ultrasonography and guided biopsy, whereas intraluminal mass lesions are best evaluated by endoscopy.

Management

All identified underlying problems should be treated. If the cause of the obstruction can be addressed in a timely manner, colonic function may be preserved. However, prolonged obstruction is ultimately associated with loss of colonic contractility.

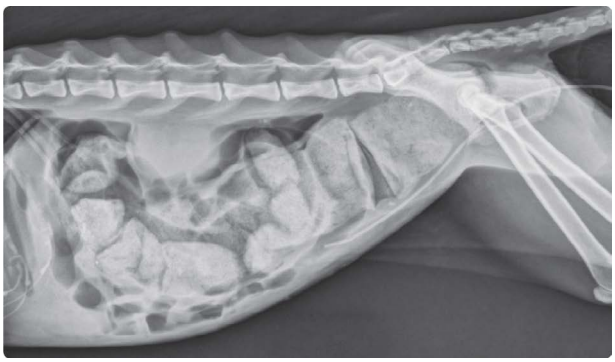


FIGURE 9.98 Ten-year-old female spayed Domestic Shorthair cat. Right lateral abdominal radiograph. There is severe dilation of the entire colon from the cecum to the rectum with large amounts of radiopaque fecal material. The cat is in poor body condition. Radiographic diagnosis is megacolon. A urinary catheter is present.



FIGURE 9.99 Ventrodorsal abdominal radiograph from the same cat as **Figure 9.98**. The severely dilated and impacted colon is displaced to the right. (*Courtesy of L. Gaschen.*)

The different methods for treatment of idiopathic, nonobstructive constipation include administration of oral laxatives, enemas (**Table 9.12**), and prokinetic agents such as cisapride (**Table 9.7**).

In cats with chronic recurrent idiopathic constipation, a stepwise approach has proven useful. Mild-to-moderate constipation (e.g., first occurrence, recurrence after a long interval with normal defecation) is best treated with an initial enema followed by treatment with laxatives. High-sodium and phosphate-containing enemas are not recommended because of their tendency to cause acute hyperphosphatemia and severe hypocalcemia. Maintaining these cats on a psyllium-enriched diet or continuing daily administration of laxatives is recommended. Addition of prokinetics is necessary when management with diet and laxatives fails. Early use of cisapride is likely to prevent the progression of constipation to obstipation and dilated megacolon in these cats. However, some cases become refractory to conservative treatment and slowly progress to obstipation and dilated megacolon.

TABLE 9.12 Therapeutic options for conservative management of constipation in cats

Laxatives (administer in well-hydrated cats only)	**Bulk-forming** (add to moist cat food) More useful in mild cases	Psyllium (1–4 teaspoons per meal); also available incorporated in a proprietary dry extruded diet (Royal Canin Intestinal Fibre Response)
		Wheat bran (1–2 tablespoons per meal)
	Emollient	Dioctyl sodium succinate (10–15 mL per cat p.o.)
	Lubricant	Mineral oil (10–15 mL per cat p.o.) Administer with caution due to risk of aspiration
		White petrolatum (1–5 mL per cat p.o.)
	Osmotic	Lactulose (0.5 mL/kg p.o. q.8–12h.)
		PEG 3350 (Colyte) 1.9 g per cat Dose can be doubled if no results are seen after 48 hours (see **Box 9.11** for CRI instructions)
	Stimulant	Bisacodyl (5 mg p.o. q.24h.)
Removal of feces	**Enemas**	Warm water (5–10 mL/kg)
		Dioctyl sodium succinate or DSS (5–10 mL per cat)
		Mineral oil (5–10 mL per cat)
		Lactulose (5–10 mL per cat)
	Manual extraction	Under anesthesia

Box 9.11 Conservative treatment of moderate-to-severe colonic impaction on cats

Polyethylene glycol (PEG) 3350 is an osmotic laxative that has been shown to be safe and palatable in cats. PEG 3350 can be administered to constipated or obstipated cats through a nasoesophageal tube as a CRI at a rate of between 6 and 10 mL/kg per hour. In a study of constipated cats, the mean total dose required was 80 mL/kg (range 40–156), and defecation occurred on average 8 hours after initiation of treatment (range 5–24). The technique has considerably decreased the need for enemas in feline practice (**Figure 9.100**).



FIGURE 9.100 Constipated cat receiving PEG 3350 as a constant rate infusion via a nasoesophageal tube. (*Courtesy of S. Little.*)

From Carr AP, Gaunt MC (2010). Constipation resolution with administration of polyethylene-glycol solution in cats. *J Vet Intern Med* 24(3):753–754. Little S (2014). Personal communication.

When treating a constipated cat, enemas should be given slowly, as rapid administration may cause reflex vomiting and rapid and excessive efflux of the liquid and may also increase the risk of colonic perforation. If several enemas fail to induce defecation, nasoesophageal administration of PEG 3350 is a relatively noninvasive method with an excellent success rate (**Box 9.11** and **Figure 9.100**). This technique has significantly decreased the number of cases that need to undergo manual extraction of feces, a technique used when all other options have failed. It is best performed on an anesthetized cat with careful transabdominal colonic massage and simultaneous rectal administration of a combination of warm water or physiologic saline with water-soluble lubricants to break down the impacted feces. Some authors recommend administering a low dose of metronidazole (7.5–15 mg/kg p.o. q.12h.) in order to limit the risk of bacterial translocation during or after the procedure.

A surgical approach is the last option for severe cases with obstipation or megacolon that does not respond to conservative treatment options. Different techniques for colectomy have been successful.

Prognosis

Many cats have one or two episodes of constipation without further recurrence, although others may progress to complete colonic failure. When conservative management

has failed, colectomy is usually associated with a favorable prognosis, although mild-to-moderate diarrhea may persist for 4–6 weeks postoperatively in some cases.

RECTAL PROLAPSE

Definition/Overview

Prolapse can be partial with protrusion of anal mucosa only (anal prolapse) or complete with protrusion of all layers of the rectum (rectal prolapse).

Etiology

Prolapse occurs secondary to tenesmus associated with disorders of the colon, anorectum, or urogenital tract. Prevalence appears to be higher in young animals. Predisposing factors include GI parasitism, typhlitis, colitis, proctitis, colorectal neoplasia, rectal FBs, perineal hernia, diseases of the urinary bladder, prostatic disorders, and dystocia.

Clinical Presentation

Anal prolapse is characterized by the presence of red, swollen mucosa protruding from the anus, particularly after defecation. In animals with a rectal prolapse, there is an often round or cylindrical mass protruding from the anus (Figure 9.101). The everted rectal mucosa and other wall layers can become ischemic and damaged and necrotic after prolonged exposure.

Diagnosis

A thorough physical examination is necessary to screen for the underlying diseases listed previously predisposing to prolapse. If indicated, additional tests, such as fecal parasitologic examination, blood analyses, and abdominal imaging should be performed.



FIGURE 9.101 Young mixed-breed dog with rectal prolapse. Sugar has been applied to the mucosa to decrease the swelling.

Management

Reduction under sedation is easiest in animals with anal prolapse using saline and water-soluble lubricant gel. When a significant amount of mucosa is exposed or in rectal prolapse, 50% dextrose can be applied to the mucosa to reduce edema prior to careful repositioning. Corticosteroid cream can also be used to decrease inflammation and straining. A purse-string suture is applied around the anus to narrow the anal orifice while allowing soft feces to pass through and kept in place for 3–5 days. The animal should be fed a low residue diet. Administering lactulose orally to effect (Table 9.12) may be helpful. If the prolapsed rectal mucosa is traumatized or necrotic, surgical resection is required. Underlying conditions must be addressed to prevent recurrence. Colopexy may be required in animals experiencing recurrent episodes despite appropriate treatment.

Prognosis

Generally good if the mucosa is viable and the prolapse can be reduced. Guarded to poor if resection is required because of the risk of stricture.

COLORECTAL NEOPLASIA

Etiology

In dogs, the prevalence of colorectal neoplasia is higher than that of gastric and small intestinal tumors. The sites of predilection are the descending colon and rectum. Adenomas and polyps are relatively common (Figure 9.102), and in situ progression to carcinoma has been documented. The most common type of malignant neoplasia is adenocarcinoma, followed by lymphoma and stromal tumors such as leiomyosarcoma. Local tumor invasion appears to be slow, and metastasis to distant sites is uncommon.

In cats, adenocarcinoma and lymphoma are the two most frequent types of colorectal neoplasia, followed by mast cell tumors. Sites of predilection are the descending colon and ileocolic junction. Malignant feline colorectal tumors have a high rate of metastasis. Alimentary lymphoma often involves both the small and large intestines.

Pathophysiology

Colorectal neoplasms may cause mechanical obstruction. Colonic dysfunction with abnormal motility and decreased water reabsorption capacity (with subsequent diarrhea) may also occur.

Clinical Presentation

In dogs, common clinical signs include hematochezia, mucoid feces, and dyschezia, with or without concurrent diarrhea. Dyschezia may be associated with passage of feces of a smaller than usual diameter (see Figure 9.97). Systemic neoplasia such as lymphoma may be associated with signs suggesting involvement of other

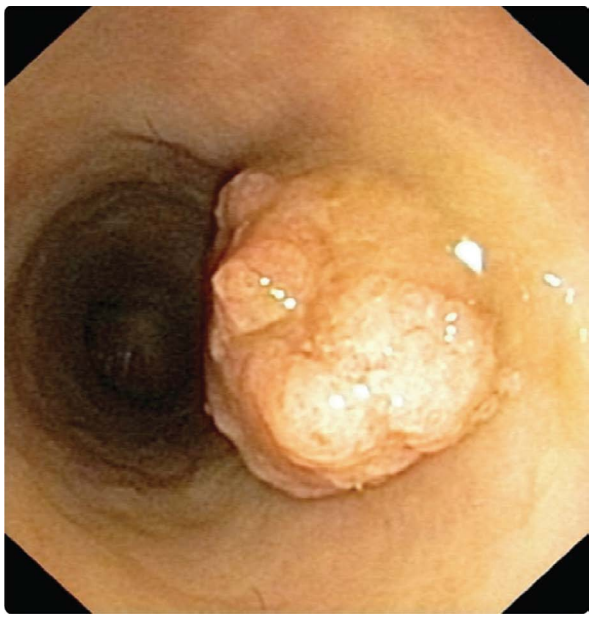


FIGURE 9.102 Colonoscopic view of an adenoma located in the distal colon of a dog. The parietal mass is pedunculated and could be removed with an electrocautery snare passed through the biopsy channel of the endoscope. (*Courtesy of R. Husnik.*)

organs, hyporexia, and weight loss. In cats, vomiting, diarrhea, and weight loss are common with or without clinical signs of large bowel disease.

Differential Diagnosis

Causes of chronic colitis such as IBD, GC, heavy whipworm infestation in dogs, IBD in cats. Also, distal colonic or rectal FB or stricture.

Diagnosis

In dogs, rectal palpation can detect up to 80% of rectal tumors. In cats, more than half of colonic masses can be palpated abdominally. Survey radiographs may show an accumulation of feces orad to the neoplasm. Mural masses can be visualized using abdominal ultrasound, and surrounding lymph nodes can also be evaluated. Cytologic evaluation of ultrasound-guided fine-needle aspirates can be useful, particularly for diagnosis of lymphoma. However, the diagnosis of most other tumors requires histopathology from a biopsy collected during colonoscopy. Endoscopy also allows a good evaluation of the severity and extent of the tumor (Figures 9.102 and 9.103). Thoracic radiographs and abdominal ultrasound are used to stage the tumor, looking for pulmonary masses and abnormal abdominal lymph nodes.

Management

Rectal tumors are usually amenable to surgical resection using the rectal pull-through technique. Masses located in the cecum and colon require standard celiotomy for resection. The benefit of chemotherapy has not been established except for alimentary lymphoma.

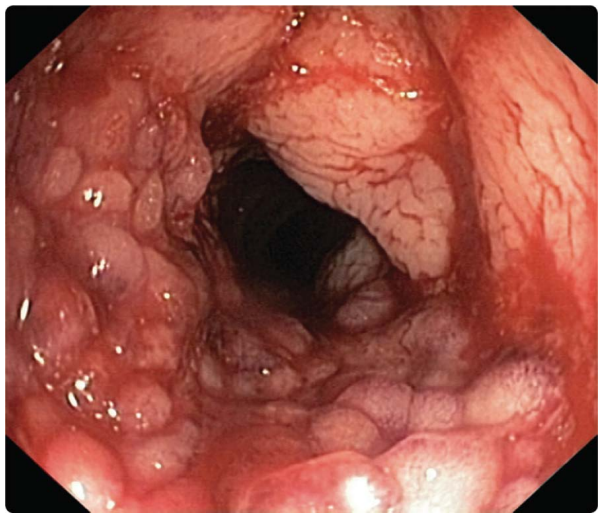


FIGURE 9.103 Endoscopic view of a dog with a severely abnormal rectal and colonic wall. The histopathologic diagnosis was adenocarcinoma. (*Courtesy of R. Husnik.*)

Currently, recommended chemotherapy protocols are best found in recent oncology texts.

Prognosis

Surgical excision is generally curative for benign tumors. The rectal pull-through technique has few complications; however, secondary infections may occur after celiotomy and resection of large bowel masses.

Canine carcinomas have been associated with a median survival of 32 months after removal in pedunculated tumors, 12 months for sessile tumors, and less than 2 months for annular tumors. The median survival time for leiomyosarcoma is 9–22 months after resection. Even though feline carcinomas benefit from an aggressive approach (subtotal colectomy), the median survival is only 4–5 months. The approach to alimentary lymphomas in cats is discussed in more detail in Part 4: Diseases of the Small Intestine.

PART 6: DISEASES OF THE ANUS AND PERINEUM

DISEASES OF THE ANAL SACS

Definition/Overview

Anal sac impaction, anal sacculitis, and abscess formation are common anal sac diseases that may occur in dogs and occasionally in cats. Small breed dogs and some large canine breeds (e.g., German Shepherd Dog) appear to be at higher risk of developing anal sac diseases.

Etiology

The exact cause of anal sac disorders is unknown. Abnormal anal sac emptying may occur with decreased fecal consistency, obesity, and inactivity or in association

with painful perianal processes such as anal furunculosis. Anal sac impaction increases the risk of infection and/or abscessation.

Clinical Presentation

Anal sac disease commonly causes anal or perianal pruritus and pain, with excessive licking and/or biting of the area, tail chasing, scooting, and rubbing the anus on the ground. If the perineal area is swollen and painful, the animal may not want to sit. Other frequently associated signs include dyschezia, tenesmus, or even reluctance to defecate. A detailed examination of the perineal area, including rectal palpation, may reveal swelling and pain to the touch.

Differential Diagnosis

Anal furunculosis, perianal or anal tumors, and bite wounds (especially in cats).

Diagnosis

History and clinical signs are suggestive. Swelling may be visible in the 4- and 8-o'clock positions ventral to the anus. Rectal palpation confirms the presence of swollen anal sacs, which are often painful. With impaction, pasty, thick, and malodorous material can be expressed from the swollen sacs. If the expressed material is bloody and/or purulent, anal sacculitis is likely and can be confirmed cytologically by the presence of large amounts of neutrophils with intracellular bacteria. Abscesses often involve the surrounding tissues, and cytology of a fine-needle aspirate is diagnostic.

Management

Anal sac impaction is treated with gentle expression of the swollen anal sacs. If digital massage and expression are not successful, flushing the anal sacs with saline is recommended. Instillation of an antibiotic and steroid ointment into the empty sacs is generally recommended. In animals with infected sacs, treatment also consists of emptying and flushing the sacs and instillation of an antibiotic ointment. However, this generally requires sedation or light anesthesia. Systemic antibiotic treatment with a broad-spectrum antibiotic for 10–14 days is usually recommended. Topical treatment with hot compresses several times daily may help reduce swelling and pain. Abscesses should be lanced, flushed, and treated with systemic antibiotics. Anal sacculectomy is a last resort option for recurring cases.

Prognosis

Usually very good. Fecal incontinence is a possible complication of anal sacculectomy.

ANAL SAC TUMORS

Definition/Overview

Anal sac tumors are uncommon and very often malignant neoplasms that occur in dogs. They may metastasize to regional lymph nodes and invade surrounding tissues.

Etiology/Pathophysiology

The etiology is unknown. Between 50% and 90% of dogs with anal sac adenocarcinomas are hypercalcemic due to production of parathyroid hormone-related peptide by cancerous cells. This malignancy-associated hypercalcemia may ultimately lead to irreversible kidney injury.

Clinical Presentation

Anal sac tumors most commonly affect older dogs, with a predilection for females. Dyschezia and perianal swelling may be observed. Up to 40% of dogs may only show clinical signs associated with hypercalcemia of malignancy: Polyuria, polydipsia, vomiting, and constipation. A thorough rectal examination is essential to identify nodules associated with the anal sacs. Metastasis to sublumbar lymph nodes is very common at the time of diagnosis (Figure 9.104), and liver and lungs may be affected as well.

Differential Diagnosis

Other perianal tumors, perineal hernia, rectal FB, or stricture. Other causes of hypercalcemia such as hyperparathyroidism, lymphoma, and other tumors should also be considered.

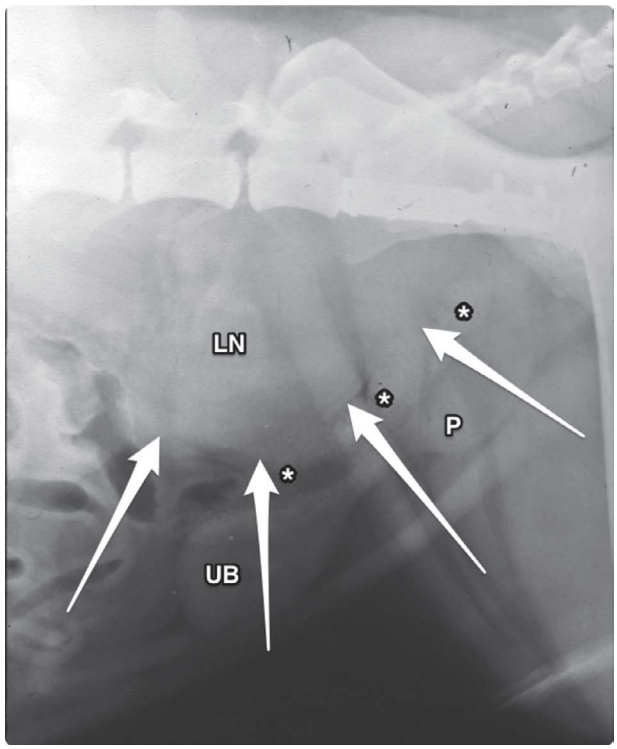


FIGURE 9.104 Radiograph of the caudal abdomen of a 10-year-old male Akita Inu. The dog was presented with severe hypercalcemia and dyschezia. While the primary anal sac tumor was a few millimeters in diameter, the sublumbar lymph node (LN) was severely enlarged (arrows). Note the ventrally displaced colon (asterisks), urinary bladder (UB), and prostate (P). A metallic plate used to repair a pelvic fracture several years prior to presentation is visible on the ileum.

Diagnosis

History and physical examination are suggestive. If a mass is present, cytologic evaluation of a fine-needle aspirate may be diagnostic. Radiographs and ultrasonography are useful to evaluate the sublumbar area, liver, and lungs for metastasis (Figure 9.104). Cross-sectional imaging may also be helpful in complicated cases. A CBC, serum chemistry profile, and urinalysis are essential to detect the presence of hypercalcemia (associated with hypophosphatemia) and possible secondary kidney damage.

Management

Wide surgical excision of the primary tumor and regional lymph node. The benefits of chemotherapy and/or radiation treatment have not been clearly established. Hypercalcemia may need to be addressed prior to surgery to avoid additional end organ damage (see Chapter 11).

Prognosis

Poor to fair, with a 40% 1-year survival. Negative prognostic factors include presence of lymph node or distant metastases and tumor size.

ANAL FURUNCULOSIS/ PERIANAL FISTULAE

Definition/Overview

Anal furunculosis is a chronic and painful disease of the canine anorectum that seems to preferentially affect middle-aged to old German Shepherd Dogs and German Shepherd Dog mixed breeds, although dogs from other breeds may be also affected. The condition is characterized by inflammation, ulceration, and sinus tracts.

Etiology

The etiology is unknown but is likely multifactorial.

Pathophysiology

The inflammatory process is chronic and consists of a mononuclear to granulomatous infiltrate. It may involve the anal sacs, their excretory ducts, the anal sphincter, and the circumanal glands. Immune dysregulation with aberrant cell-mediated immune response and excessive local production of matrix metalloproteinases has been reported in dogs with anal furunculosis. The lower carriage of the tail in affected dogs may provide the necessary environment for worsening inflammation and infection.

Clinical Presentation

Clinical signs include a painfully ulcerated perineal region with perianal discharge (Figure 9.105) and associated tenesmus, dyschezia, hematochezia, and/or constipation. In severe cases, anorexia, weight loss, and behavioral changes may be observed. Intensive perianal licking may be an early sign.



FIGURE 9.105 View of the cleaned and clipped perianal area of an 8-year-old female spayed German Shepherd Dog with anal furunculosis. Note several fistulous tracts oozing bloody or purulent exudate. (*Courtesy of LSU SVM Dermatology Service.*)

Differential Diagnosis

Anal sac abscessation, perianal tumor, bite wound, or other traumatic injury.

Diagnosis

Thorough examination of the perianal area may be difficult without sedation. The perineum should be cleaned to appreciate the extent of the disease process. The anus and rectum should be evaluated in detail, as they may be involved as well.

Management

Immunosuppression with cyclosporine (5 mg/kg p.o. q.12–24h. for 1–3 months) is effective in 60%–98% of cases but can be costly in large dogs. Concurrent use of ketoconazole, an inhibitor of cytochrome P450 enzymes, to increase the half-life of cyclosporine is not recommended because combination therapy results in unpredictable and often subtherapeutic cyclosporine levels. Immunosuppressive doses of prednisone (at least 2 mg/kg p.o. q.24h.) only help in one-third of cases. The effect of other immunosuppressive drugs has not been evaluated. Medical treatment followed by surgery (excision of remaining tracts, anal sacculectomy) is associated with a lower risk of recurrence. A significant number of dogs with anal furunculosis have concurrent adverse reaction to food

and feeding an elimination novel-protein or hydrolyzed diet may contribute to decreasing the recurrence rate.

Prognosis

Overall guarded. Recurrence is common. Anal sphincter incompetence and fecal incontinence are well known complications of surgery.

PERINEAL HERNIA

Definition/Overview

Perineal hernia results from weakness and breakdown of the pelvic diaphragm, with deviation and herniation of the rectum (and, possibly, the urinary bladder, prostate, and small intestine) into the perineum. The pelvic diaphragm consists of the levator ani and coccygeus muscles and the perineal fascia.

Etiology

The condition occurs in middle-aged, intact male dogs. Predisposed breeds include Pekingese, Boston Terrier, Welsh Corgi, Boxer, Poodle, Bouvier, and Old English Sheepdog. It is occasionally seen in cats as a surgical complication of perineal urethrostomy or colectomy.

Pathophysiology

The exact pathophysiology is unknown, and the disease is most likely multifactorial. The existence of rectal abnormalities (dilation, diverticulum), androgens, gender-related anatomic differences, relax in (a hormone synthesized in the prostate), prostatic disease, and neurogenic atrophy have all been associated with perineal hernia in dogs.

Clinical Presentation

Typical presenting signs include reducible perineal swelling (Figure 9.106), tenesmus, dyschezia, and constipation. The disease can be unilateral (if so, the right side is more commonly affected) or bilateral. Rectal examination reveals a defect in the pelvic diaphragm surrounding the rectum. If the bladder is retroflexed, dogs may not be able to void urine and develop postrenal azotemia with associated signs such as vomiting, anorexia, and lethargy.

Differential Diagnosis

Perineal tumor.

Diagnosis

History and clinical signs are usually sufficient. Survey and contrast radiographs (Figures 9.107 and 9.108) or ultrasonography (Figure 9.109) are necessary to confirm retroflexion of the urinary bladder or other organs. CBC, serum chemistry, and urinalysis are useful to evaluate kidney function.

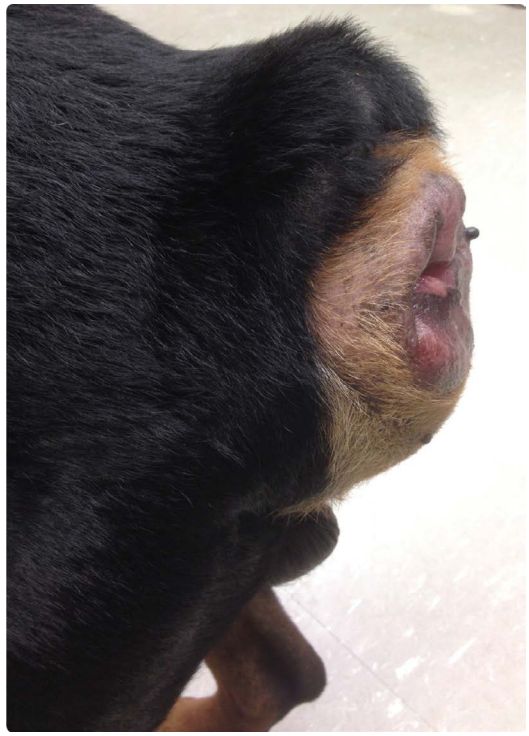


FIGURE 9.106 Severe bilateral perineal hernia in a 10-year-old intact male Rottweiler.

Management

Medical management, consisting of maintaining a soft fecal consistency with laxatives such as lactulose (0.5 L/kg p.o. q.8–12h.) or a bulk-forming agent such as psyllium (Box 9.9), and occasional enemas, may be successful in the short term with mild cases. However, most cases require surgical treatment. Herniorrhaphy using the internal obturator transposition technique is usually

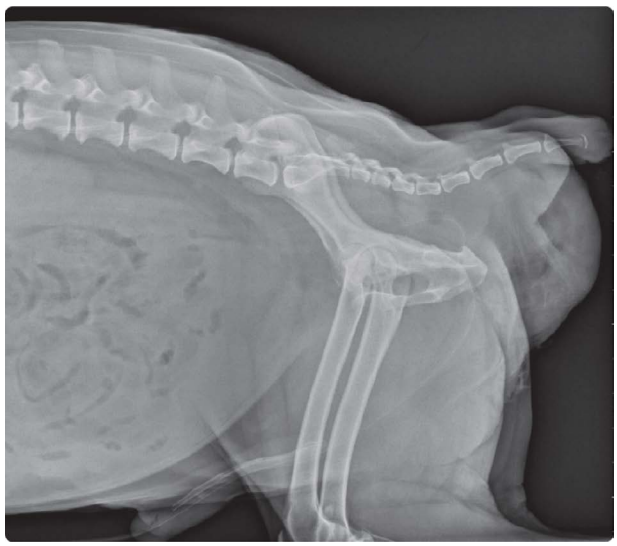


FIGURE 9.107 Another dog with a perineal hernia. Caudal abdominal radiograph. A large soft tissue mass representing the hernia can be seen in the perineum. The urinary bladder is not visible in the caudal abdomen.

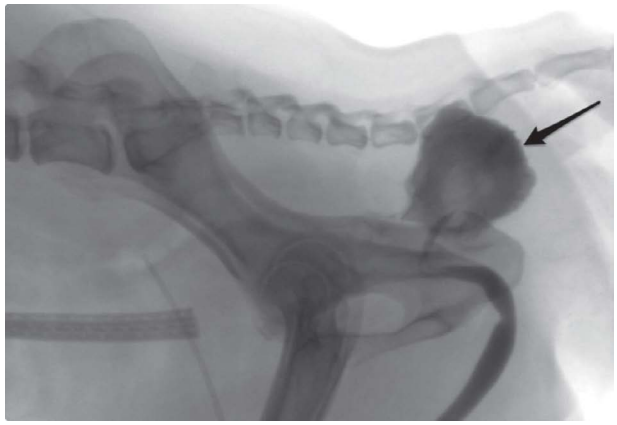


FIGURE 9.108 Positive contrast retrograde urethrocystography from the same dog as **Figure 9.107**. The bladder is retroflexed in the perineal hernia. (*Courtesy of L. Gaschen.*)

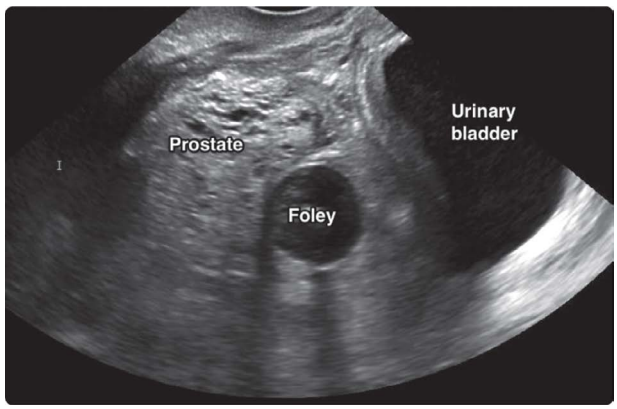


FIGURE 9.109 Ultrasound image of the dog in **Figure 9.106**. The prostate and urinary bladder are retroflexed in the retroperitoneal space. The balloon of a Foley catheter passed into the bladder is visible. Orientation: Left is cranial; right is caudal.

successful. (See surgery textbooks for further details.) Surgical complications include seroma, wound infection, fecal incontinence, and sciatic nerve paralysis.

Prognosis

Good if the hernia can be repaired early, guarded in dogs with chronic perineal hernia. In the latter group, recurrence is frequent, and repeat surgical intervention is often challenging.

PERINEAL TUMORS

Definition/Overview

The perianal region of dogs contains perianal (or circumanal) glands that are located in the dermis in a circular pattern around the anus. Perianal adenomas are the most common perianal tumors, while perianal adenocarcinomas occur considerably less frequently.

Etiology

Perianal adenomas are sex hormone dependent and occur mostly in middle-aged to older males. Cocker Spaniels, Beagles, Bulldogs, and Samoyeds may be predisposed. Adenocarcinomas are not influenced by sex hormones and occur in neutered or intact male and female dogs.

Clinical Presentation

Adenomas are slow growing, single, multiple, or diffuse nonpainful masses located around the anus or on the perineum and occasionally also on the prepuce, scrotum, and tailhead. Adenocarcinomas grow faster and may be similar to adenomas but may be firmer, adhere to underlying tissues, and become ulcerated.

Differential Diagnosis

Differentiating adenoma from adenocarcinoma is challenging but important, as more aggressive treatment is required for the malignant perineal tumor. Detection of metastases is strongly indicative of adenocarcinoma.

Diagnosis

Signalment, history, and physical examination are suggestive. Cytologic evaluation of a fine-needle aspirate reveals typical sebaceous cells that resemble hepatocytes. However, cytology does not allow reliable differentiation between adenoma and adenocarcinoma.

Management

Adenoma: Castration and conservative surgical removal. Adenocarcinoma: Wide excision of the primary tumor and affected lymph nodes. Postoperative radiation therapy may be useful. Inoperable cancers may benefit from palliative radiation treatment and chemotherapy.

Prognosis

Adenoma: Excellent, low risk of recurrence after excision if the dog is neutered. Adenocarcinoma: Removal at an early stage (diameter less than 5 cm) is associated with good survival.

CASE EXAMPLES

Case 9.1

Signalment

8-year-old female spayed Chihuahua

History

The dog was presented for a 3-week history of regurgitation. She would spit up her food with a lot of white foam approximately 5 minutes after eating but was able to hold down water and the liquid diet prescribed by her family veterinarian. Regurgitation had started around 2 weeks after having been diagnosed with pyometra and having undergone emergency ovariohysterectomy to treat pyometra.

(*Continued*)

Physical Examination

Body weight: 2.3 kg, weighed 3.1 kg 3 months ago

Body condition score: 3/9

Vital parameters: Within normal limits

Physical exam: The dog was quiet, alert, and responsive, and the exam did not reveal any abnormalities except a pre-existing grade 2/6 systolic heart murmur loudest in the left apical area.

Initial Assessment

An esophageal disorder was suspected. Because regurgitation had started a couple of weeks after general anesthesia and abdominal surgery, the most likely differential diagnoses included esophagitis and esophageal stricture occurring after severe intraoperative or postoperative gastroesophageal reflux. Recommended additional exams included a minimal database (CBC, chemistry panel and urinalysis) to evaluate the systemic impact of the disease. All laboratory parameters were within normal limits. Survey thoracic radiographs did not show any esophageal abnormality or evidence of aspiration pneumonia.

Further Investigations

As the top differential diagnoses were esophageal stricture and/or esophagitis, esophagoscopy was recommended and performed under general anesthesia. The mucosa was abnormal in both the cervical and thoracic esophagus. It appeared irregular and thickened with a cobblestone appearance (**Figure 9.110**). An intrathoracic esophageal stricture was present just cranial to the lower esophageal sphincter (**Figure 9.111**). These findings supported the hypothesis of severe intraoperative or postoperative gastroesophageal reflux causing esophagitis and the development of a stricture.



FIGURE 9.110 Endoscopic view of the cervical esophageal mucosa, which appears irregular with a cobblestone pattern (instead of smooth and shiny). The findings are indicative of chronic esophagitis.

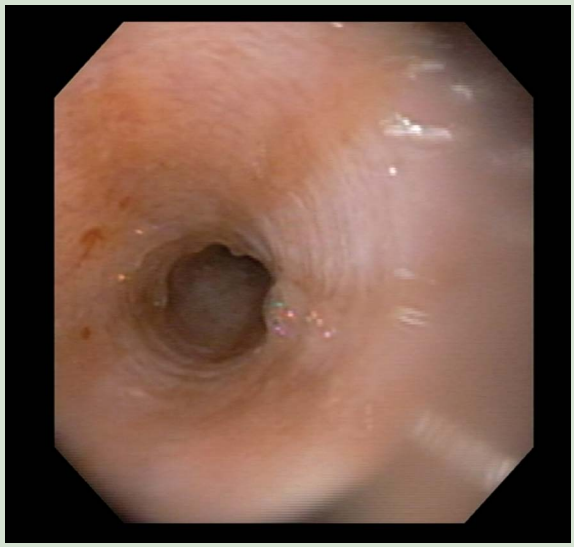


FIGURE 9.111 This endoscopic view of the thoracic esophagus past the heart base also shows an abnormally thickened mucosa and a narrowing (stricture) just craniad to the lower esophageal sphincter. The diameter of the stricture was approximately 6 mm.

Initial Treatment

The stricture was dilated using inflatable balloon dilation catheters of increasing diameters. Dilation was started with a 6 mm diameter balloon and discontinued after the 10 mm diameter balloon had been used due to moderate mucosal trauma (**Figure 9.112**). Then, triamcinolone was injected submucosally in four sites of the stricture

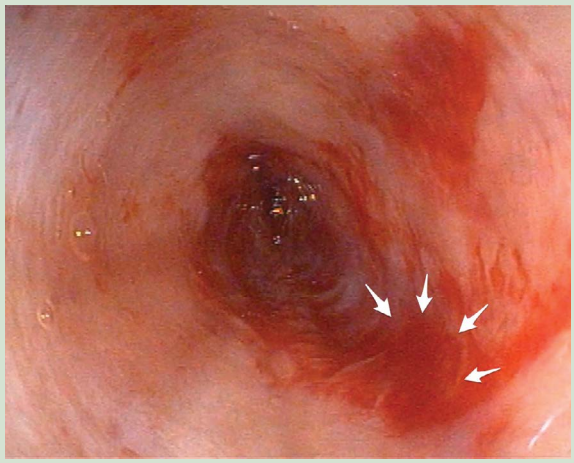


FIGURE 9.112 Following balloon dilation of the stricture to a diameter of 10 mm, there are several areas of focal bleeding. The white arrows delineate a superficial tear in the mucosa that occurred during the dilation.

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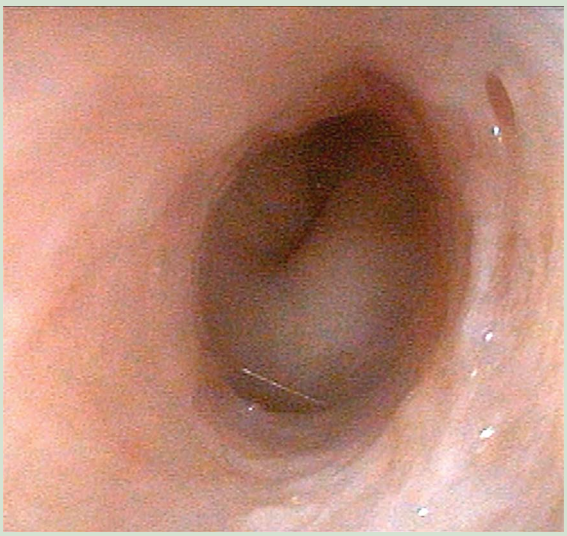


FIGURE 9.113 Endoscopic view of the stricture site 7 days after the initial dilation; the lower esophageal sphincter is visible. The opening is now approximately 8 mm. An endoscope with an outer diameter of 7.8 mm at the tip could be passed through it.

circumference to a total dose of 1 mg/kg. The dog recovered well. She was able to eat small balls of canned food without regurgitating on the day following the procedure. She was discharged with a standard treatment for gastroesophageal reflux, which included omeprazole (1 mg/kg p.o. q.12h.), sucralfate slurry (0.5 g per dog p.o. q.8h.) and metoclopramide as a gastric prokinetic (0.5 mg/kg p.o. q.8h.).

Further Treatment

The initial plan included three dilation procedures at weekly intervals. At the time of the first recheck, the dog was able to eat canned food without regurgitating. The abnormal appearance of the esophageal mucosa was unchanged. The site had strictured down to approximately 8 mm (**Figure 9.113**) and could be safely dilated to 10 mm again. The dog kept doing well, and the owner elected not to have any additional procedure performed. Medical treatment was discontinued after 4 weeks, and the dog was lost to followup.

Final Assessment

The dog was able to enjoy a good quality of life after partial restoration of the esophageal diameter leaving a focal luminal narrowing to approximately 8–10 mm, which was deemed to be between 66% and 75% of the normal diameter, i.e., 44%–56% of the normal cross-sectional area.

Case 9.2

Signalment

9-year-old female spayed Siamese mixed breed cat

History

The cat was presented for a 6-month history of small bowel diarrhea, vomiting, weight loss, and occasional hyporexia. She had initially responded to a diet change but then relapsed and was refractory to new dietary trials. She had received 1 injection of methylprednisolone acetate SC without improvement. At the time of presentation, the cat was vomiting approximately twice a week and passing soft feces resembling cow pats and had a normal appetite.

Physical Examination

Body weight: 4 kg, weighed 4.5 kg 1 year prior

Body condition score: 4/9

Vital parameters: Within normal limits

Physical exam: The cat was bright, alert, and responsive. During abdominal palpation, it was felt that the small intestinal loops were noticeably easy to palpate. No further abnormalities were noted.

Initial Assessment

Top differential diagnoses for a middle-aged to older cat with chronic vomiting, diarrhea and weight loss included chronic intestinal diseases such as inflammatory bowel disease (IBD) and low-grade alimentary lymphoma (LGAL). However, metabolic disorders such as hyperthyroidism or chronic kidney disease could not be ruled out. Recommended additional exams included a minimal database (CBC, chemistry panel, and urinalysis) and serum thyroxine concentration. The laboratory parameters were all within their reference ranges. An abdominal ultrasound exam was performed and revealed diffuse thickening of the small intestinal muscularis layer (**Figure 9.114**) and enlarged hypoechoic jejunal lymph nodes.

Further Investigations

Given the probable diagnoses, serum cobalamin and folate concentrations were evaluated, and the cat was hypocobalaminemic. Further recommendations to differentiate IBD and LGAL included exploratory laparotomy and collection of full-thickness small intestinal biopsies or upper and lower GI endoscopy to collect

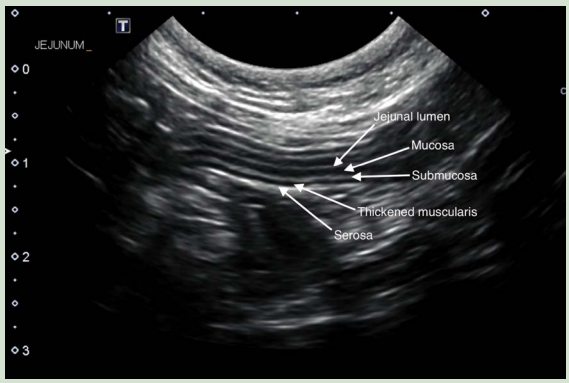


FIGURE 9.114 Sagittal ultrasonographic view of a jejunal loop. The 5 layers of the small intestinal wall are identified with arrows. While the intestinal wall thickness is not visibly abnormal, the muscular is layer is markedly thickened.

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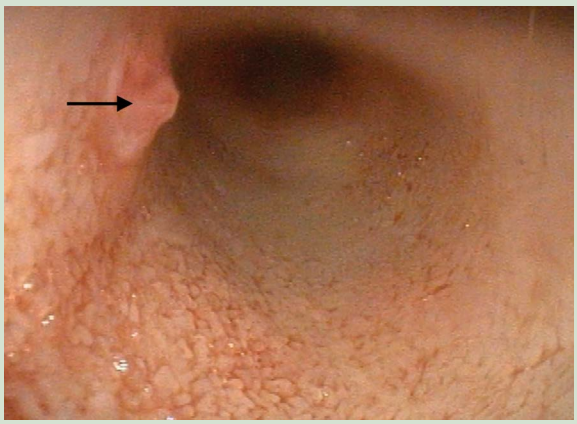


FIGURE 9.115 Endoscopic view of the proximal duodenum. The mucosa appears somewhat irregular. The black arrow points to the major duodenal papilla.

biopsies from stomach, duodenum, proximal jejunum, and ileum. They elected to proceed with endoscopy. The small intestinal mucosa appeared mildly irregular; however, no obvious lesions could be identified (**Figure 9.115**). The histological and appearance of the duodenal mucosa did not allow to differentiate between IBD and LGAL. Immunohistochemistry revealed that the lamina propria infiltrate consisted mostly of T-cells, which confirmed the diagnosis of LGAL.

Initial Treatment

The cat was administered vitamin B12 (250 ug per cat SC) and initially sent home on an immune-suppressive dose of prednisolone (1 mg/kg p.o. q.12h.) and a hydrolyzed protein diet.

Further Treatment

Upon reception of the final biopsy results, chlorambucil was added at 2 mg per cat p.o. every 3 days. The cat went into complete clinical remission and regained the weight she had lost. Over the following 3 months, the prednisolone dose was reduced in 25% steps to 1 mg/kg p.o. q.24h., and cobalamin injections were continued on a weekly basis for 6 weeks, then another dose 4 weeks later, and the serum cobalamin was checked 4 weeks later and found to be within the reference range. Starting approximately 3 months after initiation of chlorambucil treatment, the cat became moderately neutropenic. The dose was decreased to 1 mg per cat every 3 days, and the neutrophil count normalized without recurrence of GI signs.

Final Assessment

At the time of this writing, the cat has been in clinical remission for 12 months and currently receives prednisolone 0.5 mg/kg p.o. q.24h. and chlorambucil 1 mg per cat p.o. twice weekly. It is not uncommon for cats treated chronically with chlorambucil to develop neutropenia, and this cat responded well to a dose reduction that did not compromise success of LGAL treatment. Based on the literature, the median survival time for LGAL is between 14 and 36 months.

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CHAPTER

10

Hepatobiliary Disease

Andrea N. Johnston

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INTRODUCTION

Canine and feline hepatobiliary disease occurs commonly but can be challenging to diagnose and treat. Frequently, the clinical signs of hepatobiliary disease are nonspecific, and abnormalities are incidentally identified on clinicopathologic screening. Recognition of characteristic clinical presentations and application of targeted diagnostic algorithms are key to improving patient outcomes.

CONGENITAL PORTOSYSTEMIC VASCULAR ANOMALIES AND MICROVASCULAR DYSPLASIA

Definition/Overview

A portosystemic vascular anomaly is a grossly apparent abnormal connection between the portal vasculature and the systemic circulation bypassing the liver. Congenital portosystemic vascular anomalies include extrahepatic portosystemic shunts connecting a branch of the portal vein to the vena cava or azygous vein, intrahepatic portosystemic shunts (persistent ductus venosus), and, rarely, arteriovenous malformations.

Microvascular dysplasia (primary hypoplasia of the portal vein) refers to malformed intrahepatic portal microvasculature. Histologically, most cases of microvascular dysplasia are indistinguishable from portosystemic vascular anomalies.

Etiology

Congenital portosystemic vascular anomalies and microvascular dysplasia are heritable traits. Despite extensive efforts, a single causal genetic mutation has not been identified. A complex polygenic etiology is probable.

Pathophysiology

Hepatic venous hypoperfusion in dogs with macroscopic shunting reduces clearance of nutrients and waste products derived from gastrointestinal portal drainage by the liver. This results in reduced hepatic size and histomorphologic changes within the liver, including lobular atrophy, small arterialized portal tracts, and increased binucleate hepatocytes in the periportal region. Systemically, the reduced hepatic metabolism of ammonia and other substances enriched in the portal circulation upregulates inflammatory cytokine production, provokes hepatic encephalopathy through enhanced GABA receptor stimulation and astrocyte glutamine accumulation, and alters normal metabolic function.

Microvascular dysplasia causes abnormal blood flow through the hepatic sinusoids with minimal systemic consequences. Dogs with microvascular dysplasia do not have signs of illness nor do they require specific therapy.

Clinical Presentation

Dogs with congenital extrahepatic portosystemic shunts are usually identified within the first 2 years of life, but minimally symptomatic dogs may be diagnosed at any age. Dogs with intrahepatic shunts tend to have more severe clinical signs and are usually diagnosed before

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FIGURE 10.1 Dachshund littermates. The dog on the left has a portoazygous shunt.

1 year of age. Cats with portosystemic shunts can be challenging to identify and may present at any age. Extrahepatic shunts usually occur in small breed dogs. Yorkshire Terrier (19%–31%), Shih Tzu, Maltese, Pug, Miniature Schnauzer, West Highland White Terrier, Bichon Frise, Border Terriers, Jack Russell Terriers, Miniature and Toy Poodles, Havanese, Cairn Terriers, Silky Terriers, and mixes of these breeds are overrepresented. Intrahepatic shunts usually occur in large breed dogs. Labrador Retrievers, Siberian Huskies, and Irish Wolfhounds are overrepresented. There is no gender predisposition. Dogs with microvascular dysplasia have the same signalment as small breed dogs with portosystemic vascular anomalies. In some cases, both vascular malformations occur in the same dog.

Commonly noted features of dogs with portosystemic shunts are small body stature (Figure 10.1), pediatric hypoglycemia, polyuria/polydipsia, vague gastrointestinal signs, overt hepatic encephalopathy, and urinopathies associated with ammonium biurate urolithiasis. Ptyalism and atypical copper irises are frequently noted in cats with portosystemic shunts, but they may present for lower urinary tract signs, vague gastrointestinal illness, or overt hepatic encephalopathy.

Differential Diagnosis

Reactive hepatopathy, portal hypertension (prehepatic, hepatic, or posthepatic) with multiple acquired portosystemic shunts.

Diagnosis

Complete blood count abnormalities in dogs with portosystemic shunts include microcytic red blood cells and occasionally a mild mature neutrophilic leukocytosis. Dogs with portosystemic shunts typically have mild to moderately elevated hepatic transaminases (alanine aminotransferase, aspartate aminotransferase [ALT, AST]), hypoalbuminemia, low blood urea nitrogen (BUN), and hypocholesterolemia; however, one or more of these clinicopathologic values may be normal. Urine specific gravity may be normal, isosthenuric, or hyposthenuric. Urine sediment will contain ammonium biurate crystals in some dogs with portosystemic shunts (Figure 10.2). Elevated arterial and venous blood ammonia is sensitive and specific for portosystemic shunting, but false negatives are possible. Paired (2 hours apart) total serum bile acids are the best screening test for dogs and cats with portosystemic shunts. A small meal of the pet's normal food is fed after the first sample is collected. Even if the patient will not eat, the paired sample is collected at 2 hours. Cyclic contraction of the gallbladder occurs at regular intervals even in fasted patients. If either the preprandial or the postprandial bile acid is >30 µmol/L, additional testing is indicated. Protein C, an anticoagulant protein synthesized in the liver, is measured as a secondary biomarker of portosystemic shunting. Citrated plasma is frozen and submitted to the Cornell Animal Health Diagnostic Center. In dogs with abnormal bile acids and no evidence of severe liver injury, protein C <70% activity is consistent with the presence of a

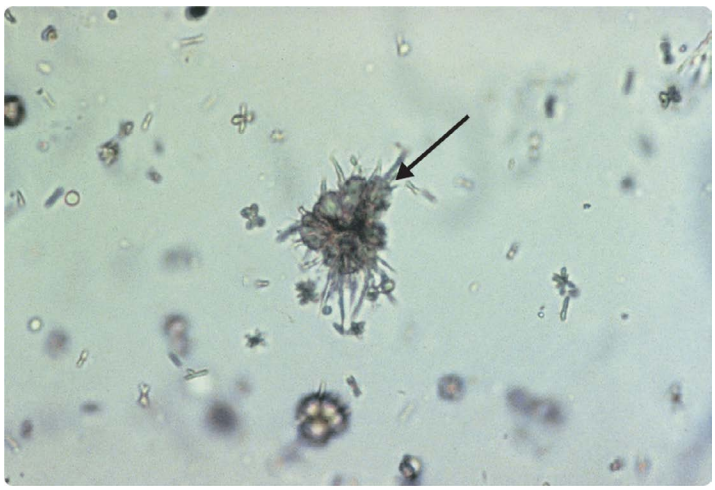


FIGURE 10.2 Ammonium biurate crystal (arrow) in the urine sediment in a dog with a portacaval shunt. (*Courtesy of J. Taboada.*)

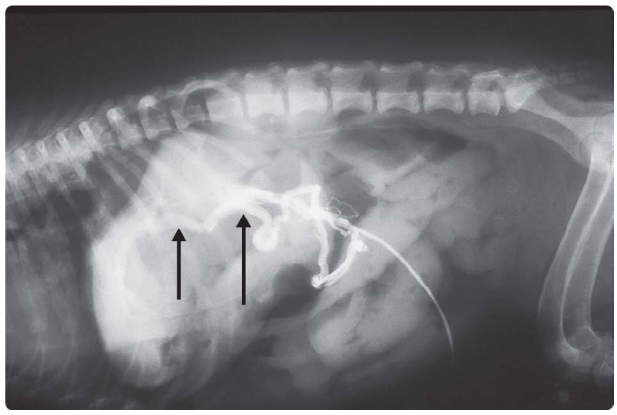


FIGURE 10.3 Mesenteric venous portography confirmed a shunt (arrows) in this 2-year-old Lhasa Apso. (*Courtesy of J. Taboada.*)

portosystemic shunt, values >100% suggest microvascular dysplasia, and values between 70% and 100% are in the gray zone, requiring diagnostic imaging.

Computed tomography angiography (CTA) is the gold standard diagnostic imaging modality for portosystemic shunt detection. Results are invaluable for surgical shunt attenuation planning. Estimates suggest that 75%–92% of portosystemic shunts may be diagnosed by abdominal ultrasonography. Abdominal ultrasound is dependent on the skill of the operator and the location of the shunt. The modality can support a diagnosis of portosystemic shunting (microhepatica, enlarged kidneys, nephrolithiasis, urolithiasis, and smaller portal vein to aorta ratio (≤0.65). Splenic or transcolonic scintigraphy has historically been used to diagnose portosystemic shunting, but the use of a radionuclide and suboptimal shunt localization limits its usefulness. Intraoperative mesenteric portovenography has also been used to locate portocaval anomalies (Figure 10.3)

Dogs with microvascular dysplasia may have mild hepatic transaminase elevations but do not routinely have other clinicopathologic abnormalities; however, serum bile acids are elevated. In many cases, protein C distinguishes between macroscopic shunting and microvascular dysplasia. Occasionally, CTA is needed to confirm the diagnosis. Liver histology will not differentiate portosystemic shunting from microvascular dysplasia.

Management

Medical management is recommended in all dogs with a portosystemic shunt regardless of whether shunt attenuation will be pursued (Table 10.1). The goal of medical management is to reduce elevated systemic ammonia levels. The therapeutic strategy consists of dietary modification to a soy- or dairy-based protein, hastening gastrointestinal transit time and modulation of gut microbiota (Table 10.1). Most owners describe an improvement in their pet's neurobehavioral condition after starting medical management. In patients that cannot undergo attenuation, medical therapy continues lifelong but is reduced to what is minimally necessary to control clinical signs. If antibiotics are used, these are withdrawn first. Diet modification is continued indefinitely. Owners are advised that medically managed patients will experience more profound episodes of illness than normal dogs or cats. Owners are encouraged to have antibiotics and lactulose available to administer as needed, thus avoiding expensive hospitalizations.

Surgical attenuation for extrahepatic portosystemic shunts may be completed using silk suture ligation, ameroid constrictor application, or cellophane banding. A recent systematic review found that ameroid constrictors were superior to thin film banding for shunt

TABLE 10.1 Medical management of hepatic encephalopathy (HE)

Therapeutic goals
- Limit hepatic encephalopathy
- Reduce adverse health events

Nutrition
- Tailor diet to the individual
- Avoid overzealous restriction of dietary protein
- Commercially available liver diets are a good starting point
- Begin with ~2.5 g/kg of protein per day and titrate up to a level that is tolerated without signs of HE
- Soy or dairy protein is better tolerated in dogs with HE
  - Adjust protein with supplementary dairy (cottage cheese, cheese, yogurt) or tofu
- Dietary fiber enhances enteric nitrogen elimination
- Avoid red meat, fish, and organ meat

Nonabsorbable disaccharides
- Lactulose (0.25–0.5 mL/kg p.o. q.8–12 h., titrate dose to achieve soft stool)
  - Laxative effects to decrease gut transit time
  - Decreases activity of bacterial ureases and enteric peptidases, increasing bacterial nitrogen fixation
  - Acidification of enteric pH traps protonates of ammonia trapping it in the gut lumen
- Lactitol (0.5–0.75 g/kg p.o. q.8–12 h.)
- Lactose (to effect)

Modulation of gastrointestinal microbiota
- Antibiotics (amoxicillin 10 mg/kg p.o. q.12 h., metronidazole 7.5 mg/kg p.o., future option: Rifaximin)
- Probiotics as an alternative to antibiotics (e.g., Visbiome, Prostora, Proviable)

Treatment of severe, overt encephalopathy
- Maintain euhydration, normal electrolyte balance, and euglycemia
- Elevate patients head (30°) to reduce risk of aspiration
- Intravenous antibiotics (metronidazole or ampicillin) to modify gut flora
- Cleansing enema (10 mL/kg warm isotonic crystalloid, repeat until clear)
- Lactulose retention enemas reduce ammonia resorption (5–15 mL 1:3 in water, use Foley catheter)
- Seizures
  - Levetiracetam (30–60 mg/kg IV loading dose, 30 mg/kg IV q.8 h.)
  - Propofol (0.3–0.6 mg/kg/min CRI) for refractory seizures
  - Mannitol (0.5–1.0 g/kg IV once or twice) to induce osmotic diuresis if intracranial pressure elevates, monitor for hypernatremia
  - **Avoid benzodiazepines**

attenuation. Both methods rely on slow occlusion of the shunting vessel; thus, incomplete occlusion or delayed portal hypertension with acquired portosystemic shunting can occur. Silk suture ligation attenuates the shunting vessel partially or fully based on portal pressure measurements at the time of surgery. Attenuation of intrahepatic shunts may be accomplished with suture ligation or endovascular coil embolization; portal pressures are routinely measured in both procedures.

Critical observation is required during the immediate postprocedure period. Common complications include hypoglycemia and hypotension, which are easily corrected if addressed early. Postoperative neurologic complications including seizure are less common. Preoperative medical management rather than pre-emptive administration of antiepileptic is currently recommended to limit postoperative neurologic decompensation (Table 10.1). The development of portal hypertension is a serious postoperative complication manifesting with melena, hemorrhagic diarrhea, ascites, and hemorrhagic shock. Aggressive supportive care and monitoring are indicated if this occurs.

Post attenuation rechecks are planned at 2 weeks, 1 month, 3 and 6 months. If clinical signs are improved, medical management is tapered over the first 1–3 months. Complete blood count (CBC) and chemistry are rechecked at each visit. Protein C is re-evaluated beginning at 1 month and every subsequent recheck. If protein C does not improve or remains below normal (<70), then a CTA is recommended after 6 months. Some dogs continue to have residual shunting and require a second procedure or ongoing medical management.

Dogs with microvascular dysplasia do not require medical management but may have delayed clearance of drugs metabolized in the liver.

Prognosis

Prognosis is dependent on the severity of clinical signs and management strategy. Portosystemic shunt attenuation reportedly results in longer survival times than medical management. Quality of life questionnaires are helpful to determine how medically and surgically managed dogs are faring long term. Dogs with microvascular dysplasia have a good prognosis.

DUCTAL PLATE MALFORMATIONS

Definition/Overview

Hepatic polycystic and fibropolycystic disorders encompass a heterogeneous group of embryologic malformations of the anatomic precursor of the intrahepatic bile ducts, the ductal plate. Malformations affecting the small bile ducts with variable severity fibrosis (congenital hepatic fibrosis) and segmental dilations of the larger intrahepatic ducts with (Caroli's syndrome) and without (Caroli's disease) small duct abnormalities have been described in dogs and cats.

Etiology

The specific environmental and molecular mechanisms leading to ductal plate malformations in dogs and cats are largely unknown. Some cats with feline polycystin-1 mutation, which causes polycystic kidney disease, will develop concurrent hepatic cysts.

Pathophysiology

Progressive expansion of cystic ductal structures and periductal fibrosis cause hepatic parenchymal damage. In cases of canine congenital hepatic fibrosis, multiple acquired portosystemic shunts eventually develop due to intrahepatic portal hypertension. Noncontiguous fluid filled cystic bile ductal structures may become infected, bleed, or develop choleliths.

Clinical Presentation

The polycystic liver diseases of dogs and cats are rare. Patients of both species may present at any age, but severe juvenile phenotypes are the most commonly reported. Persian, Siamese, Abyssinian cats and Boxer, Cairn Terrier, and West Highland White Terrier dogs are overrepresented. Clinical signs include anorexia, vomiting, diarrhea, abdominal discomfort, or ascites once portal hypertension develops. The liver is normal to small in congenital hepatic fibrosis but is enlarged in polycystic liver disease.

Differential Diagnosis

Inflammatory liver disease

Diagnosis

B-mode abdominal ultrasonography, computed tomography, and magnetic resonance imaging can identify macroscopic cysts of the intrahepatic (Figure 10.4) and extrahepatic biliary tree, but histology is necessary to identify microscopic fibropolycystic ductal disorders such as congenital hepatic fibrosis. Gallbladder agenesis is associated with ductal plate malformation.



FIGURE 10.4 Abdominal ultrasound image of polycystic liver disease in a 15-year-old male cat. Multiple large, anechoic, fluid-filled cysts compress the hepatic parenchyma.

Clinicopathologic features include mild to severe increases in liver enzymes (ALT, AST, alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT]). Hyperbilirubinemia occurs in congenital hepatic fibrosis. In dogs with acquired portosystemic shunts, red blood cell microcytosis, subnormal albumin, BUN, and cholesterol may be present along with elevated total serum bile acids.

Management

There is no specific treatment for canine and feline ductal plate malformations. Extrapolating from human medicine, treatment with octreotide (canine: 1–10 µg/kg SQ q.6–8 h., feline: 10 µg/kg SQ q.8 h.) may be attempted to reduce cyst volume in patients with multiple macroscopic cysts. Antioxidants and antifibrotics are routinely initiated but with limited success (Table 10.2). Management largely focuses on treatment of disease sequelae. Antiemetics and appetite stimulants are used for gastrointestinal signs. Diuretics are instituted as needed to manage ascites (Table 10.2).

Prognosis

Prognosis is variable dependent on the type of malformation. Congenital hepatic fibrosis has a guarded to poor prognosis.

ACUTE LIVER INJURY/ ACUTE LIVER FAILURE

Definition/Overview

Acute liver injury refers to severe hepatocellular damage in a patient without a previous history of liver disease. Clinical and biochemical signs of liver failure are not apparent until >70% of functional hepatic mass is lost. Acute liver failure manifests with hyperbilirubinemia, impaired coagulation (prothrombin time >1.5× upper limit of reference interval), and overt hepatic encephalopathy.

TABLE 10.2 A general list of various drugs used for treating various forms of liver disease in the dog and cat, depending on underlying pathology

Drug	Dose	Route	Frequency
Antibiotics			
Ampicillin sodium/sulbactam sodium	22–30 mg/kg	IV	q.8 h.
Clindamycin	10–12.5 mg/kg	IV	q.12 h.
Metronidazole	7.5–10 mg/kg	IV, p.o.	q.12 h.
Ticarcillin disodium/clavulanate potassium	15–25 mg/kg infusion over 15 minutes, followed by 7.5–15 mg/kg CRI	IV	CRI
Neomycin is no longer recommended due to potential for nephrotoxicity and ototoxicity			
Antioxidants			
N-acetylcysteine – Nonpyrogenic, 0.25 µm filter – Dilute 1:2 or 1:4 – Give over 20 minutes	140 mg/kg once, then 70 mg/kg	IV	q.6–8 h.
Ursodeoxycholic acid (UDCA) – *Do not administer in cases of bile duct obstruction or ductopenia*	5–10 mg/kg	p.o.	q.12 h. with food
S-adenosylmethionine (SAMe) – *Use a reputable manufacturer* – *Must be complexed with stable synthetic salts (disulfonate salt, tosylate salt, phytate salt) to be bioavailable*	20–40 mg/kg *Phytate salt complex may increase bioavailability, and dose reduction should be considered (8–10 mg/kg)*	p.o.	q.24 h. on an empty stomach
Vitamin E	10–15 IU/kg *Do not exceed 400 IU per dog*	p.o.	q.24 h.
Excluding the use of injectable silibinin for amatoxin ingestion, the benefit of silymarin (milk thistle) in the treatment of human liver disease has not been supported by recent prospective studies			

(*Continued*)

TABLE 10.2 A general list of various drugs used for treating various forms of liver disease in the dog and cat, depending on underlying pathology *(Continued)*

Miscellaneous vitamins			
Vitamin K_1	0.5–1 mg/kg	SQ	q.12 h. ×3 doses
Pyridoxine, vitamin B_6 – *Administered during D-penicillamine therapy*	25 mg	p.o.	q.24 h.
Immunosuppressives			
Azathioprine – *Canine only*	2 mg/kg (>25 kg, 50 mg/m^2)	p.o.	q.24 h. ×14 days, then q.48 h.
Budesonide – *If no portosystemic shunting*	3 mg/m^2	p.o.	q.24–48 h.
Cyclosporine – *Modified: Neoral or Atopica* – *Trough levels may optimize dosing*	5 mg/kg	p.o.	q.12 h. on an empty stomach if tolerated, taper to once daily at remission
Dexamethasone	0.2 mg/kg, taper to lowest effective dose	SQ, IV	q.48–72 h.
Mycophenolate mofetil	10 mg/kg	p.o.	q.12 h. with food
Prednisone, prednisolone (cats) – *If no ascites*	2–4 mg/kg, taper to lowest effective dose	p.o.	q.24 h. p.o. with food
Copper chelators			
Ammonium tetrathiomolybdate – *Cost prohibitive*	0.5 mg/kg	p.o.	q.6 h.
D-penicillamine	10 mg/kg	p.o.	q.12 h. on an empty stomach, maintenance therapy 2-3 times per week
Trientine – *Cost prohibitive*	5–7.5 mg/kg	p.o.	q.12 h.
Copper uptake antagonist			
Zinc – *Zinc acetate (30% zinc)* – *Zinc gluconate (13% zinc)* – *Monitor serum zinc levels (effective dose >200 µg/dL; toxic levels >800 µg/dL)*	8–10 mg/kg of elemental zinc	p.o.	q.24 h., give 30 minutes before meals
Diuretics			
Furosemide – Use adjunctively with spironolactone – Monitor for hypokalemia/alkalosis – Titrate to effective dose	1–4 mg/kg	p.o.	Divided q.12 h. daily
Spironolactone – Titrate to effective dose	1–4 mg/kg	p.o.	Divided q.12 h. daily
Antifibrotics			
Polyunsaturated phosphatidylcholine (PhosChol)	15–25 mg/kg *Do not exceed 4g*	p.o.	q.24 h. with food
Losartan – *Check renal panel 7–10 days after starting and full chemistry at scheduled rechecks*	0.25–0.5 mg/kg	p.o.	q.24 h.
Colchicine is no longer recommended due to unacceptable side effects			

Etiology

In canine and feline patients, acute liver injury is caused by hepatotoxin ingestion (*Amanita* sp mushrooms (amatoxin), aflatoxin, blue green algae (microcystin), sago palm (cycasin), xylitol), drugs (acetaminophen, oral diazepam (cats), carprofen, lomustine, methimazole, mitotane, phenobarbital, phenytoin, tetracycline, sulfa drugs), infection (histoplasmosis, leptospirosis, *Mycobacterium*, *Neospora*, *Sarcocystis*, schistosomiasis, toxoplasmosis), ischemia, sepsis, heatstroke, and neoplasia.

Pathophysiology

Synthetic failure results from severe, acute hepatocellular injury leading to cell death and organ dysfunction. The specific mechanism of action is dependent on etiology. The pathophysiology of acute hepatic encephalopathy is multifactorial involving increased circulating ammonia, failed intracranial oxidation-reduction mechanism, and systemic upregulation in inflammatory mediators.

Clinical Presentation

Clinical signs may include circulatory or hemorrhagic shock, hypotension, anorexia, vomiting, diarrhea, altered mental status, ascites, and jaundice (**Figure 10.5**).

Differential Diagnosis

Hemolytic crisis, severe systemic disease

Diagnosis

Laboratory tests to confirm acute liver injury/failure include elevated liver enzymes (ALT, AST), abnormal liver function tests (hyperbilirubinemia, hypocholesterolemia, hypoglycemia, hypoalbuminemia), and abnormal coagulation parameters (prolonged prothrombin and activated partial thrombin time, hypofibrinogenemia).

Management

Isotonic crystalloid fluid therapy with supplementation is initiated to address volume deficits, maintain euhydration, correct electrolyte abnormalities, and treat hypoglycemia. Impaired liver function may reduce hepatic capacity to metabolize lactate; therefore, isotonic crystalloids devoid of lactate buffer are selected. In patients with hepatic encephalopathy, 0.9% sodium chloride is administered to maintain serum osmolality and prohibit intracranial pressure elevation. In hypotensive patients that fail to respond to volume administration, vasopressors are initiated (norepinephrine, vasopressin) to address hypotension.

Decontamination of known hepatotoxins is indicated when toxin ingestion was observed. Emesis is induced (apomorphine 0.03–0.04 mg/kg IM, IV [dog], xylazine 0.44 mg/kg IM [cat]) if ingestion is recent and mentation status is appropriate. This is routinely followed by administration of activated charcoal with sorbitol (2 g/kg p.o. once); charcoal without sorbitol may be repeated every 6–8 hours. Cholestyramine (0.3–0.5 g/kg in food p.o. q.6–8 h. for 3–5 days), an anion exchange resin that binds bile acids in the gastrointestinal tract, may be useful to treat toxins that have enterohepatic recirculation (blue-green algae [microcystin], piroxicam, phenobarbital, phenytoin, sago palm [cycasin]). Antidotes are administered when appropriate (e.g., N-acetylcysteine for acetaminophen intoxication, intravenous silibinin for amatoxin ingestion (not commercially available in the United States). Specific recommendations should be sought from the ASPCA Animal Poison Control.

Hepatoprotectants (**Table 10.2**) are routinely administered to attenuate oxidative injury, replenish metabolic cofactors, and limit cell membrane lipid peroxidation (N-acetylcysteine or SAMe, vitamin B complex, vitamin E). Therapy with vitamin K_1 is started if coagulation tests are abnormal (**Table 10.2**). In patients with overt hepatic encephalopathy, management is dependent on the severity of clinical signs. In mild, overt encephalopathy, administration of oral lactulose and gastrointestinal flora modulation may be the only treatment necessary. Severe, overt hepatic encephalopathy requires aggressive supportive care (**Table 10.1**). The patient's head is elevated (30°) to reduce risk of aspiration. Intravenous antibiotics (metronidazole or ampicillin sodium/sulbactam sodium) are used to modify gut flora. Cleansing and lactulose retention enemas may reduce ammonia resorption. If seizures occur, levetiracetam is the first-line therapy followed by propofol continuous rate infusion. Benzodiazepines are avoided because they agonize GABA-mediated neurotransmission, which exacerbates encephalopathy. Mannitol may be given to induce osmotic diuresis if intracranial pressure elevation is suspected.

The extent of patient monitoring in acute liver injury/failure is dependent on the severity of illness. CBC, biochemistry, urinalysis, and coagulation panel are evaluated initially, and abnormalities are rechecked regularly. Hepatic transaminase reduction may signal improvement or loss of functional hepatic mass. Bilirubin and hepatic synthetic factors are better indicators of function, but the latter can be skewed if acquired portosystemic shunts develop.



FIGURE 10.5 Icteric patient with acute liver injury.

Prognosis

Prognosis is variable. Severely elevated transaminases are not poor prognostic indicators. Normal albumin in acute liver failure is a good indicator of survival.

CANINE CHRONIC HEPATITIS

Definition/Overview

Chronic hepatitis is an inflammatory reaction in the liver, as demonstrated by liver histology, continuing without improvement for at least 6 months. Canine chronic hepatitis is caused by a diverse group of infectious, metabolic, toxic, and immune-mediated diseases.

Etiology

Infectious organisms are an uncommon cause of canine chronic hepatitis. Leptospirosis causes acute hepatitis, which may evolve to a chronic pyogranulomatous inflammatory process. Leishmaniasis causes a granulomatous chronic hepatitis. *Ehrlichia canis* and babesiosis are sporadically associated with chronic hepatitis.

Several drugs and toxins (carprofen, amiodarone, aflatoxin, and cycasin) may lead to chronic hepatitis following acute liver injury. Drug-induced chronic hepatitis may be caused by phenobarbital, primidone, phenytoin, and lomustine (CCNU). Excess hepatic copper accumulation due to genetic (Bedlington Terrier, copper metabolism domain-containing 1 [COMMD1] mutation) or metabolic derangements is the most common cause of toxin induced chronic hepatitis.

In dogs, autoimmune chronic hepatitis is a diagnosis of exclusion dependent upon supporting evidence, including lymphocytic hepatic infiltrates, abnormal expression of major histocompatibility complex class II proteins, positive serum autoantibodies, familial liver disease, concurrent immune-mediated disorders, female gender, and response to immune modulation.

Pathophysiology

The initiating pathophysiology is dependent on etiology. Hepatic injury results in hepatocellular death and the release of inflammatory mediators. Inflammatory cell infiltration and immune regulatory dysfunction perpetuate ongoing injury, leading to necrosis and fibrosis.

Clinical Presentation

Chronic hepatitis is a disease of middle-aged to older dogs. Chronic hepatitis can occur in any breed, but some breeds are predisposed (asterisk denotes copper associated hepatitis): Bedlington Terrier*, Dalmatian*, Dobermann Pinscher*, Labrador Retriever*, West Highland White Terrier*, American Cocker Spaniel, English Cocker Spaniel (Europe), English Springer Spaniel (UK), Scottish Terriers (Sweden). The clinical signs of chronic hepatitis are often episodic and may include anorxia, fever, abdominal pain, vomiting, diarrhea, weight loss, polyuria/polydipsia, lethargy, jaundice, and weakness.

Differential Diagnosis

Reactive hepatopathy secondary to systemic disease, degenerative hepatopathy, neoplasia.

Diagnosis

The diagnosis and treatment of chronic hepatitis is a complex process that requires integration of clinical presentation with clinicopathologic findings, diagnostic imaging, and hepatic biopsy. Initially, hepatocellular leakage enzyme (ALT, AST) elevations predominate, but the cholestatic enzymes may also become elevated. These values wax and wane over the course of months. As hepatocytes are lost and fibrosis limits normal sinusoidal blood flow, the markers of hepatic synthetic function are disturbed. Diagnostic ultrasonography is helpful to identify neoplastic masses, ascites, and acquired portosystemic shunting vessels but is not sensitive nor specific for the diagnosis of chronic hepatitis. Hepatic cytology is typically performed to rule out diffuse neoplastic infiltration and identify suppurative inflammation, but it is inadequate for the diagnosis of chronic hepatitis.

Hepatic biopsy is necessary for definitive diagnosis (Table 10.3 and Figures 10.6 and 10.7). The characteristic histologic features of chronic hepatitis include hepatic inflammation (lymphocytic, plasmacytic, or granulomatous) in any region of the liver in conjunction with hepatocellular death and variable grades of fibrosis. In addition to the histology panel, liver tissue is submitted for aerobic/anaerobic culture and dry weight copper quantification (20–40 mg of tissue is required) by atomic absorption spectroscopy.

TABLE 10.3 Liver biopsy guidelines

Histology
- 15 portal tracts needed for accurate histologic evaluation
  - 5 laparoscopic or surgical samples, multiple 14- to 16-G needle biopsies
- Biopsy multiple lobes (n ≥ 2)
- Handle tissue carefully to avoid crush artifact and immediately place in neutral buffered formalin (10:1, fixative to tissue, no sample should be >0.5–1 cm to ensure proper fixation)
- Histology should include
  - H&E stain
  - Rhodanine or rubeanic acid stain—quantify and localize copper
  - Masson's trichrome or Picrosirius red—fibrosis
  - Reticulin stain—lobular architecture
  - Perls' Prussian blue stain—quantify and localize iron
  - Special stains added to identify infectious organisms if granulomatous or pyogranulomatous inflammation is present

Aerobic and anaerobic culture
- Use appropriate transport media

Copper quantification (canine)
- Dry weight atomic absorption spectrometry
- 20–40 mg of liver (wet weight)
- Empty glass tube; if using red top tube, do not allow sample to contact top as it contains copper
- Tissue can be frozen or extracted from paraffin block for copper quantitation later
- Normal hepatic copper quantification is <400 μg/g dry weight liver

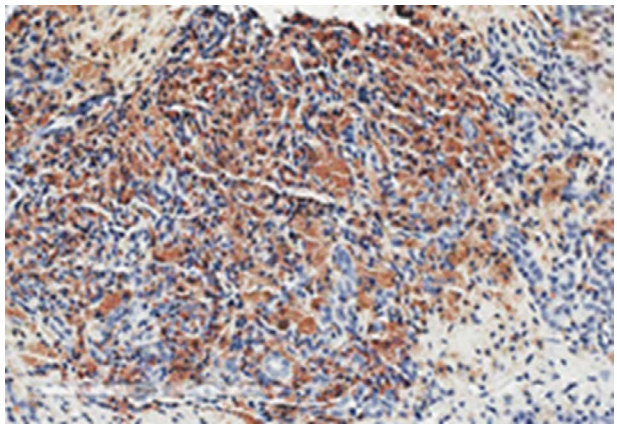


FIGURE 10.6 Rhodanine stain (orange) to identify copper on hepatic histology from a dog with chronic hepatitis. Copper grade is 5 out of 5. Photomicrograph at 10× magnification.

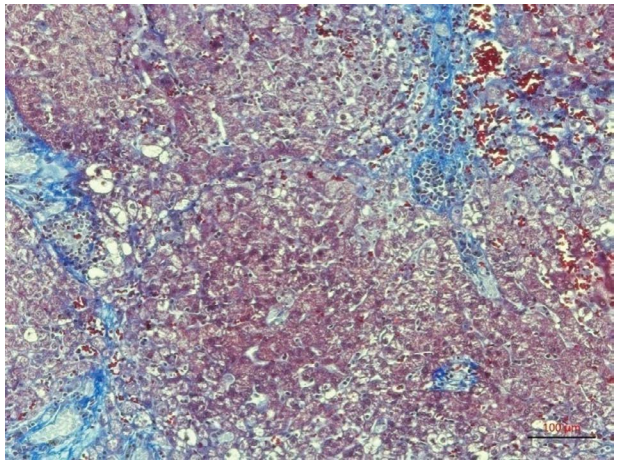


FIGURE 10.7 Masson's trichrome stain on liver histology from a dog with chronic hepatitis demonstrating increased deposition of extracellular collagen matrix (blue) and sinusoidal distortion. Photomicrograph at 10× magnification.

Management

Treat the underlying etiology. Discontinue hepatotoxic drugs. Monotherapy targeted at infectious organisms may be sufficient to halt progression of the inflammatory process. In all causes of chronic hepatitis, antioxidant therapy is added to treat ongoing necroinflammatory (SAMe, vitamin E) and cholestatic processes (ursodeoxycholic acid). Antioxidants are administered until liver enzymes normalize (Table 10.2). Antifibrotic medications (phosphatidylcholine or losartan) are initiated if fibrosis is present on histology (Table 10.2). Human and murine research has shown that fibrosis can be reversible with targeted therapy. Treatment with a protein-restricted liver diet is contraindicated in patients with chronic hepatitis unless multiple acquired shunts or overt hepatic encephalopathy exist.

Increased hepatic copper concentration (>600 µg/g) in dogs with chronic hepatitis is treated with lifelong dietary copper restriction (<0.12 mg of copper per 100 kcal). The commercially available liver diets are appropriately copper restricted and may be used as a base diet but must be supplemented with low-copper protein sources (cheese, yogurt, eggs, white meat, chicken, and turkey) to achieve 3–4 g of protein intake per kilogram body weight a day. Chelation therapy is indicated in dogs with >1,000 µg/g of copper per dry weight liver or centrilobular hepatic copper accumulation associated with hepatitis on histology. D-penicillamine is the most popular chelator due to affordability and patient tolerance (Table 10.2). The most common side effect is vomiting, which may be managed by dividing the dose or administering an antiemetic. Rare side effects include immune-mediated diseases of the kidney and lung. Pyridoxine is supplemented during therapy because D-penicillamine antagonizes vitamin B_6. D-penicillamine binds hepatic copper, enhancing renal clearance. It secondarily upregulates metallothionein in enterocytes, promoting fecal elimination of dietary copper. D-penicillamine therapy is continued for 2–6 months or until ALT improves to less than twice the upper limit of normal. At that time, the frequency of D-penicillamine therapy may be reduced for maintenance therapy, or zinc may be initiated to block enteric copper absorption (Table 10.1). D-penicillamine and zinc should not be administered concurrently because zinc will be preferentially chelated, negating the benefit of both drugs.

Immune modulatory drugs are initiated if nonsuppurative immune-mediated disease is suspected. Prednisone is the first-line glucocorticoid (Table 10.2). Dexamethasone is selected if ascites is present because prednisone's mineralocorticoid component may exacerbate effusion. Glucocorticoids are administered in combination with a second immunosuppressive drug (azathioprine, mycophenolate, or cyclosporine) for 2–4 weeks. Clinical and biochemical parameters are reevaluated before medication modification (every 2–4 weeks initially). Prednisone is rapidly tapered if there is a good response to therapy. The second immunosuppressive is continued with CBC and chemistry rechecks occurring initially every 2–4 months. The second immunosuppressive drug is tapered when biochemical remission is achieved, or adverse drug effects are noted. Biochemical values are rechecked 1 month and 6 months after discontinuation of therapy. Most dogs require lifelong therapy.

Prognosis

Prognosis is dependent on the etiology and histologic grade of chronic hepatitis. The prognosis for infectious and copper associated hepatopathy is good. Inadequate canine studies exist to comment on the outcome of drug-induced, idiopathic, or autoimmune hepatitis in dogs. Accumulating evidence in human and research models suggest that fibrosis is a reversible process; therefore, treatment is indicated even if severe fibrosis is identified.

FELINE CHOLANGITIS

Definition/Overview

Feline cholangitis is an inflammatory process targeting the bile ducts/ductules expanding within the portal tract. The classification of cholangitis is based on the predominant cellular infiltrate and duration of illness. There are three main subtypes: Chronic cholangitis (fluke associated), neutrophilic cholangitis (acute and chronic), and lymphocytic cholangitis. Common co-morbidities frequently include pancreatitis and inflammatory bowel disease.

Etiology

Fluke-associated cholangitis is caused by trematodes from the *Dicrocoeliidae* (*Platynosomum concinnum* (previous nomenclature fastosum) (feline specific), *Eurytrema procyonis*, and Opisthorchiidae (*Opisthorchis* spp., *Amphimerus* spp., *Clonorchis* spp., and *Metorchis* spp.) families. Infection with *Platynosomum concinnum* is reported most often. This species requires two to three intermediate hosts, a snail, a terrestrial isopod, and a lizard, toad, gecko, or skink (paratenic host). Cats are infected after ingesting the vertebrate host. The disease is also referred to as "lizard poisoning." Metacercariae excyst in the feline gastrointestinal tract and migrate to the common bile duct, hepatic bile ducts, and the gallbladder where the adult flukes reside. Once mature (12 weeks post infection), the flukes reproduce. Ova are shed intermittently in feces.

Acute and chronic neutrophilic cholangitis also has an infectious etiology and is most commonly caused by bacterial infection and rarely protozoal (toxoplasmosis, hepatozoonosis) infection. The inciting factor for lymphocytic cholangitis is unknown but may be due to an overzealous immune response or molecular mimicry, resulting in adaptive immune response to a biliary epithelial epitope.

Pathophysiology

Infectious organisms cause direct injury to the biliary epithelium. Secondary induction of innate and adaptive immune responses targeted at clearing dead cells and eliminating the infection may perpetuate inflammation and tissue damage. Extrahepatic duct obstruction may occur due to fluke obstruction, inspissated bile, or cholelithiasis. Lymphocytic cholangitis is an immune-mediated disease targeting the biliary epithelium. This results in periductal and intraductal lymphoplasmacytic infiltration, activation of myofibroblasts, leading to extracellular matrix deposition and, in some cases, bile duct destruction.

Clinical Presentation

Trematode-associated cholangitis occurs in free-roaming cats in tropical and subtropical regions. Acutely, cats with fluke-associated cholangitis may be asymptomatic or experience anorexia and lethargy. Cats with chronic infections may present for cyclic abdominal pain, chronic mucoid diarrhea, and icterus. High fluke burden can result in severe inflammation, extrahepatic bile duct occlusion, and death.

Cats with acute neutrophilic cholangitis are often young with a short duration of illness. Clinical signs include abdominal pain, dehydration, fever, gastrointestinal signs, and jaundice. Chronic neutrophilic cholangitis affects cats of any age and shares clinical signs with waxing and waning clinical signs.

Lymphocytic cholangitis is typically identified in middle-aged to older cats but can occur at any age. There is no breed or gender predisposition. Clinical signs include intermittent vomiting, diarrhea, anorexia, and jaundice.

Differential Diagnosis

Differential diagnoses for neutrophilic and fluke-associated cholangitis include hepatic abscess, pancreatitis, or extrahepatic bile duct obstruction due to cholelithiasis, stricture, or neoplasia. Differential diagnoses for lymphocytic cholangitis include hepatobiliary neoplasia, chronic pancreatitis, or reactive hepatopathy.

Diagnosis

Clinicopathologic Abnormalities

Complete blood count abnormalities with fluke-associated cholangitis may include mild nonregenerative anemia, hypereosinophilia, and lymphocytosis. Biochemical derangements may include hyperbilirubinemia and hepatic transaminase elevations in severely infected cats. Definitive diagnosis is through identification of fluke ova in feces (double centrifugation with Sheather's sugar flotation solution, formalin-ether sedimentation), but intermittent ova shedding may lead to a false-negative result.

Approximately one-third of cats with acute neutrophilic cholangitis have a neutrophilia with left shift and toxic change. Hyperbilirubinemia is the most common biochemical abnormality. Transaminases are moderately to severely elevated (ALT, AST). ALP and GGT may be modestly increased, but concurrent hepatic lipidosis will cause marked ALP elevations. Hyperglobulinemia is occasionally reported. Severe systemic illness can precipitate electrolyte derangements, coagulopathy, prerenal and renal azotemia.

Cats with lymphocytic cholangitis commonly have a regenerative or nonregenerative anemia with poikilocytosis. White blood cell counts are not reliably elevated. Moderate-to-severe elevations in ALT and AST are the most common biochemical abnormality. Relatively higher GGT-to-ALP ratios are consistent with cholangitis, but cholestatic enzyme elevations may not be present. Mild hyperglobulinemia is present in approximately 50% of cats. Hyperbilirubinemia is common but cyclic.

Diagnostic Imaging

B-mode abdominal ultrasonography may identify hepatobiliary abnormalities, including heterogenous liver

with hyperechoic periportal markings and hyperechoic gallbladder contents, but the majority of cats with neutrophilic and lymphocytic cholangitis have normal hepatobiliary ultrasounds. The modality is more helpful in cats with fluke-associated cholangitis where hyperechoic/thickened gallbladder wall, double-rimmed gallbladder, and gallbladder sludge are common. Gallbladder distention or common bile duct dilation (>4 mm) may be present if flukes are obstructing the biliary outflow tract.

Percutaneous ultrasound-guided cholecystocentesis is a valuable means of obtaining bile samples for cytology, Gram stain, and aerobic/anaerobic bacterial culture. Direct bile microscopy is the preferred diagnostic modality for ova detection and may also identify suppurative inflammation in neutrophilic cholangitis.

Histology (See Biopsy Guidelines in Table 10.3)

Hepatic histology in fluke-infected cats has lymphoplasmacytic and occasional eosinophilic portal infiltrates. Severe fibrosing cholangitis, cholangiectasis, and bile duct hyperplasia may be observed. Adult flukes can be identified in the bile ducts (Figure 10.8a–c).

Neutrophilic cholangitis is defined by bile duct centric neutrophilic infiltrates within the portal tract. Lymphoplasmacytic inflammation may be present. Variable grades of periductal fibrosis are present dependent on chronicity. Bacteria are rarely visualized on histology.

Liver biopsy is required for the diagnosis of lymphocytic cholangitis. Cats with lymphocytic cholangitis have lymphocytic or lymphoplasmacytic duct centric infiltrates within portal tracts (Figure 10.9). Periductal fibrosis increases with chronicity (Figure 10.10). Bile ducts may involute (ductopenia), which marks a more serious disease process. Immunohistochemical staining and clonality testing may help to distinguish lymphocytic cholangitis from small-cell lymphoma in cases where profound lymphocytic proliferation makes definitive diagnosis challenging.

Management

Fluke-associated cholangitis is treated with praziquantel. High-dose (praziquantel 20–25 mg/kg q.24 h. for 3 days) and low-dose (Droncit, Bayer, 5.75 mg/kg, p.o. repeated in 3 weeks) protocols are both reportedly effective. Response is measured by improvement of biochemical parameters, clinical signs, and negative fecal analyses (every 3 months for 1 year).

Treatment for neutrophilic cholangitis is initially centered on broad-spectrum antimicrobial therapy. Bile/hepatic Gram stain or culture should guide antibiotic selection. Commonly isolated organisms include *Escherichia coli*, *Enterococcus* spp., *Streptococcus* spp., *Clostridium* spp., *Bacteroides* spp., *Pseudomonas* spp., and *Actinomyces*. Aggressive supportive care, including intravenous fluid administration to correct volume deficits and electrolyte abnormalities, is critical. Cats are treated with vitamin K_1 (Table 10.2) prior to invasive procedures, particularly if hyperbilirubinemic. Antioxidants are administered in the initial course of treatment (N-acetylcysteine, SAMe, vitamin E, or ursodeoxycholic acid) and continued dependent clinical response for 2–4 weeks. Enteral nutrition is implemented

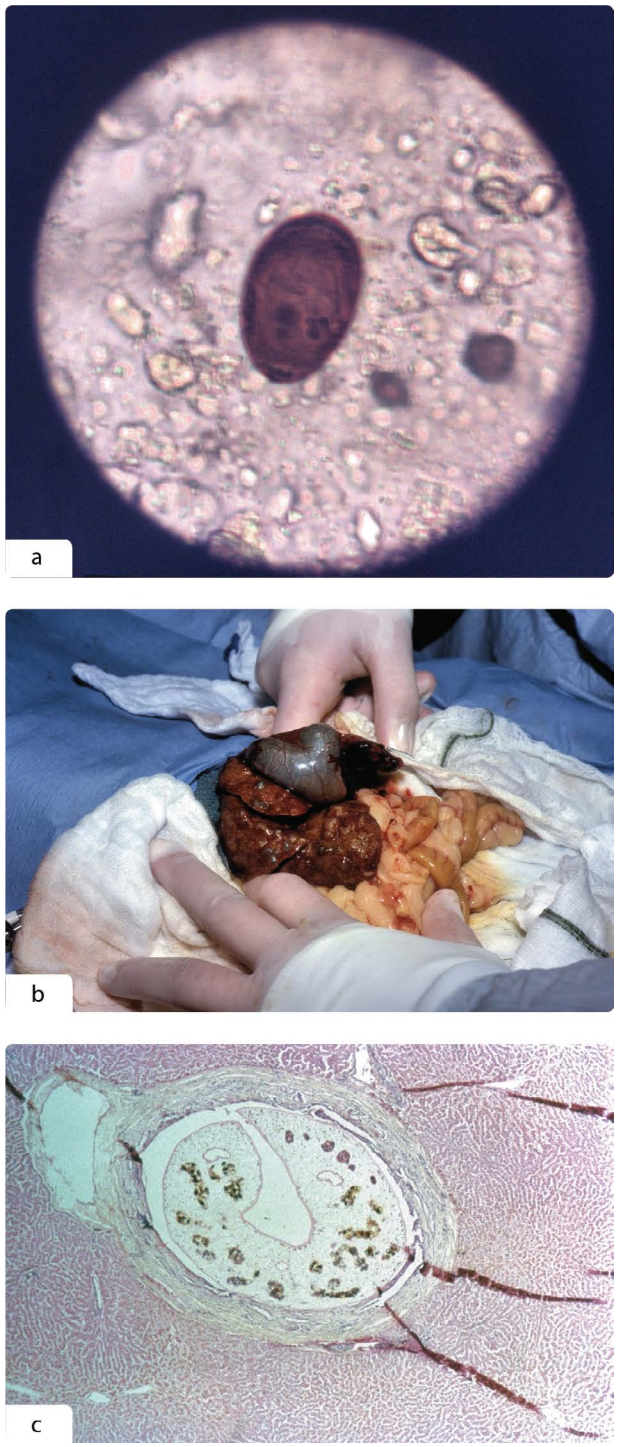


FIGURE 10.8 Liver fluke. **(a)** Microscopic view of a liver fluke (*Platynosum concinum*) ovum from a cat living in South Florida. **(b)** Surgical view of liver fluke-induced chronic cholangitis in a cat living in North Central Florida. **(c)** Histopathology section of liver fluke residing in a bile duct causing inflammation and fibrosis. Taken from the cat in 10.8b. (*Courtesy of M. Schaer.*)

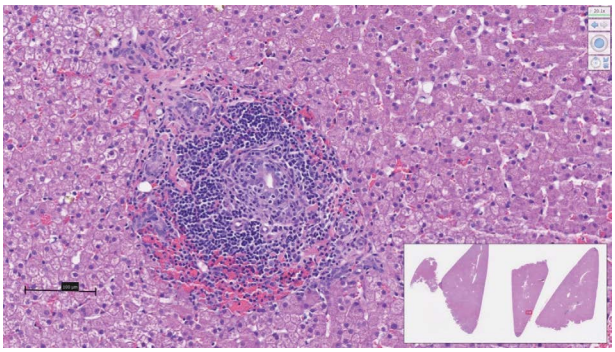


FIGURE 10.9 Hematoxylin and eosin stain on hepatic histology from a cat with lymphocytic cholangitis. Dense lymphoplasmacytic infiltrates expand the portal tract.

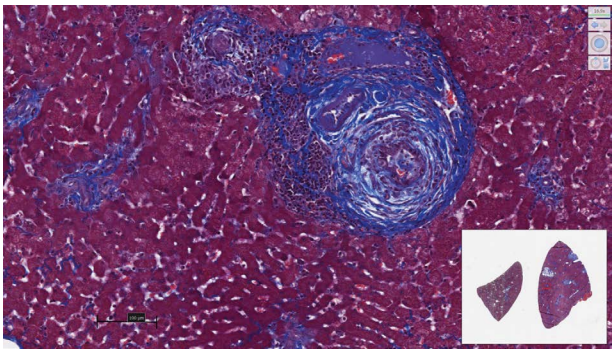


FIGURE 10.10 Masson's trichrome stain on hepatic histology from a cat with lymphocytic cholangitis. Concentric fibrosis (blue) encircles the bile duct.

via nasoesophageal feeding once the patient is hydrated and emesis is controlled. Antibiotic therapy is continued for a minimum of 4–6 weeks. Because antibiotics are often initiated prior to obtaining a culture, failure to identify the inciting organisms is possible, but empiric antibiotic therapy is continued if cytologic or histologic evidence of neutrophilic cholangitis is present.

The mainstay of treatment for lymphocytic cholangitis is immunosuppression with prednisolone (Table 10.2). If a clinical response is noted, glucocorticoid therapy is titrated to the lowest effective dose after the first 2–4 weeks of treatment. Ursodeoxycholic acid is used in cats without ductopenia. SAMe and vitamin E can be added as additional or alternative antioxidants. Modulation of gut flora is an important component of therapy. Historically, metronidazole was administered, but probiotics are a viable alternative. If clinical response (reduction in clinical signs, normalization of bilirubin, reduction in ALT) is not achieved after 2 months, an additional immunosuppressive is added (chlorambucil 2 mg p.o. q.48–72 h., advise owners to wear gloves when administering). CBC and chemistry are rechecked monthly for the first 6 months after starting chlorambucil and then every 2–3 months. Ductopenic cats should be monitored closely for weight loss and signs of malabsorption due to insufficient bile acid release into the gut.

Cats with cholangitis often have concurrent inflammatory bowel disease and pancreatitis. These comorbidities should be identified and treated concurrently.

Prognosis

The prognosis is good for fluke-associated and neutrophilic cholangitis if identified early in the course of disease.

Lymphocytic cholangitis requires chronic therapy and monitoring. Many cats achieve long-term remission (years) with immunosuppressive and antioxidant therapy, but relapse or progression to lymphoma eventually occur. Ductopenic cats have a poorer long-term prognosis.

GALLBLADDER MUCOCELE

Definition/Overview

Gallbladder mucoceles are an abnormal accumulation of mucin and inspissated bile within the gallbladder lumen.

Etiology

Although multiple predisposing factors have been associated with gallbladder mucocele formation, the specific etiology remains unknown. Correlated co-morbidities include dyslipidemia, endocrinopathy (diabetes mellitus, hyperadrenocorticism, and hypothyroidism), gallbladder hypomotility, and cholelithiasis.

Pathophysiology

Excessive secretion of abnormal gel-forming mucin from the gallbladder epithelium, which results in gallbladder distension, mural ischemia, and necrosis. Obstruction of the cystic and common bile ducts may occur secondary to extension or migration of mucin.

Clinical Presentation

Gallbladder mucoceles occur most commonly in older, small to mid-sized dogs, but any dog may be affected. Overrepresented breeds include Shetland Sheepdogs, Bichon Frisé, Cocker Spaniels, Chihuahuas, Miniature Schnauzers, Scottish Terriers, Shih Tzu, and Pomeranians. Dogs may be asymptomatic or present with gastrointestinal signs (anorexia, vomiting, and diarrhea), cranial abdominal pain, or icterus. Elevations in cholestatic hepatic enzymes predominate (ALP, GGT) in most cases but may be accompanied by elevated leakage enzymes (ALT, AST) and variable disturbances in white blood cell count, bilirubin, and cholesterol.

Differential Diagnosis

Cholecystitis, hemocholecyst, or accumulation of gravity-independent gallbladder sludge due to outflow obstruction (cholelithiasis, neoplasia, bile duct stricture).

Diagnosis

Gallbladder mucoceles are diagnosed via ultrasonography and are characterized by accumulation of intraluminal hypoechoic mucus adjacent to the gallbladder

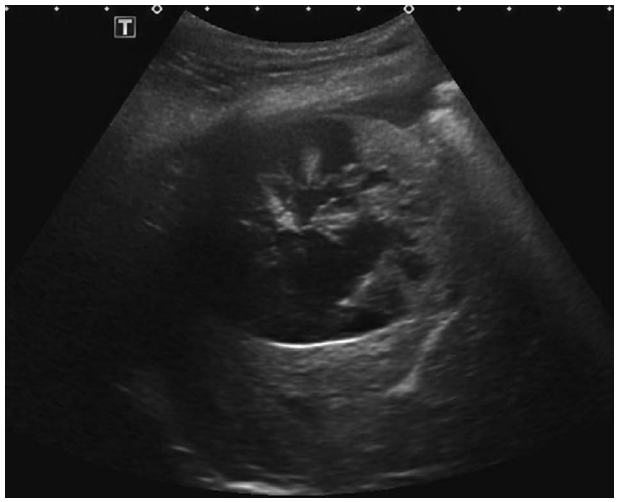


FIGURE 10.11 Gallbladder mucocele with gallbladder wall rupture. The pericholecystic echogenic free fluid, free gas, and hyperechoic mesentery suggest gallbladder wall rupture. (*Courtesy of K. Wilson.*)

wall with central hyperechoic, nongravity-dependent biliary sludge with a stellate pattern (kiwi fruit-like). Gallbladder rupture is suggested by discontinuity of the gallbladder wall, pericholecystic hyperechoic fat, or effusion (Figure 10.11).

Management

Cholecystectomy is the only treatment option for dogs with ruptured gallbladder mucoceles (Figure 10.12). Surgery is indicated for symptomatic patients and those with moderate-to-severe biochemical derangements. Preoperatively, parental fluid therapy with a balanced electrolyte solution and parental pain control are the top treatment priorities. Bacterial cholecystitis is emerging as a common co-morbidity. Broad-spectrum antibiotics are administered pre-emptively to limit complications from septic peritonitis in patients with fever or CBC alterations consistent with infection. Antimicrobials are continued pending gallbladder wall culture results or 2 weeks beyond resolution of clinical signs. Vitamin K_1 (0.5–1 mg/kg SQ ×3 doses) is administered perioperatively in cases of bile duct obstruction because of the inhibition of fat-soluble vitamin absorption. Choleretics should not be administered preoperatively in dogs with a compromised gallbladder wall or evidence of bile duct obstruction. Ursodeoxycholic acid may promote smooth muscle contraction of the gallbladder wall, potentiating rupture, and will increase bile flow, enhancing bile volume and elevating intraluminal pressure in bile duct occlusion. Clinicopathologic abnormalities will normalize within 2–3 weeks of surgery.

Medical management with oral choleretics may be attempted in asymptomatic or minimally affected patients (intermittent gastrointestinal signs, mild ALP/GGT elevations). Ursodeoxycholic acid stimulates bile acid dependent bile flow (10 mg/kg q.12 h. with food). Choleresis is also stimulated with high-dose S-adenosylmethionine (SAMe, 40 mg/kg p.o. q.24 h.) through a nonbile acid dependent mechanism. Medical management includes treatment of underlying dyslipidemias and endocrinopathies. Serial reassessment during medical therapy, including CBC, chemistry, and recheck abdominal imaging, is performed every 1–2 months initially. Monitoring frequency is reduced if improvement in biochemical parameters and gallbladder ultrasonographic appearance are noted. Cholecystectomy is recommended if no improvement occurs after 4–6 months of therapy or there are worsening clinical signs, biochemical parameters, or ultrasonographic changes.

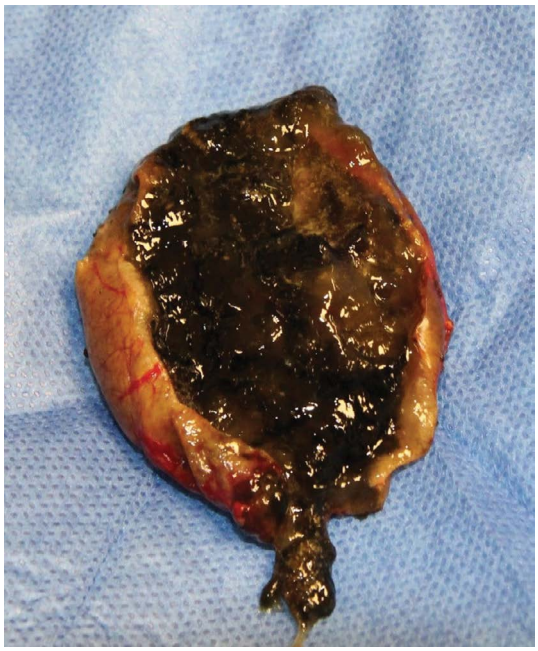


FIGURE 10.12 Gross image of a gallbladder mucocele opened to reveal bile and mucin.

Prognosis

Reported postoperative survival following cholecystectomy ranges from 68% to 91%. Survival rates improve substantially in patients undergoing elective surgery. Hyperbilirubinemia is a consistent poor prognostic indicator in the majority of retrospective studies.

CANINE VACUOLAR HEPATOPATHY

Definition/Overview

Vacuolar hepatopathy is the excessive accumulation of cytosolic glycogen within hepatocytes.

Etiology

Known causes of hepatocyte glycogen overload include rare genetic abnormalities (congenital glycogen storage diseases), glucocorticoid administration, and endogenous hypercortisolemia. Vacuolar hepatopathy has been correlated with chronic systemic inflammatory conditions,

dyslipidemias, endocrinopathies (diabetes mellitus, hyperadrenocorticism, hypothyroidism), gallbladder mucoceles, hepatocutaneous syndrome, necroinflammatory liver disease, neoplasia, nodular hyperplasia, and pancreatitis. A breed-specific vacuolar hepatopathy occurs in Scottish Terriers, which has been correlated to abnormal androgenic hormone production. In some cases, the cause of vacuolar hepatopathy is idiopathic.

Pathophysiology

Hepatic glycogen storage is a normal metabolic process, but dysregulation in the synthesis, storage, and catabolism of glycogen leads to hepatocellular dysfunction. If the underlying disease process is not addressed, hepatocellular swelling due to glycogen accumulation will affect normal intracellular processes and mechanically disrupt extracellular canalicular bile flow. Cellular degeneration and dropout will eventually ensue leading to stromal collapse and distortion of sinusoidal blood flow.

Clinical Presentation

Vacuolar hepatopathy affects middle-aged to older dogs. Any breed or gender may be affected, but some studies report a female predisposition. An enlarged liver may be palpable on physical exam or visualized radiographically. The primary clinicopathologic feature is a moderate-to-severe elevation of ALP and ALT, while the AST and GGT are initially normal to mildly elevated. The hepatic leakage enzymes will progressively increase with ongoing hepatocellular damage and cell death. Other biochemical abnormalities are dependent on the etiology or correlated disease process. For example, exogenous glucocorticoid administration frequently results in an increased GGT activity.

Differential Diagnosis

Primary or secondary cholestatic liver diseases, neoplasia (osteosarcoma, mammary carcinoma)

Diagnosis

In many cases, a moderate-to-severe ALP elevation, the characteristic features of an enlarged liver on abdominal radiographs and hyperechoic hepatic parenchyma with poorly defined hypoechoic nodules on ultrasound, and hepatocyte rarefaction on cytology are sufficient for a preliminary diagnosis. These findings should prompt a more in-depth search for an underlying cause or correlated condition prior to biopsy. Hepatic histology is necessary to identify concurrent necroinflammatory liver disease. In isolated vacuolar hepatopathy, hematoxylin and eosin staining highlights hepatocytes with lacy cytoplasm, defines zonal distribution, and identifies lobular distortion. Periodic acid Schiff (PAS) staining differentiates glycogen from lipid vacuolation. Rhodanine staining will identify copper accumulation, which is a common co-morbidity in vacuolar hepatopathy of Scottish Terriers.

Management

Treat underlying conditions. Discontinue glucocorticoids, steroidogenic drugs, or herbal remedies. Initiate antioxidant therapy (vitamin E, SAMe; Table 10.2).

Prognosis

Prognosis is good if an underlying etiology can be identified and treated. In some dogs, such as Scottish Terriers, vacuolar hepatopathy is a progressive degenerative process that is correlated with the development of hepatocellular carcinoma.

CANINE HEPATOCUTANEOUS SYNDROME

Definition/Overview

Hepatocutaneous syndrome is a metabolic disease affecting the liver and skin. The liver has a characteristic honeycomb pattern on ultrasound with a glycogen-type vacuolar change on histology. Skin lesions are histologically classified as necrolytic migratory erythema (superficial necrolytic dermatitis). The syndrome is associated with hypoaminoacidemia and aminoaciduria.

Etiology

The etiology is unknown, but hepatocutaneous syndrome is associated with dysregulated protein metabolism.

Pathophysiology

Progressive skin lesions result in discomfort when ambulating and progressive glycogen accumulation in the liver leads to degenerative vacuolar hepatopathy. Some dogs develop diabetes mellitus.

Clinical Presentation

Hepatocutaneous syndrome affects middle-aged to older dogs that are predominantly male. Shih Tzus, Maltese, Schipperkes, West Highland White Terriers, Shetland Sheepdogs, and Labrador Retrievers are overrepresented. Dogs may present for pain associated with their paw pad, hyperkeratosis, fissures, and erosions (Figure 10.13). Crusting and ulceration of mucocutaneous junctions is also typically present. Additionally, ALP and/or ALT elevations are usually identified in combination with diffuse hypoechoic nodules surrounded by a hyperechoic parenchyma.

Differential Diagnosis

Necrolytic migratory erythema with endocrine neoplasia (glucagonoma), pemphigus foliaceus, leishmaniasis, zinc responsive dermatitis, cutaneous or hepatic neoplasia



FIGURE 10.13 Typical paw pad lesions associated with hepatocutaneous syndrome in the dog. Erythema, crusting, ulceration, and hair loss are evident. (*Courtesy of R. Marsella.*)

Diagnosis

Diagnosis is based on skin histology that identifies the necrolytic migratory erythema in combination with either hepatic histology that identifies glycogen-type vacuolar hepatopathy or the characteristic hepatic honeycomb appearance on ultrasound. Plasma hypoaminoacidemia and aminoaciduria (lysinuria and prolinuria) confirm the diagnosis.

Management

Treatment focuses on pain management for paw pad lesions and correction of the amino acid deficit. Aminosyn 10% crystalline amino acid solution is administered (24 mL/kg or 500 mL per dog,) through a central venous catheter over 8–12h and repeated every 7–10 days until skin lesions improve. Aminosyn infusion frequency is adjusted based on patient response. Hepatic encephalopathy can occur following infusions but will usually resolve within 12 hours. Ancillary therapy incudes feeding a high-protein commercial diet is fed and supplementation with body builder amino acid concentrate. Secondary skin infections are treated as they arise. Antioxidants may be added to support hepatic health (Table 10.2). Patients are monitored for hyperglycemia and progressive liver enzyme elevations.

Prognosis

Prognosis is poor for long-term survival.

FELINE HEPATIC LIPIDOSIS

Definition/Overview

Feline hepatic lipidosis is a metabolic syndrome that manifests with hepatocellular lipid overload. Cytosolic distension with triglyceride causes intracellular dysfunction and extracellular compression of the canaliculi, resulting in cholestasis.

Etiology

Hepatic lipidosis is a consequence of negative energy balance due to anorexia, typically occurring in over conditioned cats. The inciting cause of the anorexia, and thus hepatic lipidosis, is usually secondary to another disease process. Causal conditions include gastrointestinal disease, pancreatitis, and cholangitis. In cases where an underlying etiology is not identified, hepatic lipidosis is considered idiopathic.

Pathophysiology

The specific mechanisms leading to dysregulated lipid metabolism are unclear.

Peripheral fat mobilization occurs secondary to a negative energy balance. The delivery of nonesterified fatty acids to the liver exceeds the mitochondrial β-oxidative capacity, resulting in triglyceride accumulation in the hepatocyte.

Clinical Presentation

Hepatic lipidosis tends to affect middle-aged cats but can occur in cats of any age, breed, or gender. Many cats are over conditioned prior to onset of the syndrome. Owners typically report hyporexia, anorexia, vomiting, weight loss, diarrhea, or lethargy. Physical exam abnormalities may include dehydration, hepatomegaly, and icterus.

CBC findings are nonspecific but may include a mild nonregenerative anemia with poikilocytosis and Heinz bodies. There is occasionally a mature neutrophilic leukocytosis. The most common and earliest clinicopathologic abnormality is a marked ALP elevation. Hyperbilirubinemia, ALT, and AST elevations occur as hepatic lipidosis progresses and with other underlying diseases. Electrolyte derangements and mild hyperglycemia are also common. Dependent on concurrent disorders, elevated GGT, hypoalbuminemia, and hyperglobulinemia may also be present. Urine sediment frequently contains lipid. Coagulation parameters may be abnormal. Characteristic abdominal ultrasound findings include a diffusely hyperechoic liver and hepatomegaly.

Differential Diagnosis

Cholangitis, extrahepatic bile duct obstruction, hepatocellular neoplasia

Diagnosis

Definitive diagnosis is based on consistent clinical signs, clinicopathology abnormalities, and hepatic cytology wherein >80% of the hepatocytes have lipid-type vacuolation. Hepatic biopsy is not recommended unless another hepatobiliary disease is suspected (Figure 10.14).

Management

Treatment is targeted at achieving euhydration, correcting electrolyte derangements, and reversing the negative energy balance. Impaired liver function may reduce hepatic capacity to metabolize lactate; therefore, isotonic crystalloids devoid of lactate buffer are

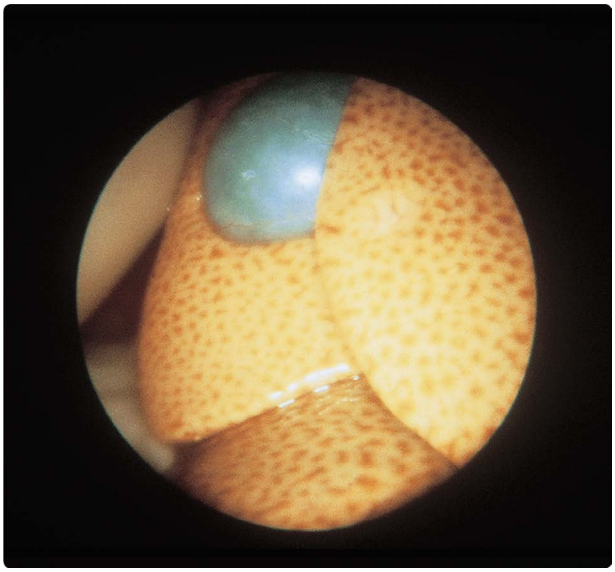


FIGURE 10.14 Laparoscopic view of the liver of a cat with hepatic lipidosis. Note the fatty liver. (*Courtesy of J. Taboada.*)

used for volume replacement. Fluid administration rate is calculated based on lean body mass to avoid overhydration. Crystalloids are supplemented with potassium and phosphorous based on basal electrolyte levels. Phosphorous supplementation (0.01–0.03 mmol/kg per hour) is pre-emptive during refeeding to avoid profound hypophosphatemia. Fluids are also supplemented with water soluble B-vitamin complex (2 mL/L). If this is unavailable, thiamine is administered orally (50–100 mg/d), and cyanocobalamin is administered SQ (250–500 µg) following blood collection for B_{12} quantification. Vitamin K_1 (Table 10.2) is supplemented prior to invasive procedures such as fine-needle aspirate. Dextrose supplementation is avoided because it delays catabolism of hepatic triglycerides. Antioxidants (N-acetylcysteine or SAMe, vitamin E, Table 10.2), excluding ursodeoxycholic acid which may be detrimental in a state of profoundly elevated bile acidemia, are administered throughout treatment to combat excess glutathione consumption. Metabolic supplements, particularly L-carnitine (250–500 mg per cat per day) which shuttles fatty acids into the mitochondria enhancing β-oxidation, may expedite recovery.

The cornerstone of hepatic lipidosis therapy is nutritional support. Enteral feeding is started once the cat is euhydrated and electrolytes are normal. Gut motility may be adversely affected if feeding is started too early. Nasoesophageal or nasogastric feeding tubes can be placed with minimal to no sedation. Placement is confirmed radiographically. Feeding of a protein enriched diet (e.g., Royal Canin, Recovery Liquid, 1 kcal/mL) is initiated at a quarter to a third of the resting energy requirement (RER = 70 × $(kg)^{0.75}$), which is increased gradually over 2–3 days. Feedings are administered as a continuous rate infusion or in 4–6 small bolus feedings per day. Placement of an esophagostomy tube is postponed until the patient is stable and has received 2–3 doses of vitamin K_1. Esophageal feeding tubes

CASE EXAMPLE

Case 10.1

Signalment

"Bob," 2-year-old male neutered Domestic Shorthair cat from Baton Rouge, Louisiana

History

Bob presented to the LSU School of Veterinary Medicine Teaching Hospital Emergency Service for 48 hours of anorexia, multiple episodes of bilious vomiting, and lethargy. He has no previous health problems. His medical records indicate that he tested negative for FeLV/FIV at 6 months of age, is up to date on vaccinations, and is with heartworm preventative monthly. He is an indoor cat but goes out into the backyard occasionally. There is one other cat in the household, and she has no clinical signs of illness.

Physical Examination

Body weight: 4.1 kg

Vital parameters: T = 103.9°F, HR = 250 beats per minute, RR = 24 breaths per minute, BP = 90 mmHg

Physical exam: Bob was quiet, alert, responsive, and ~8% dehydrated. Abnormal physical exam findings included enophthalmos and icteric sclera OU, dry and icteric mucous membranes, diminished skin turgor, discomfort on palpation of the cranial abdomen, and mild hepatomegaly.

Clinicopathologic Findings

Point of care analysis: PCV/TS: 30%/8.0. BG: 135 mg/dL (90–120 mg/dL). Lactate: 3.0 mmol/L (0.5–1 mmol/L).

CBC: Mild nonregenerative anemia with normal red blood cell morphology, moderate mature neutrophilic leukocytosis with toxic change, and normal platelet count.

Plasma chemistry: Mild ALT and AST elevation 3× the upper limit of normal (ULN), normal ALP, mild GGT elevated 1.5× ULN, severe hyperbilirubinemia (10× ULN), high-normal albumin and globulin, normal cholesterol, BUN and creatinine (2× ULN), mild hypokalemia and hypochloremia, high-normal sodium.

Urinalysis: USG 1.050, no abnormalities on urine dipstick, clear sediment

Diagnostic Imaging

Abdominal radiographs: No abnormalities identified

Abdominal ultrasound: The liver was normal, and the gallbladder contained a small amount of dependent sludge but had a normal wall. The extrahepatic bile duct was normal. The remainder of the exam was unremarkable.

Cytology and Culture

Cytology liver: Liver cytology mild hepatocyte rarefaction. No other abnormalities.

Cytology bile: Bile cytology identified multiple bacterial organisms with rare with degenerate neutrophils cells (Figure 10.15).

Aerobic and anaerobic bacterial culture: Escherichia coli >100,000 CFU/µL, sensitive to Clavamox (MIC <0.4).

(Continued)

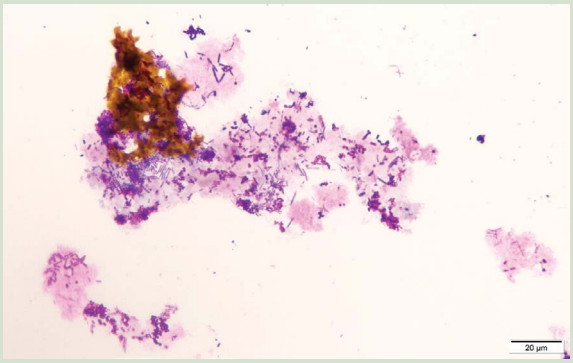


FIGURE 10.15 Bile cytology. Multiple bacterial species identified on bile cytology. (*Courtesy of S. Dehghanpir.*)

Comments

Bob's hypotension was responsive to a bolus of isotonic crystalloids. Abdominal focused assessment with sonography for trauma (AFAST) and thoracic focused assessment with sonography for trauma (TFAST) were negative for free fluid. Abdominal radiographs were normal. Maintenance fluids with deficit replacement over 12 hours were continued. Fluids were supplemented with 20 mEq KCl/L. Maropitant (1 mg/kg IV q.24 h.) and vitamin K1 (0.5 mg/kg SQ q.12 h. ×3 doses) were initiated pending invasive diagnostics the following day. Vital parameters were monitored every 6 hours. His heart rate improved, but he remained febrile overnight. Point-of-care analysis and electrolytes were rechecked 8 hours post admission and identified a mild reduction in PCV, total solids, lactate, and normalization of chloride with persistent mild hypokalemia. Bob was transferred to the internal medicine service 12 hours after hospital admission. He was sedated with butorphanol (0.3 mg/kg) for his abdominal ultrasound, which was normal excluding a small amount of sludge in the gallbladder. Hepatic fine-needle aspiration was performed and identified lipid-type rarefaction in 20% of hepatocytes but no other abnormalities. Supportive care was continued for 24 hours, but Bob remained febrile and anorexic. Recheck serum chemistry 24 hours after admission identified persistently elevated liver enzymes and bilirubin. Antibiotics were initiated due to concern for cholangitis (ampicillin sodium/sulbactam sodium 22 mg/kg IV q.8 h.). Approximately 36 hours after admission, the anesthesia service anesthetized Bob for cholecystocentesis. Bile was collected from gallbladder by percutaneous ultrasound-guided cholecystocentesis (PUC) without complication (**Figure 10.16**). Complications of PUC include vasovagal response, bile or septic peritonitis, and hemorrhage. Bile samples were submitted for cytology and aerobic/anaerobic culture. Bob's temperature normalized following anesthesia, and he ate a small meal. Bile cytology identified bactibilia and scant neutrophilic inflammation.

Bob's clinical signs continued to improve, and he was discharged 3 days after admission with oral SAMe (Denamarin 20 mg/kg p.o. q.24 h.), Clavamox (15 mg/kg p.o. q.12 h.), and maropitant (2 mg/kg p.o. q.24 h. p.r.n.). The culture identified *E. coli*, the most common bacterial isolate in cats with neutrophilic cholangitis. An empiric broad-spectrum antibiotic was initiated prior to sample collection, which likely limited the number of organisms cultured. Recheck serum chemistry 2 weeks was normal. Antibiotics and SAMe were continued for 6 weeks. Recheck serum chemistry at 8 weeks and 3 months remained normal.

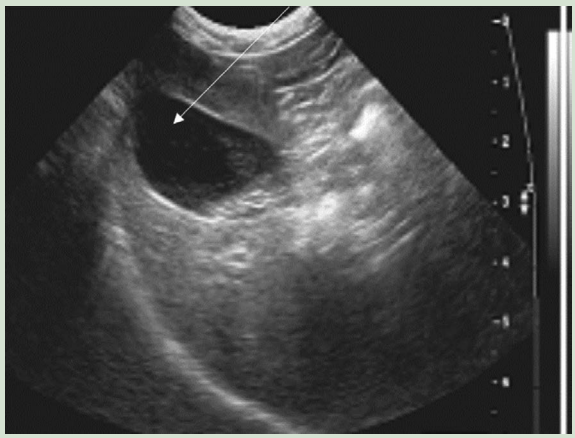


FIGURE 10.16 Percutaneous ultrasound guided cholecystocentesis. Arrow depicts the right transhepatic approach to access the gallbladder. The gallbladder was emptied completely to limit bile peritonitis. Repeat imaging to check for leakage was performed immediately and 6 hours after the procedure to check for pericholecystic fluid.

facilitate medication administration, increase food options, and can be managed by owners at home. Antiemetics (maropitant, metoclopramide, or ondansetron) are frequently added to prevent vomiting and expulsion of the tube. Cats will rarely develop hepatic encephalopathy. Begin antibiotic modulation of gastrointestinal flora if this occurs (**Table 10.1**).

Owners are informed that 1–4 weeks of esophagostomy tube feeding may be necessary. Owners are advised to offer a palatable diet every 12 hours prior to esophagostomy tube feeding to encourage the cat to eat on its own. Owners are shown how to check and clean the esophagostomy tube site daily and how prepare administer food and water through the tube. Rechecks are scheduled weekly to evaluate the esophagostomy tube site and recheck laboratory values.

Prognosis

The prognosis is good if hepatic lipidosis is diagnosed early, treated aggressively, and if an underlying problem is identified and addressed. A reduction in β-hydroxybutyrate during hospitalization and a reduction in bilirubin within the first 1–2 weeks of therapy are good prognostic indicators. Poor prognostic indicators include hypotension, effusions, and progressive hypoalbuminemia and hyperbilirubinemia.

In acute neutrophilic cholangitis, a presumptive diagnosis can be made based on clinical signs, biochemical

abnormalities, bile cytology/culture, and response to antibiotics. In some cases, histology is needed for definitive diagnosis.

RECOMMENDED FURTHER READINGS

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CHAPTER 11

Exocrine Pancreatic Disorders

Frédéric Gaschen

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PANCREATITIS

Definition/Overview

The exact prevalence of pancreatitis in dogs and cats is unknown. However, studies have shown that up to 51% of dogs and 66% of cats undergoing necropsy have histologic evidence of pancreatic inflammation. Thus, the prevalence of pancreatitis is probably largely underestimated clinically in dogs and cats. These observations show that most pancreatitis cases have a subclinical, often chronic course. Accordingly, the typical picture of acute pancreatitis (AP) only represents the very tip of the iceberg and is not representative of the most frequent form of pancreatic inflammation. Moreover, these facts also underscore how difficult it is to diagnose milder forms of chronic pancreatitis in small animals

Acute pancreatitis is a common disease that must be included in the differential diagnosis of dogs presented with acute vomiting with or without abdominal pain. In cats, the clinical signs may mimic those of acute canine pancreatitis or, more frequently, be so vague that veterinarians need to consider chronic pancreatitis (CP) among a wide range of other chronic diseases. Most frequently, CP is considered a late complication of AP. However, in dogs, it may also be part of a chronic immune-mediated inflammation, as was reported in English Cocker Spaniels.

Epidemiological studies reviewing the signalment of dogs diagnosed with AP in the United States identified an increased risk for small and toy breed dogs such as terriers (e.g., Yorkshire Terrier), Toy Poodles, and Miniature Schnauzers. Moreover, Yorkshire Terriers were also significantly overrepresented among the dogs with AP with a fatal outcome. Case series of confirmed CP in dogs identified an increased relative risk for nonsporting and toy breeds in the United States and Cavalier King Charles Spaniels, Boxers, Cocker Spaniels, and Border Collies in the UK. There is no documented breed predisposition in cats.

Etiology

The cause of pancreatitis remains largely unknown in dogs and cats. Several risk factors have been identified in dogs (Table 11.1). Most cases of feline pancreatitis appear to be idiopathic, even though associations have been reported with trauma (e.g., high rise syndrome), systemic hypotension (e.g., general anesthesia), and pancreatic duct obstruction (e.g., feline liver and pancreatic flukes). Genetic mutations have been associated with pancreatitis in people, but none could be identified in dogs and cats to date. Several widely used drugs have been suspected to rarely trigger AP in dogs. These include azathioprine, clomipramine, and potassium bromide. Consequently, it might be prudent to exercise caution when prescribing these drugs to dogs that have had a prior episode of pancreatitis.

TABLE 11.1 Risk factors associated with pancreatitis in dogs

Neutered
Overweight/obese
Recent abdominal surgery (other than neutering)
Ingestion of – Unusual food items – Table scraps Access to trash
Hyperlipidemia

DOI: 10.1201/9781003254591-30

Based on research done in rodent models, inflammation results either from a failure of protective mechanisms in the acinar cells or from abnormal intracellular activation of proinflammatory cytokines and chemokines. This causes activation of trypsinogen to trypsin within the pancreas with ensuing self-digestion of the glandular tissue.

Pathophysiology

Activation of trypsinogen within the pancreas is the initial event leading to activation of other enzymes causing severe damage to the acinar cells, pancreatic interstitium, and vascular endothelium with further amplification and extension of the reaction throughout the pancreas. Pancreatic histopathology in animals with AP reveals neutrophilic inflammation and necrotic foci (Figure 11.1). In addition, the proteolytic cascade may propagate to neighboring structures (e.g., with necrosis of parapancreatic fat, Figure 11.2) and via the bloodstream, which may cause repercussions in remote organs. Conversely, chronic pancreatitis as it frequently occurs in cats is characterized by intralobular and extralobular fibrosis, acinar atrophy, and lymphocytic or lymphoplasmacytic inflammation (Figure 11.3).

Pancreatic perfusion may be compromised, leading to formation of free oxygen radicals and to the disproportionate amplification of the inflammatory process (Figure 11.4). Thus, severe AP may elicit a systemic inflammatory response (SIRS) and multiple organ dysfunction (MODS) (Figure 11.5). These two conditions are responsible for the high mortality associated with this form of disease.

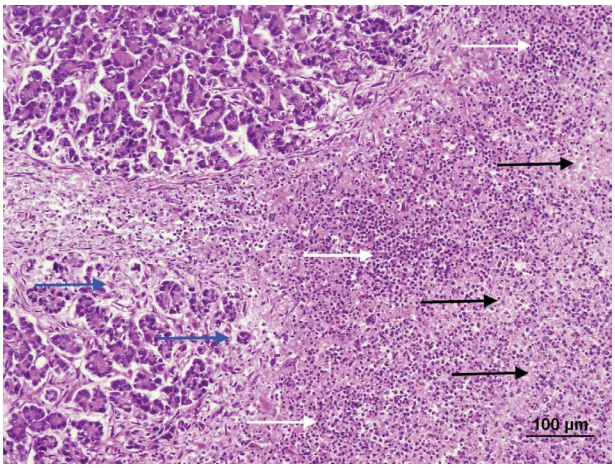


FIGURE 11.1 Histopathologic micrograph of the pancreas of an 8-year-old female spayed Miniature Schnauzer with diabetes and AP and fatal outcome. There is severe neutrophilic infiltration (white arrows) interspersed with areas of necrosis (black arrows). Lesions to the pancreatic acinar cells in the lobules are also visible (blue arrows). The final diagnosis was severe necrotic suppurative pancreatitis.

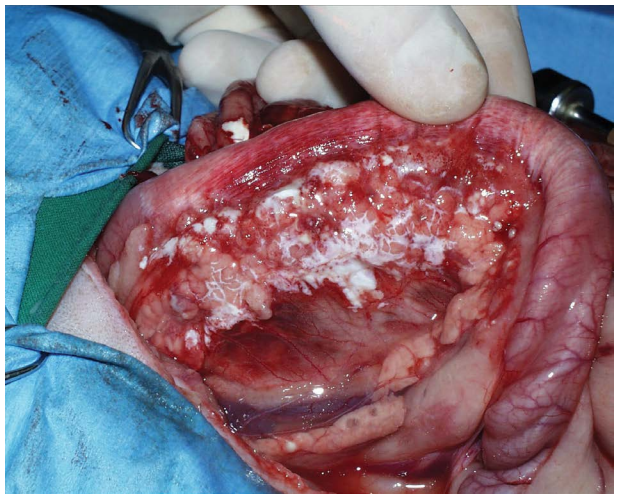


FIGURE 11.2 Intraoperative view during laparotomy of a 7-year-old MN Domestic Shorthair cat with severe AP. The right limb of the pancreas and the duodenum are visible. The pancreas is thickened, nodular, and edematous with hemorrhagic areas extending to the duodenal wall. There is diffuse saponification and necrosis of the peripancreatic fat.

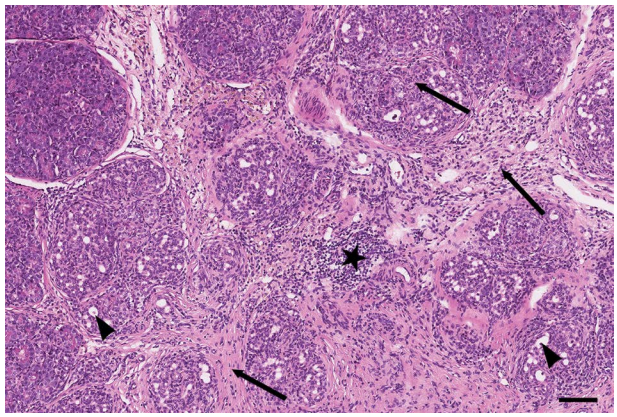


FIGURE 11.3 Histopathologic image of chronic pancreatitis in a cat, showing moderate lymphocytic infiltration (star), interlobular and intralobular fibrosis (arrows), and acinar-to-ductal metaplasia (arrowheads). Scale bar = 100 µm. (*From Forman MA, Steiner JM, Armstrong PJ, et al. (2021). ACVIM consensus statement on pancreatitis in cats.* J Vet Intern Med *35(2): 703–723. With permission.*)

CANINE PANCREATITIS

ACUTE PANCREATITIS

Clinical Presentation

While mild pancreatic inflammation may go unnoticed, moderate-to-severe AP is associated with a characteristic set of clinical signs that includes vomiting, abdominal pain, anorexia/hyporexia, and lethargy (Figures 11.6 and 11.7). Moderate-to-severe dehydration may occur due to lack of fluid intake and vomiting, and cause weakness. Diarrhea, sometimes with

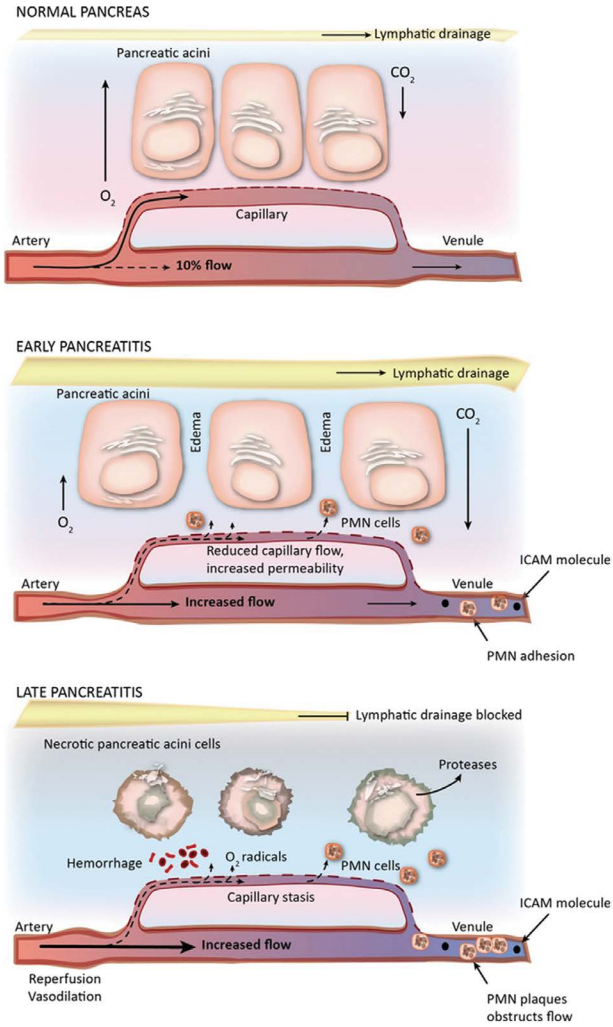


FIGURE 11.4 Pancreatic microcirculation in health and disease. Early pancreatitis is associated with decreased perfusion and increased shunting of blood away from the pancreatic acinar cells. In late pancreatitis, reperfusion injury with generation of free oxygen radicals is associated with capillary stasis, continued bypass of the acinar cells, possible hemorrhage in the tissue, and formation of PMN plaques that further compromise perfusion. Lymphatic drainage is also blocked. (*From Mansfield CM (2012). Pathophysiology of acute pancreatitis: Potential application from experimental models and human medicine to dogs.* J Vet Intern Med *26(4):875–887. With permission.*)

hematochezia or melena, may reflect the extension of inflammation to neighboring structures such as the small intestine or the colon.

The physical examination findings vary with the severity of the problem. Dogs with mild pancreatitis might only show mild lethargy, normal vital signs, and equivocal palpable abdominal tenderness. Signs associated with more severe forms include marked lethargy, fever, hypotension with accompanying tachypnea, tachycardia, weak femoral pulse, a painful abdomen, and a moderate-to-marked degree of dehydration. Clinically detectable icterus will not occur initially with pancreatitis, but it might be evident by the third day and usually results from cholestasis or more rarely pancreatitis-associated bile duct obstruction (PABDO). Abdominal distension can result from paralytic ileus. Presence of abdominal fluid consisting of a reddish brown colored exudate can sometimes be detected with hemorrhagic necrotic pancreatitis.

Diagnosis

Typically, the clinical diagnosis of canine AP is based on a combination of four factors (**Box 11.1**). In the presence of acute vomiting and abdominal pain, abdominal radiographs are essential to rule out gastric or intestinal obstruction (e.g., by a foreign body) and should be obtained as a first step in the diagnostic workup.

A wide range of abnormal laboratory results may occur with AP depending on the extent of the secondary systemic inflammatory process and the consequences of vomiting and anorexia (**Table 11.2**). Complete blood count (CBC) may reveal leukocytosis, often with neutrophilia and left shift, and sometimes thrombocytopenia. Chemistry panel may show electrolyte abnormalities such as hypokalemia and hypochloremia secondary to vomiting. Azotemia may initially be of prerenal origin, associated with dehydration, but may evolve into renal azotemia due to ischemic kidney injury. Hypoalbuminemia and hypoproteinemia are seen in approximately 50% of severe cases. Hyperbilirubinemia may reflect cholestasis due to extension of inflammation to the biliary tree and liver or indicate the presence of PABDO. It may be accompanied by increased serum activity of liver enzymes (alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT], alanine aminotransferase [ALT], and aspartate aminotransferase [AST]). However, liver enzymes may also be increased in association with hypovolemia and poor liver perfusion. Rarely, hyperglycemia may be present due to diabetes mellitus. This may occur following widespread destruction of pancreatic tissue. However, pancreatitis may also occur in dogs diagnosed with diabetes mellitus. It is often associated with diabetic ketoacidosis, particularly in toy and small breed dogs. In addition, serum triglyceride concentration should be measured as high concentrations have been reported to be a risk factor for development of AP.

There is ongoing debate about the most accurate test to document the presence of increased pancreatic enzymes in the bloodstream. A recent study showed that pancreatic lipase immunoreactivity (PLI) and 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6'-methylresorufin) ester (DGGR) lipase are most useful in the presence of additional supporting clinical data to diagnose pancreatitis. Generally, these tests are quite sensitive, but their specificity is not optimal, as they can be positive for instance in association with other gastrointestinal diseases. The poor diagnostic accuracy of serum total activities of amylase and lipase is the reason why their use in the diagnosis of canine AP cannot be recommended any more.

Diagnostic imaging is a central element in the diagnosis of pancreatitis. Abdominal radiographs are very helpful in ruling out gastrointestinal (GI) obstruction. However, with a reported sensitivity of 24%, they have a low yield to confirm the diagnosis of AP. Radiographic changes, if present, consist of decreased abdominal contrast mass effect in the right cranial quadrant with

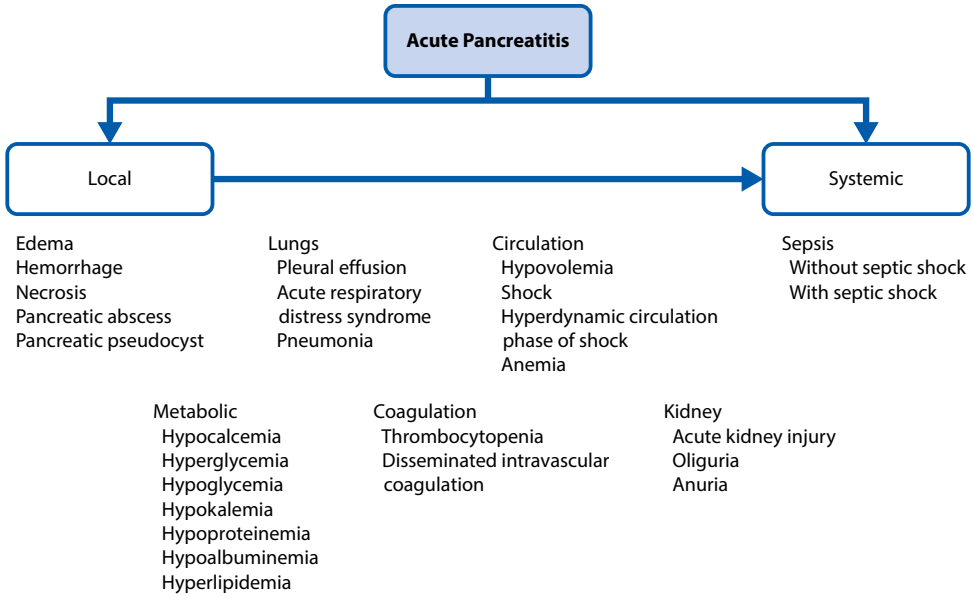


FIGURE 11.5 Pathophysiologic consequences of acute pancreatitis. The adverse effects of acute pancreatitis are far reaching, with involvement of several organ systems. In many cases, this can lead to multiple organ dysfunction and the patient's demise. (*Modified from Büchler MW, Uhl W, Malfertheiner P, et al. (2004).* Diseases of the Pancreas. *Karger, Basel.*)



FIGURE 11.6 This 5-year-old, male, neutered West Highland White Terrier had acutely developed profuse vomiting followed by anorexia, lethargy, and abdominal pain. He vomited bile and water on the exam table.

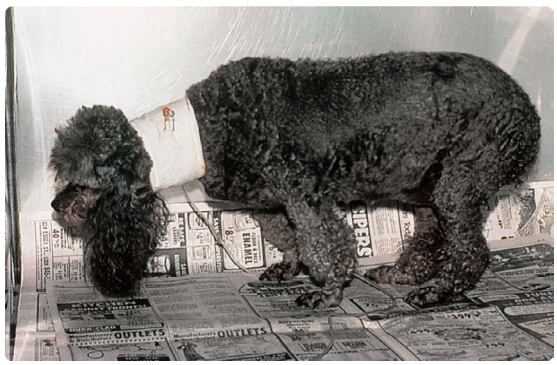


FIGURE 11.7 This 13-year-old female Poodle had acute vomiting, mental depression, and marked abdominal pain peracutely immediately after dinner. Despite the use of intensive fluid therapy, the dog died from hemorrhagic necrotic pancreatitis. (*Courtesy of M. Schaer.*)

Box 11.1 Elements required for a diagnosis of acute pancreatitis in dogs

- Presence of typical clinical signs
- Elimination of other possible differential diagnoses
- Increased serum pancreatic lipase (pancreatic lipase immunoreactivity [cPL®, Idexx] or DGGR lipase activity)
- Presence of typical ultrasonographic lesions of the pancreas and surrounding tissue

lateral displacement of the descending duodenum, which may have a rigid appearance and contain gas due to localized paralytic ileus (Figures 11.8 and 11.9).

Because it is widely available, abdominal ultrasound is the preferred modality to examine the pancreas. Numerous lesions can be detected such as increased in pancreatic volume, presence of nodules, cysts or abscesses, hypoechoic or hyperechoic lesions in the pancreas and in the peripancreatic mesentery, peripancreatic abdominal effusion, etc. Diagnostic sensitivity of ultrasound is good for moderate to severe pancreatitis (Figures 11.10 and 11.11). However, the detailed ultrasonographic evaluation of the pancreas, in particular its left lobe, may be challenging in obese dogs, if the abdomen is painful, or when excessive amounts of gas are present in the stomach and small intestine. A recent study showed the value of repeating the ultrasound exam within the first 2 days, particularly in dogs with suspect pancreatitis based on clinical signs and an increased pancreatic lipase immunoreactivity, but mild or absent ultrasound changes.

Multislice CT scanners are now increasingly available to veterinarians and allow sedated examinations

TABLE 11.2 Clinicopathologic abnormalities accompanying acute pancreatitis in the dog

Abnormality	Proposed mechanism(s)
Anemia	Hemorrhagic abdominal effusion
Azotemia	Prerenal from dehydration, renal from hypovolemia, SIRS or DIC
Hemoconcentration	Dehydration, translocation of plasma into abdominal cavity
Hyperglycemia	Diabetes mellitus
Hyperlipidemia	Might pre-exist as separate entity Can occur with pancreatitis, but exact mechanism unknown
Hypernatremia	Dehydration
Hypoalbuminemia	Abnormal capillary permeability with loss of albumin in the interstitial space, possibly into the abdominal cavity if effusion
Hypocalcemia	Calcium soap formation is most widely accepted mechanism
Hypoglycemia	SIRS or sepsis with impaired gluconeogenesis
Hypokalemia	Vomiting, failure to supplement parenteral fluids, osmotic diuresis from hyperglycemia
Hyponatremia	Vomiting, pseudohyponatremia from hyperlipidemia
Leukocytosis	Inflammation, stress, hemoconcentration, secondary infection
Leukopenia	Mobilization to inflamed site, bone marrow suppression from endotoxemia
Liver enzyme and bilirubin elevations	Cholangitis, hepatic inflammation, PABDO, hepatic lipidosis (in dogs with diabetes mellitus)
Prolonged prothrombin and partial thromboplastin times, thrombocytopenia, low antithrombin level, hypofibrinogenemia	DIC
Thrombocytopenia	Consumption from thrombus formation, SIRS

DIC, disseminated intravascular coagulation; PABDO, pancreatitis-associated bile duct obstruction; SIRS, systemic inflammatory response syndrome.
Source: Modified from Table 10.5 in 3rd ed.

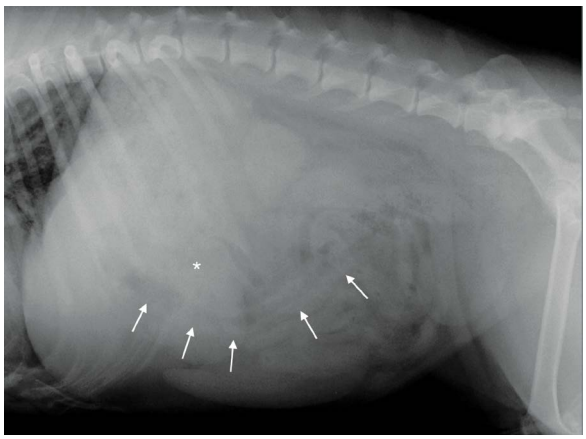


FIGURE 11.8 Radiographic appearance of AP in a dog. Right lateral view: There is decreased contrast in the cranial abdomen (asterisk). Content can be seen in the stomach. The descending duodenum is visible (arrows), filled with gas and shows a rigid appearance.

of dogs and cats. CT provides useful additional information about the pancreas, including evaluation of vasculature through intravenous contrast administration (Figure 11.12). Recent studies have shown that CT angiograms can highlight poorly vascularized areas in

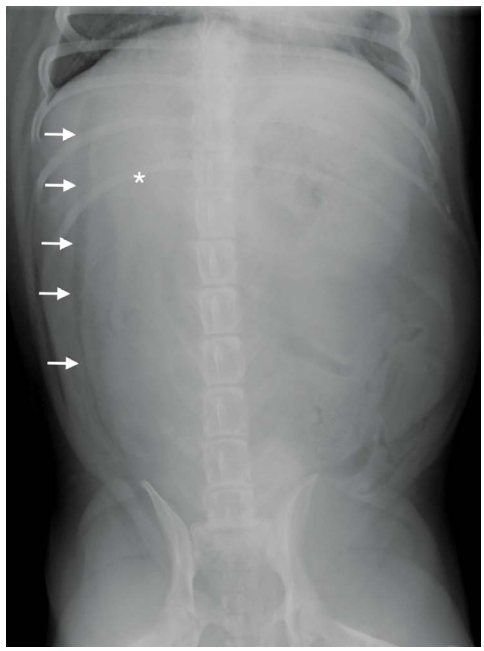


FIGURE 11.9 Ventrodorsal view from the same dog as Figure 11.8. There is decreased contrast in the right cranial abdominal quadrant (asterisk). The duodenum is laterally displaced (arrows) and has a rigid appearance. There is gas in the duodenal lumen.

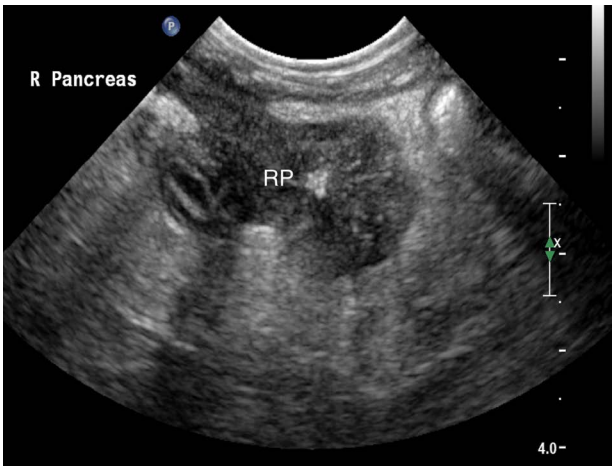


FIGURE 11.10 Ultrasound appearance of AP in the dog. A 5-year-old, male neutered West Highland White Terrier shown in **Figure 11.6**. The right pancreatic limb (RP) is enlarged, hypoechoic, and has a lobulated shape, and the peripancreatic mesentery is hyperechoic.

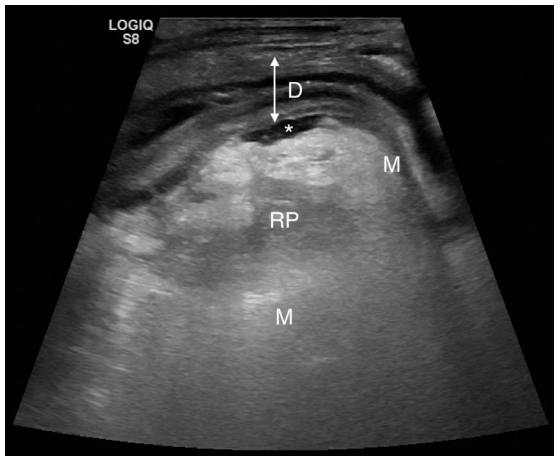


FIGURE 11.11 A 13-year-old, male neutered Maltese Terrier with severe AP. The duodenum (D) is fluid filled and appears rigid. The right pancreatic limb (RP) is enlarged and irregularly shaped. The surrounding mesentery (M) is very hyperechoic indicating peripancreatic inflammation, and a pocket of free abdominal fluid is visible (asterisk).

the pancreas that represent tissue necrosis and portal vein thrombosis, conditions that are associated with prolonged hospital stay and more relapses.

Differential Diagnosis

The initial differential diagnosis of AP includes many clinical disorders that share the same clinical signs, which may mimic most acute abdominal syndromes (**Table 11.3**). Several differential diagnoses are surgical emergencies that require rapid diagnosis and treatment.

Management

Any possible predisposing factor such as hyperlipidemia, drugs that might cause idiosyncratic reactions, etc., should be addressed. However, treatment of AP in dogs is essentially supportive and relies on four important components (**Box 11.2**).

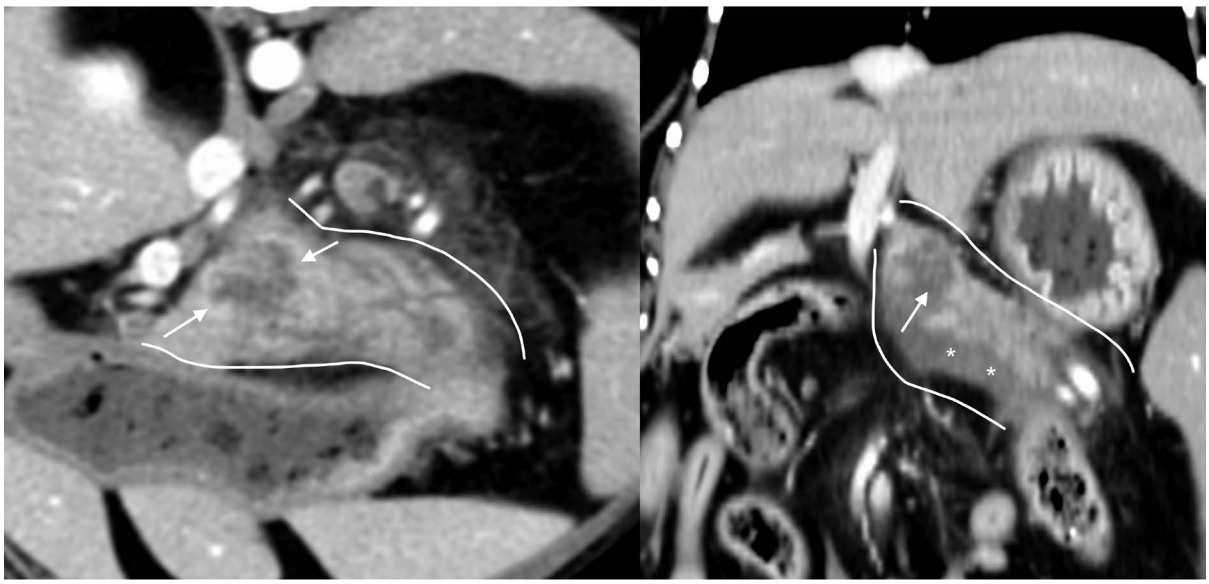


FIGURE 11.12 Contrast-enhanced CT of a 5-year-old female spayed Beagle presented for acute onset vomiting and abdominal pain. The body and left pancreatic limb (outlined in white lines) are enlarged with ill-defined margins and widened interlobular fissures that are fluid attenuating. In the body of the pancreas, there is an irregularly shaped zone of poor intralesional contrast enhancement and a thin irregular rim of enhancement (white arrows). There is extensive fat stranding extending from the pancreas into the mesentery and peritoneal effusion around the left limb of the pancreas (asterisks). The right lobe of the pancreas is normal. Diagnosis was pancreatitis in the body and left limb with a focal region of necrosis and secondary peritonitis. The nonenhancing lesion with an enhancing rim could represent an abscess. (*Courtesy of L. Gaschen.*)

TABLE 11.3 Differential diagnoses of acute pancreatitis in the dog

- Acute gastroenteritis
- Gastrointestinal obstruction
- Gastrointestinal perforation
- Intestinal volvulus
- Intestinal ischemia and infarction
- Intoxications
- Blunt abdominal trauma
- Emphysematous cholecystitis
- Ruptured organs (e.g., uterus, urinary bladder, gallbladder)
- Acute kidney injury
- Acute hepatopathy

Box 11.2 Essential components of the supportive treatment of acute pancreatitis in dogs

- Quick reestablishment of fluid and electrolyte balance
- Successful management of vomiting
- Pain management
- Early enteral nutrition

Rapid support of pancreatic perfusion is essential. Aggressive fluid therapy is required, and large intravenous fluid volumes are often necessary to compensate the losses that occurred with vomiting and diarrhea. Electrolyte disturbances (particularly hypokalemia) should be corrected as needed. Acid–base imbalances (often due to metabolic acidosis) can usually be corrected with proper fluid therapy and do not require administration of alkalinizing solutions. Plasma transfusion is beneficial if DIC is present. Guidelines for treatment of dehydration and hypovolemic shock can be found in Chapter 23.

Antiemetics are important as well. Available drugs and recommended doses are described in Table 2.17.1. The efficacy of metoclopramide is maximal when administered as a constant rate infusion (CRI). A combination of antiemetics is often required to address vomiting and nausea in dogs with moderate and severe AP. Antiemetic treatment should be continued beyond the resolution of vomiting to control nausea to maximize the chances for a rapid return of appetite.

Pain control is traditionally attempted with opiate analgesics, using buprenorphine or fentanyl CRI. Transdermal fentanyl patches are also useful, but there is generally a 12- to 24-hour lag time before therapeutic levels can be reached in serum. However, opiates further compromise the already delayed GI motility in dogs with AP. Therefore, preference should be given to other analgesics such as lidocaine, ketamine, or dexmedetomidine that can be administered alone or in combination with reduced doses of opiates as CRI and provide analgesic relief without delaying GI motility. Guidelines for pain management including dose recommendations can be found in Chapter 24.

It is not advisable to fast dogs for longer than 24–48 hours, starting when they last ate at home. Longer fasting may suppress the immune system, delay healing, compromise the integrity of the intestinal mucosal barrier, and increase the risk of bacterial translocation through the intestinal mucosa and the risk of sepsis. Early enteral feeding improves intestinal mucosal function and has proven beneficial in dogs with AP. However, the dog's interest in food may be compromised if dehydration, vomiting/nausea, and pain are not controlled. Appetite stimulants such as ghrelin agonists (capromorelin 3 mg/kg p.o. q.24 h.) may help accelerate the return of appetite. Importantly, many dogs with moderate-to-severe pancreatitis experience delayed gastric emptying with generalized adynamic ileus in association with their pancreatic and abdominal inflammation. In these patients, support of GI motility is a prerequisite to return of appetite. GI prokinetics can be administered alone or in combination if necessary. Recommended drugs include metoclopramide administered as a CRI (1–2 mg/kg over 24 hours), erythromycin (0.5–1 mg/kg IV q.8 h.), or azithromycin (2 mg/kg IV q.8 h.) (Figure 11.13). Cisapride, another good choice, is not easily available as an injectable drug (0.1–0.5 mg/kg IV q.8–12 h.).

Recommended diets should be easily digestible with a low-fat content and be fed in small amounts several times daily. Initially, it is not necessary to cover the dog's energy and protein requirements. In dogs that remain anorexic for more than 2–4 days since their last meal in the home environment, a nasoesophageal (NE) tube should be placed. Easily digestible, low-fat liquid diets are available commercially for NE tube feeding. Oral feeding or, in anorexic dogs, feeding via NE tube was shown to be superior to prolonged fasting. Guidelines for enteral nutrition and placement of feeding tubes can be found in Chapter 25.

Bacteria do not play a role in the pathogenesis of canine AP. Consequently, the use of antibiotics should be limited to dogs that are in a critical condition with evidence of sepsis. Therefore, there is no indication to use antimicrobials in most dogs with AP. Similarly, there is no benefit in treating AP dogs with gastric protectants such as proton pump inhibitors (PPI) except for those showing intractable vomiting and/or signs of esophagitis.



FIGURE 11.13 A 10-year-old female spayed Miniature Schnauzer with acute-onset anorexia, vomiting, and lethargy that was diagnosed with acute pancreatitis. The dog was hospitalized in the intensive care unit and treated with IV fluids and constant rate infusions of lidocaine and metoclopramide.

Local and Distant Complications

Complications occur relatively commonly in dogs with moderate-to-severe AP (Table 11.4). They can be local and affect the pancreas and immediate surrounding structures, including the GI tract and the liver. They can occur in distant organs such as the lungs and the kidneys, or they can be systemic (SIRS, sepsis, DIC, MODS) (Figure 11.5).

Various lesions may develop as local complications of severe pancreatic inflammation. They include necrotic foci, abscesses, and pseudocysts. Necrotic foci are typically associated with peripancreatic fat necrosis. In human patients, pancreatic abscesses are characterized by a septic purulent inflammation. In dogs, most abscesses are sterile; however, positive bacterial culture of peritoneal exudate was shown in up to one-third of cases. Abscesses occur in <6.5% of cases of AP. The associated clinical signs cannot be differentiated from those of severe AP. Diagnostic confirmation of local complications relies mainly on abdominal ultrasound or CT scans. Cytological exam of an ultrasound-guided fine-needle aspirate may allow differentiation of abscesses from other lesions (Figure 11.14). Emptying of pseudocysts may be attempted under ultrasound guidance or with celiotomy. Therapeutic approach of necrotic foci and abscesses is more challenging. Currently, surgical intervention is only recommended in the presence of infected necrotic foci and fluid accumulations (abscesses), and possibly with total obstruction of bile flow due to PABDO. Importantly, affected dogs are often severely debilitated and surgical interventions are usually associated with a high mortality in the post-operative period (up to 70%).

TABLE 11.4 Complications of pancreatitis in dogs

Complication	Phase of disease
Acute kidney injury	Acute
Acute lung injury, acute respiratory distress syndrome	Acute
Adynamic ileus	Acute
Cholestasis (cholangitis, PABDO)	Acute
Diabetes mellitus	Acute or chronic
DIC	Acute
EPI	Chronic
MODS	Acute
Pancreatic abscess, pseudocyst	Acute
Pleural effusion	Acute
Relapsing pancreatitis	Chronic
SIRS, sepsis	Acute

DIC, disseminated intravascular coagulation; EPI, exocrine pancreatic insufficiency; MODS, multiple organ dysfunction; PABDO, pancreatitis-associated bile duct obstruction; SIRS, systemic inflammatory response syndrome.

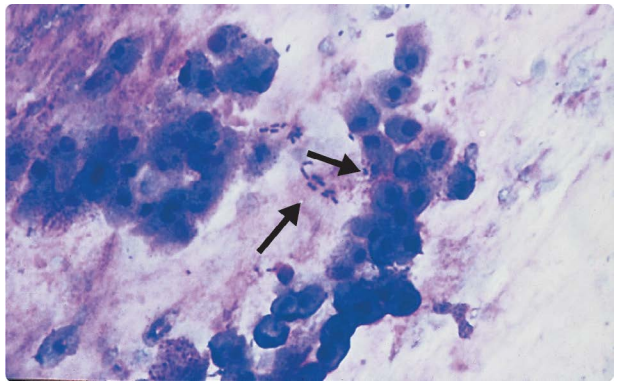


FIGURE 11.14 Cytology sample, from abdominal fluid in a dog with marked pancreatic necrosis with abscess formation, shows toxic neutrophils containing bacteria as well as free bacteria (arrows). Gram-negative bacteria are the most common organisms present on culture if infection occurs. (*Courtesy of D.J. Meyer.*)

As shown in Table 11.4, while acute complications of AP often concern the GI tract (with decreased GI motility) and the liver and biliary tract (with cholestasis and, less frequently, PABDO), organs and systems outside the GI tract and pancreas are also important targets, with the potential for life-threatening consequences. These "remote" complications may occur in the lungs and pleural space (acute lung injury, pleural effusion, with onset of sudden acute respiratory distress) (Figures 11.15 and 11.16), the kidneys (acute kidney injury), or impact hemostasis (DIC). Treatment for these disorders is outlined in other chapters of this book. In addition, inflammation may extend beyond the pancreas and cause SIRS. Ultimately, MODS can lead to the demise of the dog.

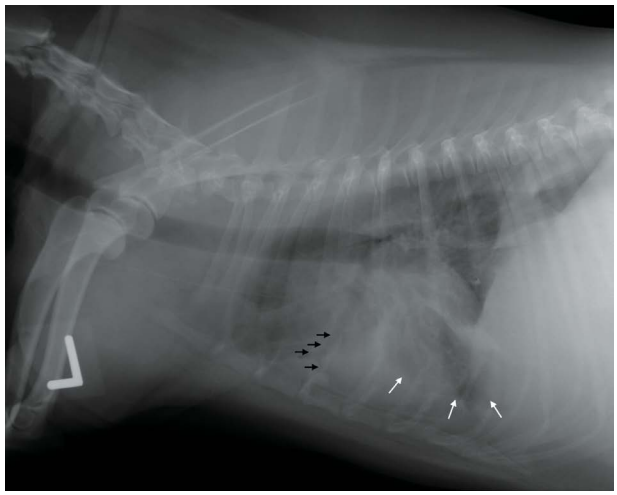


FIGURE 11.15 Chest radiographs of an 11-year-old, male neutered Miniature Poodle with AP and sudden-onset tachypnea and dyspnea due to acute lung injury. Left lateral view—a large air bronchogram is visible in the right cranial lung lobe (black arrows) indicating alveolar infiltration. There is scalloping in the caudal lung lobe (white arrows) indicating presence of pleural fluid.

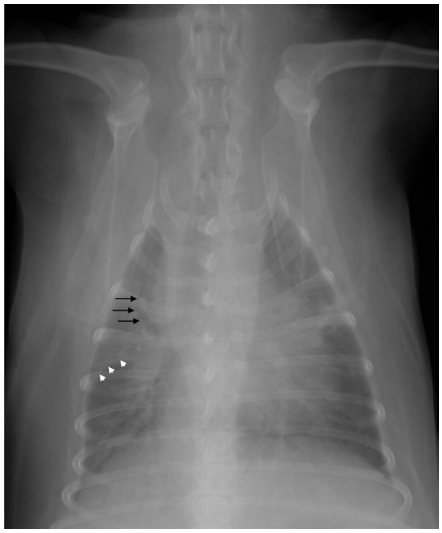


FIGURE 11.16 Ventrodorsal view—The air bronchogram is visible in the right cranial lung lobe (black arrows). There is a lobar sign between the right cranial and middle lung lobes (white arrowheads) and interstitial infiltration in the caudal lobes.

Prognosis

Most cases of mild-to-moderate pancreatitis respond favorably to supportive treatment. Early and aggressive treatment is thought to mitigate the risk of systemic complications. In severe cases, pancreatitis may trigger an uncontrollable cascade of complications that leads to SIRS and MODS. Severely affected dogs should be treated in a hospital offering intensive care with 24-hour monitoring. Prognosis for abscesses and necrotic foci is generally guarded to poor.

Several scoring systems have been established with the goal to help with management decisions and prognostication of AP. A severity score established >20 years ago remains valid and useful to date and is shown in Table 11.5. In addition, a canine acute pancreatitis severity (CAPS) score and a simplified version (sCAPS) have been established recently with the goal to identify dogs with AP at increased risk of death. (Table 11.6). In the sCAPS, checking for presence of SIRS is replaced by evaluation for tachypnea (respiratory rate ≥24 breaths per minute) which, if present, adds 3 points to the sCAPS. A CAPS score ≥11 or a sCAPS score ≥6 were shown to be accurate predictors of short-term death (within 30 days of initial presentation).

CHRONIC PANCREATITIS

Clinical Presentation

Chronic pancreatitis (CP) causes a more varied clinical picture than AP in dogs. In short, patients can present with recurrent signs of generally mild-to-moderate AP (acute-on-chronic pancreatitis) or with a more subtle set of clinical signs that may originate from the GI tract or other organ systems. Common clinical signs of CP are listed in Table 11.7. CP may ultimately lead to organ failure with onset of exocrine pancreatic insufficiency (EPI) and diabetes mellitus (Figure 11.17). In a necropsy case control study, dogs with CP were more likely to have concurrent endocrine diseases (particularly diabetes mellitus) than the reference population or than dogs with AP. They were also more likely to have hepatobiliary or neurologic disease compared to the reference population.

Diagnosis

The diagnosis of CP is often challenging, particularly when the clinical signs are vague and mild. In addition, the diagnostic tests used with success in AP have lower sensitivity for CP. Based on one study, PLI had a low

TABLE 11.5 Practical AP severity scoring in dogs

Disease severity	Score*	Prognosis	Clinical presentation and required support
Mild	0	Excellent	– Often resolves spontaneously – Recovery is uncomplicated – Managed as an outpatient if hydration status is good – Antiemetics are commonly prescribed
Moderate	1	Good to guarded	– Usually dehydrated—prerenal azotemia is common – Recovery is usually uncomplicated, provided adequate supportive treatment can be administered (see text)
	2	Guarded to poor	– Dehydrated, hypovolemic, often prerenal azotemia and neutrophilia with degenerative left shift – Pulmonary and renal function and hemostasis need to be closely monitored – Referral to a 24-hour intensive care unit is often required – Dogs usually recover with intensive therapy
Severe	3	Poor	– These dogs are in critical condition – Intensive monitoring of these critical patients is critical – Extensive therapy and life support are required – Death is a common outcome
	4	Grave	

Modified from Ruaux and Atwell (1998). A severity score for spontaneous canine acute pancreatitis. *Aust Vet J* 76(12):804–808.

* The severity scoring system is based on the number of organ systems, apart from the digestive tract, that show evidence of failure or compromise at initial presentation.

TABLE 11.6 Canine acute pancreatitis severity (CAPS) score

Parameter	Definition	Present	Absent
Systemic inflammatory response syndrome (SIRS)	≥2 of the following criteria – Heart rate >120/min – Respiratory rate >20/min – Body temperature <38.1C (100.6F) or >39.2C (102.6F) – White blood cell count <6,000/μL or >16,000/μL	8	0
Coagulation disorder	Thrombocytopenia (platelet count <63,000/μL), prothrombin time (PT), activated partial thromboplastin time (APTT) prolonged by more than 25% of the upper end of the reference interval, or both	3	0
Increased creatinine	Serum creatinine concentration above the reference range	4	0
Ionized hypocalcemia	Serum ionized calcium concentration below the reference range	3	0

From Fabrès V, Dossin O, Reif C, et al. (2019). Development and validation of a novel clinical scoring system for short-term prediction of death in dogs with acute pancreatitis. *J Vet Intern Med* 33(2): 499–507.

sensitivity (58%), even though it appeared to be the most sensitive laboratory test. Therefore, it is extremely important for clinicians to keep the disease "on their radar" when they see dogs with vague GI-related signs such as those listed in Table 11.7. The test of reference for diagnosing CP is pancreatic histology; however, pancreatic biopsies are infrequently collected in dogs with suspect CP. In addition, disease distribution throughout the pancreas may be patchy, and a negative biopsy may not allow to rule out CP.

The recommended diagnostic workup for a dog with suspect CP consists of a minimal database, including CBC, chemistry profile, and urinalysis. Abdominal imaging (radiographs, ultrasound, possibly CT) can help rule out other possible diagnoses and hopefully identify pancreatic changes. Abdominal ultrasound was shown to have a low-to-moderate sensitivity for CP (56%). PLI or DGGR lipase may also help confirming the presence of pancreatic inflammation. If EPI is suspected, serum concentration of trypsin-like immunoreactivity (TLI) should be assessed. Therefore, the purpose of the diagnostic workup is to rule out other diseases that could cause similar signs and define the extent of CP complications.

TABLE 11.7 Common clinical signs in dogs with chronic pancreatitis

Gastrointestinal signs	Other signs
Low-grade waxing and waning intermittent anorexia with or without vomiting or (large bowel) diarrhea	Sudden onset of extrahepatic biliary obstruction
Occasional anorexia and frequent evidence of postprandial pain and learned food aversions, without other gastrointestinal signs	Back pain (when all other causes such as intervertebral disc disease have been ruled out)
Acute presentation with signs typical of AP as a single episode or recurrent acute flare ups	Polydipsia/polyuria
Diabetes mellitus developing in an older dog of a predisposed breed	Keratoconjunctivitis sicca or protein-losing nephropathy in an English Cocker Spaniel
Exocrine pancreatic insufficiency in an older dog of a breed other than German Shepherd Dog Concurrent diabetes mellitus and exocrine pancreatic insufficiency in any dog	

Adapted from Watson P (2012). Chronic pancreatitis in dogs. *Topics in Comp An Med* 27(3): 133–139. With permission.



FIGURE 11.17 5-year-old FS Cavalier King Charles Spaniel with chronic relapsing pancreatitis, PU/PD, polyphagia, and weight loss. The dog was diagnosed with diabetes mellitus and exocrine pancreatic insufficiency.

Differential Diagnosis

Due to the vague signs associated with CP, many differential diagnoses need to be considered. These may include chronic gastritis, chronic enteropathies, chronic hepatitis and/or cholangitis, and hypoadrenocorticism, to name a few.

Management

For dogs presenting with acute-on-chronic disease, recommended treatment is identical to what is outlined earlier for treatment of AP.

For dogs with a more chronic presentation, the three main components of treatment for CP are analgesia, appropriate nutrition, and addressing functional loss (EPI, diabetes mellitus). Postprandial pain has been described in dogs with CP, and the currently recommended approach is to feed a low-fat diet. If the dog is hospitalized, parenteral analgesia is provided as recommended for AP. For use at home, acetaminophen has been recommended if there is no concurrent liver disease (10 mg/kg p.o. q.12–24 h.). Gabapentin is another analgesic to consider (10–20 mg/kg p.o. q.12 h.). NSAIDs are best avoided because they can cause GI and renal side effects. Chapter 24 extensively discusses pain and its management. Pancreatic enzyme supplementation is recommended in the presence of EPI or weight loss in CP dogs. Immune-suppressive glucocorticoid treatment has been suggested in English Springer Spaniels, a breed in which CP is thought to be a manifestation of polysystemic autoimmune disease.

Prognosis

CP is a disease that can be managed but not eradicated. Ultimately, prognosis depends on the success of prevention of recurrence of acute episodes through feeding of a low- to ultralow-fat diet and avoidance of dietary triggers. In patients with a more chronic course, success of pain management and the ability to efficiently address exocrine and/or endocrine pancreatic dysfunction if present are other important factors.

FELINE PANCREATITIS

Feline pancreatitis has been the subject of a recent consensus statement by the American College of Veterinary Internal Medicine (ACVIM). This open access document is an excellent resource (see Recommended Further Readings).

In a necropsy study, 67% of cats showed histological lesions in their pancreas. More than half of necropsied cats had chronic changes, while only 6% of lesions were indicative of acute disease, and acute and chronic pancreatic changes were present in simultaneously in approximately 10% of cats. These statistics underscore the importance of CP in the feline population, even though most cases seem have a subclinical course. Two forms of AP have been described: Necrotizing pancreatitis and suppurative pancreatitis. CP is often recurring, not suppurative, and can lead to EPI.

Clinical Presentation

Feline pancreatitis can be associated with a wide range of nonspecific clinical signs (Table 11.8). Most cats are presented to their veterinarian because of lethargy and lack of appetite; insidious weight loss may also be one of the presenting complaints (Figure 11.18). Because it has been historically challenging to assess pain in cats, it is likely that the prevalence of abdominal pain is underestimated in feline pancreatitis. The type and severity of clinical signs are generally not helpful to differentiate acute from chronic pancreatitis.

TABLE 11.8 Clinical signs of feline pancreatitis

Clinical signs	Prevalence in %
Reported by owners	
Lethargy	51–100
Hyporexia/anorexia	62–97
Vomiting	35–52
Weight loss	30–47
Diarrhea	11–38
Dyspnea	6–20
Documented during physical exam	
Dehydration	37–92
Hypothermia	39–68
Icterus	6–37
Apparent abdominal pain	10–30
Hyperthermia/fever	7–26
Abdominal mass or organomegaly	4–23

Adapted from Forman MA, Steiner JM, Armstrong PJ, et al. (2021). ACVIM consensus statement on pancreatitis in cats. *J Vet Intern Med* 35(2): 703–723.

Diagnosis

The diagnostic workup of cats with acute or chronic pancreatitis has two main goals: First to rule out the numerous other diseases that could cause similar clinical



FIGURE 11.18 10-year-old MN Domestic Shorthair cat with acute-on-chronic pancreatitis. The cat was presented because of ongoing lethargy, anorexia, and occasional vomiting. He was dehydrated and in poor body condition.

signs and second to confirm pancreatic inflammation. Therefore, obtaining a minimum database consisting of CBC, chemistry profile, urinalysis, and imaging is essential.

CBC may show neutrophilia or neutropenia, reflecting acute inflammation, particularly in AP. The chemistry panel may reveal increased activity of hepatic enzymes (ALT, GGT, ALP) and hyperbilirubinemia because of concurrent inflammation of the biliary tree, extrahepatic biliary obstruction, hepatic lipidosis, or some combination of these. In cats with severe AP, azotemia may be present as exemplified by increased creatinine, urea, or symmetric dimethylarginine (SDMA) concentrations. Hyperglycemia may be associated with stress and concurrent diabetes mellitus. Azotemia, changes in blood glucose, and ionized hypocalcemia have been identified as negative prognostic factors.

A feline specific PLI test is available both for in hospital and laboratory use. A recent retrospective study reported a positive predictive value of 90% and a negative predictive value of 76% for the proprietary PLI performed in labs. Therefore, the test was found to have good but not excellent sensitivity. A biochemical test with increased affinity for pancreatic lipase (DGGR lipase) appears to be diagnostically useful as well. However, the specificity of that test for pancreatic lipase is the subject of ongoing debate.

Abdominal radiographs can be very useful in ruling out differential diagnoses such as diseases causing GI obstruction (e.g., foreign bodies and neoplasia compressing the intestinal lumen, see Chapter 9); however, they do not offer much help in the assessment of the pancreas with exception of large pancreatic masses.

Abdominal ultrasound findings in feline AP may include pancreatic enlargement, a hyperechoic surrounding mesentery, and focal abdominal effusion. The duodenum can be distended or corrugated. The sensitivity of ultrasound for diagnosis of AP varied widely between studies (11%–67%) and is considered to depend on severity of disease and operator skills. Sonographic features of CP are not well established in cats. They may include a hyperechoic or mixed echoic pancreas, a dilated common bile duct, enlarged pancreas, and irregular pancreatic margins (**Figure 11.19**). Importantly, in most cases, ultrasound does not allow to differentiate acute from chronic pancreatitis. Pancreatic nodular hyperplasia with enlargement and nodules up to 1 cm is an incidental finding in older cats and should not be misinterpreted. Advanced imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) have not been established as routine diagnostic tools for feline pancreatitis.

Pancreatic cytology from ultrasound-guided aspirates may be useful to confirm inflammation in cats with AP (neutrophils present in close vicinity to pancreatic acinar cells). However, aspirates from cats with CP are often poorly cellular.

Histological evaluation of pancreatic biopsies collected during exploratory laparotomy or laparoscopy remains the reference to which other methods are compared (**Figure 11.3**).

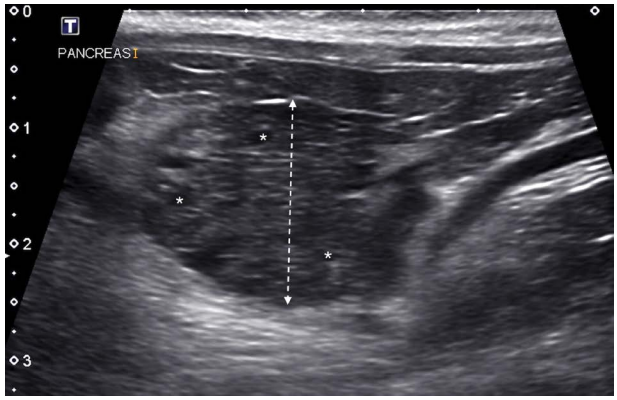


FIGURE 11.19 Ultrasound appearance of the pancreas of an 8-year-old female-spayed Domestic Shorthair cat with suspected acute-on-chronic pancreatitis. The pancreas is enlarged (1.7 cm, double arrow), irregularly shaped, of heterogenous echogenicity, with multiple small, ill-defined hypoechoic nodules (asterisks). The peripancreatic tissue is hyperechoic.

In summary, diagnosis of feline pancreatitis may be challenging, particularly in CP. Therefore, the best approach consists of combining several diagnostic modalities to achieve the best possible accuracy.

Differential Diagnosis

The clinical signs of pancreatitis in cats are nonspecific; therefore, many differential diagnoses need to be considered. The most important ones include chronic intestinal diseases (obstruction with foreign body or neoplasia, chronic enteropathy, IBD, alimentary lymphoma), cholangitis, chronic kidney disease, and hyperthyroidism.

Management

Treatment of AP in cats focuses on the same priorities as listed for treatment of canine AP (see **Box 11.2**): Fluid therapy, antiemetics, pain management, and nutrition. However, a few feline specificities must be considered. Metoclopramide does not have any antiemetic effect in cats due to lack of dopamine-2 receptors in the chemoreceptor trigger zone (CRTZ) (see Chapter 2.17). However, it was shown to have good gastric prokinetic effect and can be used to treat functional ileus, if present, preferably as a CRI. Recommendations for feline analgesia can be found in Chapter 24. Also, mirtazapine is an appetite stimulant that has proven useful in various feline diseases. The ghrelin analogue capromorelin has recently been approved for use in cats as well. Early feeding is recommended and should be initiated within 2–4 days after the last meal. While cats with mild-to-moderate AP will often resume eating rapidly, severe cases and cases with comorbidities will benefit from nasoesophageal tube feeding (see Chapter 25). The optimal diet for cats with AP has not been defined; cats have high dietary protein requirements and a higher tolerance to fat compared to dogs. Highly digestible diets are recommended. Importantly, severely ill cats often develop food aversion. It is, therefore, preferable to

delay use of the long-term diet of choice until after the cat is discharged from the clinic.

Fluorescent in situ hybridization revealed the presence bacteria (probably ascending from the gut) in 35% of cats with moderate-to-severe pancreatitis. However, the ACVIM consensus statement does not recommend treating cats with AP with broad-spectrum antibiotics unless definite clinical indications are present: Infection in the pancreas (e.g., abscess), ascending bile/pancreatic duct infection, or CBC findings suggestive of sepsis.

The treatment of CP is also mostly supportive in addressing the four priorities listed for AP earlier. In addition, it should include management of any concurrent disease such as chronic enteropathy and/or cholangitis (see Chapters 9 and 10). There is currently no data suggesting that dietary fat should be avoided in cats with pancreatitis. Cobalamin supplementation may be indicated, particularly in cats with concurrent chronic enteropathy (**Table 9.13**). Corticosteroids have been used successfully in cats with CP. Recommended prednisolone doses vary between 0.5 and 2 mg/kg per day. In the absence of evidence from the literature, there is still debate on the best dosing regimen, but periodic reassessment of the cat with measurement of PLI is recommended to guide treatment. Corticosteroids should be avoided in cats with hyperglycemia. Cyclosporine has also been used with success in the treatment of feline CP (5 mg/kg q.24 h.). However, immune suppression could potentially unmask latent infectious diseases such as toxoplasmosis.

Prognosis

The prognosis of feline pancreatitis varies considerably between studies with a mortality rate between 9% and 41% for cats with AP. Cats with mild-to-moderate disease generally have a good prognosis when appropriately managed. Some laboratory abnormalities have been identified as negative prognostic factors. Cats with mild-to-moderate recurring chronic pancreatitis usually have a guarded to good prognosis. However, the prognosis may vary due to concomitant diseases (cholangitis, chronic enteropathy) and complications such as EPI or diabetes mellitus.

FELINE TRIADITIS

Triaditis describes a chronic condition with simultaneous occurrence of CP, neutrophilic cholangitis, and chronic enteropathy. While the cause of triaditis is not known, it is suspected that the three diseases share a common etiology. One hypothesis is that enteropathy causes small intestinal dysbiosis, which facilitates penetration of bacteria in the common bile duct and then in the pancreatic and bile ducts and ascending infection or inflammation. Alternately, chronic enteropathy could also facilitate translocation of bacteria into the portal system.

As can be seen in this chapter and Chapters 9 and 10, many of the clinical signs of CP, chronic enteropathy, and cholangitis are nonspecific and overlap. The minimal database may also identify changes in laboratory parameters that are known to occur in all three diseases. Evaluation of serum cobalamin concentration and PLI is recommended. Abdominal ultrasound examination is used to investigate the small intestinal wall (thickness, layering), the liver and biliary system, and the pancreas and may provide useful information about the presence of multiorgan disease. Even though it is not indicated or feasible for each animal, laparotomy and biopsy of all three organs is the diagnostic standard.

Management of cats with triaditis revolves around the same components recommended for chronic enteropathy, cholangitis, and pancreatitis. These include fluid therapy, antiemetics, analgesics, appetite stimulants, early enteral nutrition, vitamins, nutraceuticals, and possibly immunosuppressants and/or antibiotics. Importantly, antibiotics should only be used after sampling of material for culture and sensitivity (e.g., bile in cholangitis) or in patients with signs and laboratory changes suggestive of sepsis.

The prognosis is generally good for cats with mild disease. Reported negative prognostic factors include hypoalbuminemia and hypoglycemia, and systemic hypotension also negatively affect prognosis in severely ill cats. Cats recovering from triaditis may experience recurrent episodes overt time. EPI and diabetes mellitus are chronic complications of CP. Biliary cirrhosis and possibly cholangiocarcinoma are long-term complications of chronic cholangitis, and alimentary lymphoma is a complication of chronic enteropathy.

EXOCRINE PANCREATIC INSUFFICIENCY

Definition/Overview

While the prevalence of exocrine pancreatic insufficiency (EPI) in the general canine population is unknown, it was approximately 9% among dogs with gastrointestinal clinical signs suggestive of EPI for which a TLI test was requested in a study from the UK. Thus, it is a relatively rare condition in dogs and occurs even less frequently in cats.

Etiology

In the dog, several etiologies have been identified. Congenital pancreatic hypoplasia is a very rare disorder. In German Shepherd Dogs, Rough Hair Collies, and Eurasian Dogs, pancreatic acinar atrophy (PAA) causes pancreatic insufficiency when more than 90% of the gland has disappeared. PAA was shown to be is a slowly progressive immune-mediated disease. It is characterized by lymphocytic plasmacytic infiltration that may lead to the destruction of the gland. An autosomal recessive heredity pattern has been shown. However, no specific gene defect could be identified to date despite intensive research. Therefore, a multifactorial etiology with a strong hereditary component is suspected.

In dogs with CP, pancreatic parenchymal destruction can occur because of chronic recurring inflammation, and diabetes mellitus may also occur when the endocrine pancreas is affected. However, signs of EPI usually precede those of diabetes. Finally, pancreatic neoplasia or masses impinging the pancreatic duct may also cause progressive destruction of glandular tissue and EPI.

In the cat, EPI is typically associated with chronic pancreatic inflammation, pancreatic neoplasm, or pancreatic duct obstruction. Diabetes mellitus may also develop.

Pathophysiology

EPI causes a deficiency in digestive enzymes. This prevents adequate predigestion of macromolecules in the intestinal lumen. Moreover, lack of pancreatic bicarbonate can lead to an acidic intestinal content and dysfunctional transport mechanisms for monosaccharides and disaccharides, amino acids, and fatty acids in the enterocyte brush border. The absence of pancreatic trophic factors also has negative effects. Maldigestion leads to malabsorption or malassimilation of nutrients, which can cause nutritional deficiencies. Lack of pancreatic intrinsic factor prevents absorption of cobalamin in the ileum. Low concentrations of fat-soluble vitamins (A, D, E) have been reported in dogs with EPI. Additionally, dogs with EPI develop gut dysbiosis with a loss of alpha-diversity of microbiota, which most likely has a significant impact on their gut metabolome.

Clinical Presentation

The clinical signs of EPI in dogs and cats result from a maldigestion/malabsorption syndrome. Dogs lose weight and may become emaciated despite a good and sometimes voracious appetite (Figures 11.17, 11.20, and 11.24a). Defecation frequency is increased with large amounts of feces of cow-patty consistency (Figure 11.21).

Feces may contain excessive amounts of fat (steatorrhea) that can give them a gray color. Liquid or severe diarrhea is rarely observed in dogs. Coprophagia may occur in some canine cases. Borborygmus and flatulence



FIGURE 11.21 Feces of cow-patty consistency from a 9-month-old female Mastiff with EPI.

may elicit a nervous, sometimes aggressive behavior in affected dogs. Moreover, skin lesions and greasy hair coat with a rancid smell have been described in some canine cases. These clinical signs are typical but not pathognomonic for EPI. In a retrospective study of 199 German Shepherd Dogs with EPI, 10.5% developed a mesenteric torsion, a complication unknown to occur in other breeds.

In a recent retrospective study of EPI in cats, 91% of cats had lost weight for a median duration of 6 months (Figure 11.22). Only two-thirds of cats with EPI had unformed feces (Figure 11.23), and diarrhea was occasionally watery. Half of the cats were presented with increased appetite, while 42% had decreased appetite, which may have been due to ongoing CP, and 50% had poor hair coat. Importantly, only one-third of cats presented with a combination of weight loss, unformed feces, and increased appetite (as is typical for dogs), and 56% had weight loss and unformed feces.

Diagnosis

The test of reference for diagnosis of EPI is the serum level of trypsin-like immunoreactivity (TLI), which detects circulating concentration of cationic trypsinogen



FIGURE 11.20 A 10-month-old male German Shepherd Dog showing its frail body and stunted growth. (*Courtesy of M. Schaer.*)



FIGURE 11.22 A 10-year-old male neutered Domestic Shorthair cat with EPI. The cat had lost weight over the previous 6 months despite a maintained appetite. He had a 3/9 body condition score. (*Courtesy of M. Cousins.*)



FIGURE 11.23 The feces from the cat shown in **Figure 11.22** are voluminous and of pale consistency but well formed. (*Courtesy of M. Cousins.*)

and trypsin produced by the pancreas and cleared by the kidneys. Because the functional mass of their pancreas is significantly decreased, animals with EPI show very low serum concentrations of TLI. The test is strictly species specific. It is best performed after a 12-hour fast. Results can be falsely high in animals with decreased renal function or those with chronic pancreatitis (even if the amount of functional pancreatic tissue is severely diminished). EPI dogs with clinical signs generally have serum TLI values below 2.5 µg/L. Values between 2.5 and 5.0 µg/L may indicate early pancreatic dysfunction. A subclinical phase of unknown duration may precede clinical EPI. In such cases, the test should be repeated after a few weeks. In cats, values below 8 µg/L are indicative of EPI.

Serum cobalamin should be measured in all animals with suspect EPI. Studies have shown that 36%–76% of dogs and 65% of cats with EPI have hypocobalaminemia.

Differential Diagnoses

Other chronic diseases that cause maldigestion/malabsorption may cause a similar clinical picture (e.g., severe parasite infections, chronic enteropathy, CP without EPI [dogs, cats], low-grade alimentary lymphoma, hyperthyroidism [cats], etc.)

Management

Treatment of EPI in dogs and cats relies on pancreatic enzyme supplementation (**Figure 11.24a, b**). Enzyme supplements derived from pancreatic extracts of bovine or porcine origin can be administered in powder form. Treatment is initiated with a standard dose of powder (1 teaspoon per 10 kg of body weight) mixed with the meal, which can then be increased or decreased to effect. There is no added benefit to incubate the food with the supplement prior to feeding. Treatment with pancreatic enzyme supplement is lifelong and can be expensive, particularly in large breed dogs. In some dogs, enzyme supplementation may cause oral mucosal ulcerations with bleeding. Though thorough mixing of the powder with food is generally sufficient to resolve the problem, reducing the dose of enzyme may be necessary in some cases. Also, it is prudent to check animals with oral bleeding for coagulopathies and treat if present (vitamin K, 2.5 mg/kg SC q.12 h.). Importantly, full restoration of digestive activity is not an achievable goal, and the realistic objective is successful management of clinical signs and restoration of appropriate quality of life for the animal. In most animals, special diets are not required in the long term, and a high-quality regular diet may be appropriate.

In case of failure of initial enzyme supplementation, a systematic approach is recommended (**Table 11.9**). Fat digestion remains a problem in dogs and cats with EPI despite treatment, since most of the supplemented lipase is destroyed in the stomach. It was recently shown that deficiencies in fat-soluble vitamins persist after treatment; however, no study to date documented any benefit from supplementation of these vitamins, and empirical treatment with vitamins A and D may induce toxicosis. Vitamin E supplementation is generally well tolerated (dog: 100–400 U p.o. daily for 1 month, then as needed; cat: 10–15 U/kg p.o. daily). Gut dysbiosis is probably the consequence of both a lack of pancreatic bacteriostatic factors and the high concentration of organic substrate in the intestinal lumen due to maldigestion/malabsorption secondary to EPI. Enzyme supplementation does not lead to normalization of the gut microbiota.

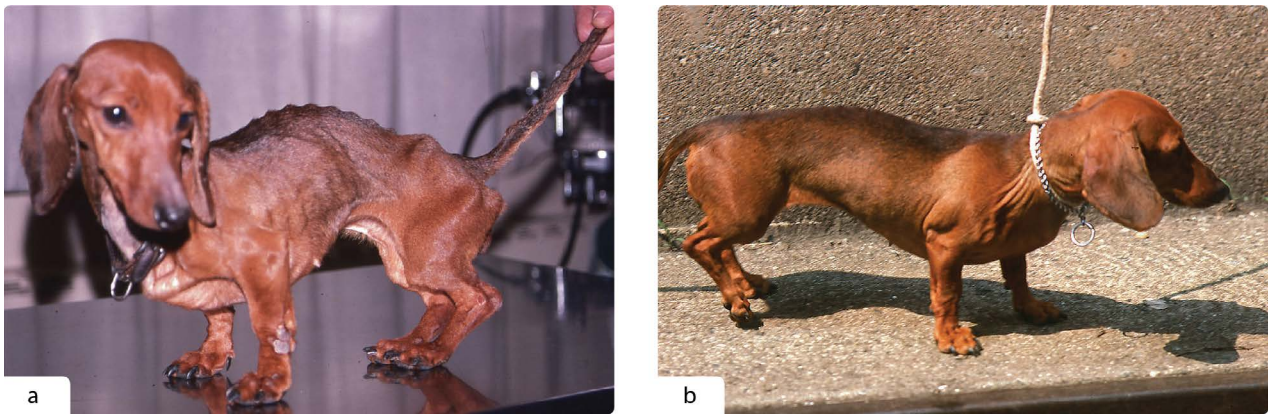


FIGURE 11.24 This young female Dachshund suffered severe emaciation from exocrine pancreatic insufficiency **(a)**. The same dog is shown approximately 4 months after pancreatic enzyme replacement treatment **(b)**. (*Courtesy of M. Schaer.*)

TABLE 11.9 Recommended procedure when initial enzyme therapy fails

- Modification of enzyme supplementation
  - Increase the dose of enzyme supplement (excessive doses generally do not cause side effects, except oral ulcerations)
  - Change to another brand of enzyme supplement
  - Consider raw porcine or bovine pancreas (30–90 g replace 1 teaspoon powder) (raw pancreas may be stored frozen in aliquots)
- Make sure hypocobalaminemia is appropriately corrected; recheck serum cobalamin may be required, followed by dose correction if needed (see **Table 9.14**)
- Dietary modification
  - Highly digestible diets
  - Low-fat diet, with associated risk of further decreasing intake of fat-soluble vitamins
- Other options
  - Evaluate for concurrent disease such as diabetes mellitus or IBD
  - Treat probable gut dysbiosis (consider measuring fecal dysbiosis index)
    - High-potency multistrain probiotic or
    - Tylosin 20–25 mg/kg p.o. q.12 h. for 4 weeks

Prognosis

A recent study reviewed the initial response to treatment in a cohort of 127 dogs with EPI. The response was good in 60%, partial in 17%, and poor in 23% of cases. The mean survival of the group was more than 5 years; however, 19% of the dogs were euthanized in the year following diagnosis. The authors concluded that long-term prognosis was favorable for dogs that survived the initial treatment period. Hypocobalaminemia at initial presentation was shown to be a negative prognostic factor in several studies. In addition, in a recent study of 299 dogs with EPI, lack of appetite at the initial visit, male sex, and not receiving cobalamin supplementation were independent risk factors for decreased survival, while hyperfolatemia was associated with an improved prognosis. In other studies, type of enzyme supplementation and diet, administration of antimicrobials, and gastric acid suppression were all without effect on the prognosis.

Response to enzyme supplementation was reported in a cohort of 121 cats with EPI. It was good in 60%, partial in 27%, and poor in 13% of cats. In that group, TLI concentration between 4 and 8 µg/L (versus below 4 µg/L) and ongoing treatment with cobalamin were predictors of a higher likelihood of response to treatment. Antibiotic treatment did not have any beneficial impact on outcome.

CASE EXAMPLE

Case 11.1

Signalment

13-year-old female spayed Terrier mixed breed weighing 6 kg

History

The dog was presented for a 1-month history of lethargy, hyporexia/anorexia, and markedly increased serum liver enzymes and total bilirubin at the referring veterinarian. She was treated with amoxicillin, clavulanic acid, and S-adenosylmethionine with silymarin. She had stopped eating and vomited twice on the day of prior to presentation.

Physical Examination

Body condition score: 5/9; however, had lost 1.5 kg over 2 months

Vital parameters: Within normal limits

Physical exam: The dog was quiet, alert, responsive, and diffusely icteric (**Figure 11.25**). Cranial abdominal pain was noticed during abdominal palpation.

Initial Assessment

The dog's main problems were chronic hyporexia/anorexia, weight loss, icterus, and increased liver enzymes. The top differential diagnoses included hepatopathies (e.g., toxicosis, inflammation) or liver neoplasia, diseases of the biliary tract (e.g., cholecystitis, cholangitis), and pancreatitis.

Further Investigations

In the minimum database, CBC showed revealed moderate leukocytosis and neutrophilia suggestive of active inflammation. The chemistry panel showed markedly increased ALT, ALP, and GGT and a total bilirubin of 19.8 mg/dL (reference range 0.2–0.4). Abdominal ultrasound showed an irregularly shaped, hypoechoic pancreas surrounded by hyperechoic mesenteric fat. The common bile duct was



FIGURE 11.25 A 13-year-old mixed-breed dog with icteric sclera and probable acute-on-chronic pancreatitis with pancreatitis-associated bile duct obstruction (PABDO).

(*Continued*)

segmentally enlarged but could not be followed over its whole length. Pancreatitis-associated bile duct obstruction (PABDO) was suspected. The PLI was severely increased, indicating pancreatitis. Bile was obtained from a cholecystocentesis and submitted for aerobic and anaerobic cultures, which were negative.

Initial Treatment

The dog was treated with fluid therapy, antiemetics (maropitant 1 mg/kg SC q.24 h. and ondansetron 0.7 mg/kg q.12 h.), capromorelin 3 mg/kg p.o. q.24 h., SAMe and silymarin (225/24 mg q.24 h.), and ursodiol (10 mg/kg p.o. q.24 h.). She started eating again 2 days after admission and was offered a home-cooked, low-fat diet (boiled skinless chicken breast and rice).

Further Treatment

The treatment with antiemetics, appetite stimulants, liver protectants, and ursodiol was continued after discharge from the hospital. The dog was rechecked weekly and continued improving clinically with increased appetite and energy and activity levels. Serum bilirubin and liver enzymes started decreasing significantly at week 4. All were back to the reference range by week 6 except ALP, which was still mildly increased (**Figure 11.26**).

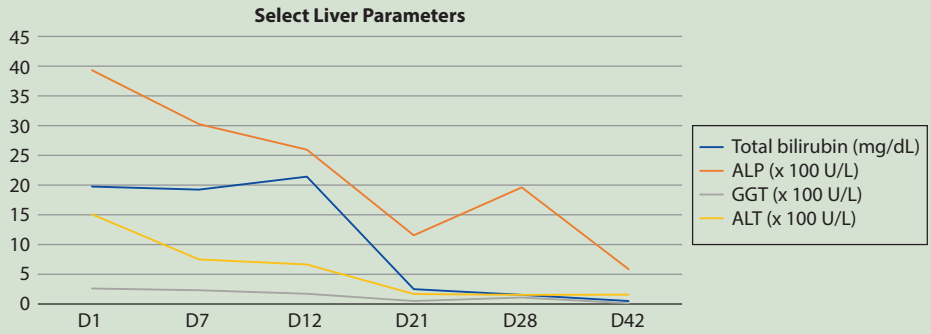


FIGURE 11.26 Evolution of select liver parameters on serum chemistry over 6 weeks in a dog with pancreatitis and PABDO.

Final Assessment

The dog had an acute-on-chronic pancreatitis with PABDO. A recent review of 42 dogs with PABDO reported 79% survival rate, with 94% of dogs receiving medical management alone. Median time to peak bilirubin elevation and initial decline in serum bilirubin were 8 and 15 days, respectively.

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CHAPTER 12

Endocrine Disorders

Michael E. Herrtage

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INTRODUCTION

The presentations of endocrine diseases are diverse, and the findings in the history and physical examination reflect this diversity. Some of the more common presentations are listed in Table 12.1. Although multiple endocrine disorders can occur in the same animal (for example, autoimmune polyendocrine syndromes or multiple endocrine neoplasia), most abnormalities affect a single hormone system. A working knowledge of endocrine physiology is essential not only for a good understanding of the pathophysiology of endocrine disease but also for understanding the rationale and limitations of endocrine function tests.

Advances in our knowledge of endocrine diseases have been made possible by the widespread availability of sensitive methods for measuring hormone concentrations and improved diagnostic imaging techniques. The release of some hormones shows marked diurnal variation, making single determinations difficult to interpret. The pattern of release may also vary with age, sex, stress, diet, or concurrent disease or medication. In the laboratory, hormone assays can vary in their performance, and it is important to consult individual laboratories and equipment manufacturers regarding the precision and accuracy of their hormone test results. The reference intervals given in this chapter are only intended as a general guide. Commercial diagnostic laboratories and veterinary practices should be members of a quality-control scheme and should be comparing their results with other laboratories to ensure that their interpretation is fully justified.

In order to overcome some of these problems of interpretation, dynamic tests have been developed that determine the response of a gland to stimulation or suppression. Stimulation tests assess the functional reserve of an endocrine gland by its ability to increase its hormonal output. The response may be exaggerated in conditions where there is excessive function or reduced if the gland is structurally or functionally damaged. Suppression tests use the administration of a pure hormone to test the negative feedback mechanism. Hormonal production is normally suppressed in these tests, but production persists where the gland is hyperplastic or if a functional endocrine tumor is present.

This chapter has been structured to provide a practical guide for veterinarians in the diagnosis and management of the more common endocrine disorders.

TABLE 12.1 Common presentations of endocrine disease

- Polyuria–polydipsia
- Weight gain / obesity
- Weight loss
- Poor growth or stunting
- Symmetrical alopecia
- Episodic weakness and collapse
- Hypertension

DISORDERS OF THE PITUITARY

The pituitary gland is a small, ovoid structure that lies in a distinct fossa, the sella turcica, just ventral to the hypothalamus and caudal to the optic chiasma. The pituitary consists of two distinct parts, an anterior and a posterior lobe, each of which has separate functions. The hypothalamus and the pituitary form a complex functional unit that controls much of the endocrine system, and any space-occupying lesions arising in this area can, therefore, cause a wide range of effects.

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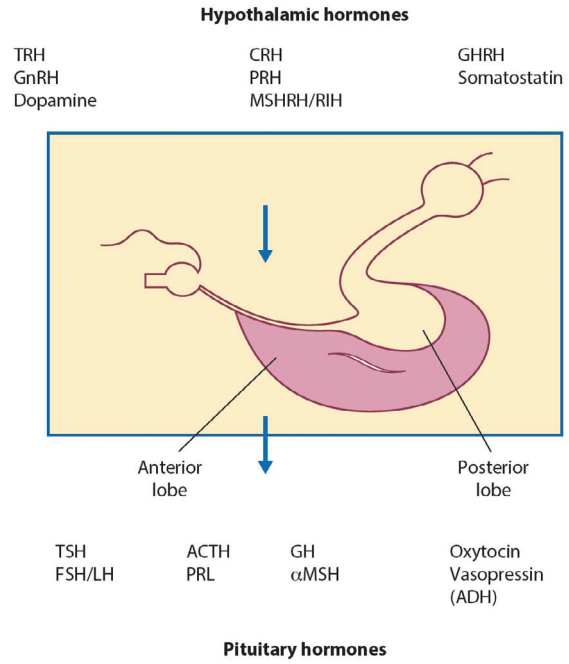


FIGURE 12.1 Physiology of hypothalamic–pituitary function.

The hypothalamus is important in the regulation of anterior and posterior pituitary function. The release of hormones from the anterior lobe of the pituitary is controlled by hypothalamic peptides, which are transported to the anterior pituitary by the capillaries of the hypothalamic–hypophyseal portal circulation (Figure 12.1). The hypothalamus contains a number of autonomic centers that control thirst, satiety, body temperature, emotional reactions, and sympathetic responses, and it serves as an important link between the brain and the endocrine system.

The posterior pituitary releases stored vasopressin (antidiuretic hormone [ADH]) and oxytocin, which have been synthesized in the supraoptic and paraventricular nuclei of the hypothalamus.

CONGENITAL HYPOPITUITARISM

Definition/Overview

Congenital hypopituitarism results from inadequate secretion of growth hormone (GH) and resultant retardation of growth (pituitary dwarfism).

Etiology

The condition is rare, but it has been reported in a number of breeds of dog. It is most commonly seen in German Shepherd Dogs, where it has been shown to be inherited as an autosomal recessive trait. In the dog, pituitary dwarfism is most commonly associated with cystic dilatation of Rathke's cleft, which arises as a result of the failure of the anterior lobe of the pituitary to develop normally and results in reduced secretion of anterior pituitary hormones (Figure 12.2). Hypoplasia of the pituitary has been reported in the cat but also appears to be rare (Figure 12.3).

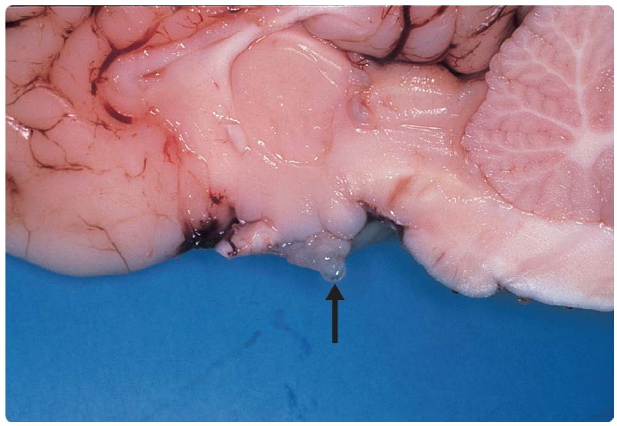


FIGURE 12.2 Cystic dilatation of Rathke's cleft cysts (arrow) in a German Shepherd Dog with hypopituitarism.

Pathophysiology

In many affected animals, a cystic vestigial adenohypophysis is present, although some animals have either a hypoplastic pituitary or one that appears grossly normal. Pituitary dwarfism is not usually caused by isolated GH deficiency but is due to a combined pituitary hormone deficiency affecting anterior lobe function.

Clinical Presentation

Affected animals appear normal at birth, but growth retardation is usually evident by weaning (Figure 12.4).



FIGURE 12.3 A 5-month-old kitten with congenital hypopituitarism.



FIGURE 12.4 Three 6-week-old German Shepherd puppies. The middle puppy is affected with congenital hypopituitarism and shows obvious growth retardation compared to its littermates.

A deficiency of GH produces proportionate dwarfism (Figure 12.5). The degree of stunting is variable and probably depends on the extent of the pituitary compromise. Delayed growth plate closure and dental eruption have been reported in some cases.

GH is required to produce a normal adult hair coat in the dog. In pituitary dwarfism, the fine puppy coat is retained and becomes matted and woolly in appearance (Figure 12.5). The hair coat is slowly lost from the trunk, leading to the development of bilaterally symmetrical, nonpruritic alopecia by 1 year of age (Figure 12.6). Other areas, such as the head and feet, are generally spared, and affected dogs retain the facial characteristics of a puppy (Figure 12.7). Hair loss does not appear to be a feature of congenital hypopituitarism in the cat.

The function of other endocrine systems controlled by the anterior pituitary is also often affected. In German Shepherd Dogs with congenital hypopituitarism, there is usually a combined deficiency of GH, thyroid-stimulating hormone (TSH), and prolactin together with impaired release of gonadotropins. While clinical signs of secondary hypothyroidism may develop, signs of secondary hypoadrenocorticism are not seen in the German Shepherd Dog and Tibetan Terrier because adrenocorticotropic hormone (ACTH) secretion is preserved. Gonadal involvement may result in testicular atrophy in the male and abnormal estrous cycles in the bitch.



FIGURE 12.5 An 8-month-old German Shepherd Dog with congenital hypopituitarism demonstrating proportionate dwarfism and a woolly coat.



FIGURE 12.6 An 18-month-old German Shepherd Dog with congenital hypopituitarism showing bilaterally symmetrical alopecia. The hair loss is mainly from areas of friction, such as the flanks, neck, and ventral abdomen, and where hair is lost, the skin usually becomes hyperpigmented.



FIGURE 12.7 The same dog as in **Figure 12.6** showing the retention of puppy-like facial features.

Differential Diagnosis

See Table 12.2 for the list of differentials for failure to thrive, poor growth, or stunted growth.

Diagnosis

Diagnosis of congenital hypopituitarism can be made by measurement of plasma GH concentrations. Since GH is secreted in pulsatile fashion, basal plasma GH concentrations may be low in healthy animals, and a stimulation test using GH-releasing hormone or an alpha-2 adrenergic agonist, such as clonidine or xylazine, should be performed (Table 12.3). GH concentration can be assessed indirectly by measuring insulin-like growth factor-1 (IGF-1). IGF-1 has the advantage of a long half-life, and its secretion is not episodic. Pituitary dwarfs also have abnormally low serum IGF-1 concentrations.

TABLE 12.2 Differential diagnosis of poor growth or stunting

Endocrine causes
- Congenital hypopituitarism (pituitary dwarf)
- Congenital hypothyroidism (disproportionate dwarf)
- Juvenile-onset diabetes mellitus
- Hyperadrenocorticism
- Hypoadrenocorticism
- Diabetes mellitus

Nonendocrine causes
- Malnutrition
- Maldigestion (e.g., exocrine pancreatic insufficiency)
- Malabsorption (e.g., villous atrophy)
- Severe intestinal parasitism
- Severe metabolic disorders associated with major organ dysfunction, for example
  - Portosystemic shunting
  - Congenital renal dysplasia
  - Congenital heart defects (e.g., tetralogy of Fallot)
  - Mucopolysaccharidoses
- Osteochondral dysplasias causing disproportionate dwarfism, for example
  - Chondrodystrophy in the English Pointer
  - Chondrodysplasia of the Alaskan Malamute and Labrador Retriever

Thyroid function tests and, if necessary, adrenal function tests should be performed to assess thyroidal and adrenal function (see Tables 12.8 and 12.15).

Genetic testing is available for German Shepherd Dogs and related breeds such as the Saarloos and Czechoslovakian Wolfdogs and, more recently, Tibetan Terriers with pituitary dwarfism, which have a mutation of the gene encoding the transcription factor LHX3. The genetic test not only identifies affected individuals in these breeds but also identifies carriers of the mutation, which is important eradication of the condition.

Management

Canine GH is not available for therapeutic use, but bovine, porcine, and human GH preparations have been used for treatment. The diagnosis of hypopituitarism is usually made too late in development to influence growth significantly, and affected animals are likely to remain permanent dwarfs. However, GH administration (0.1 IU/kg SC 3 times a week for 4–6 weeks) has been shown to be effective in some cases in producing regrowth of hair. Treatment with exogenous GH can be associated with the development of antibodies, which could interfere with its subsequent action. GH is expensive, and its repeated use may result in the development of diabetes mellitus.

More recently, progestogens, principally proligesterone and medroxyprogesterone acetate, have been used to stimulate endogenous GH production and release from the mammary gland in both male and female pituitary

TABLE 12.3 Protocols for testing growth hormones

GH stimulation test
Indication – Used to diagnose pituitary dwarfism (congenital hypopituitarism) and acromegaly and to evaluate patients with adult-onset GH-responsive alopecia – Basal concentrations of GH are often difficult to interpret due to the overlap between normal dogs and those with GH deficiency; therefore, provocative testing with GH-releasing hormone (GHRH) or an alpha-2 adrenergic agonist (such as clonidine or xylazine) is recommended
Method – Collect 5 mL of blood into EDTA, centrifuge immediately, and store plasma frozen (<–20°C) for basal GH concentration – Inject either GHRH (1 µg/kg IV) or clonidine (10 µg/kg IV, maximum dose 300 µg) or xylazine (100 µg/kg IV) – Collect second 5 mL blood sample into EDTA 20 minutes later, centrifuge immediately, and store plasma frozen (<–20°C) for GH concentration
Interpretation – Reference range in dogs for basal GH concentration is 1–4 ng/mL (µg/L), and peak poststimulation value is 10–58 ng/mL (µg/L), but check laboratory reference range – GH concentrations are generally reduced in pituitary dwarfism (<1 ng/mL [µg/L]) and show little or no response to stimulation with GHRH, clonidine, or xylazine – Reduced GH concentrations and little or no response to stimulation may be found in adult-onset GH-responsive alopecia; however, reduced responses may be found in dogs with hypothyroidism or hyperadrenocorticism, and these more common disorders must be excluded as possible diagnoses first – Basal GH concentrations are generally elevated in acromegaly (>100 ng/mL [µg/L]) and are not usually further stimulated by GHRH, clonidine, or xylazine
Basal serum insulin-like growth factor-1
Indication – Used in the diagnosis of pituitary dwarfism and acromegaly – IGF-1 concentration is regulated by GH and nutritional status and is less subject to fluctuation than GH – This makes a single determination more meaningful. The assay is more readily available.
Interpretation – Reference range for IGF-1 in normal adults is >200 ng/mL and for animals up to 1 year of age is >500 ng/mL – Serum IGF-1 concentrations are decreased in pituitary dwarfs (<50 ng/mL). The sensitivity can be increased by comparing IGF-1 concentrations with those of normal littermates. IGF-1 concentrations may also be depressed in chronic debilitating disease. – Elevated IGF-1 concentrations are seen in dogs and cats with acromegaly (>1,000 ng/mL)

dwarfs with some success. This treatment avoids the development of autoantibodies to GH. Proligesterone given subcutaneously at a dose of 10 mg/kg every 3 weeks until the serum IGF-1 concentration has normalized has been recommended. Adverse effects such as cystic endometrial hyperplasia, pyometra, and acromegaly have been reported in some cases.

Thyroid hormone replacement should be used in cases of secondary hypothyroidism (see Hypothyroidism). Thyroid hormone therapy has been used, with variable success, in an attempt to stimulate hair growth in pituitary dwarfs with normal thyroid function. Half the normal replacement dose of thyroxine is administered for several months to assess the response to treatment.

Quality of life and survival times are improved with treatment. The administration of progestogens or GH has been shown to improve body size.

ACROMEGALY

Definition/Overview

The excessive secretion of GH in adult animal results in acromegaly, an insidious condition associated with overgrowth of connective tissue and bone.

Etiology

In the dog, acromegaly is mainly caused by progestogen therapy or by endogenous progesterone produced during the diestrus phase of the estrous cycle, which induces GH secretion. Progesterone-induced GH excess originates from hyperplastic ductular epithelium in the mammary gland and not from the pituitary.

In the cat, acromegaly is caused by a pituitary tumor that secretes excess GH. This cause has been reported in one dog.

Pathophysiology

GH antagonizes the effects of insulin. In acromegaly, mild glucose intolerance or overt diabetes mellitus develops, which can lead to polyuria and polydipsia. Diabetes mellitus induced by GH may be reversible or permanent depending on the duration and degree of the excessive GH secretion. Initially, hyperglycemia is associated with increased insulin concentrations, but as the disease progresses, beta-cell exhaustion will result in lowered insulin secretion. Most cases of acromegaly present with insulin-resistant diabetes mellitus, and patients usually require abnormally high doses of exogenous insulin to control blood glucose concentrations.

Clinical Presentation

Clinical signs of acromegaly develop slowly and insidiously in middle-aged to older cats and bitches. The bitches are entire and are either cycling normally or being given regular treatment with progestogens to prevent estrus.



FIGURE 12.8 A 14-year-old Domestic Shorthair cat with acromegaly. Note the broad muzzle.

Initially, patients may be presented for investigation of insulin-resistant diabetes mellitus without phenotypic changes associated with acromegaly. Later, there is increased soft tissue swelling, particularly around the head and neck, and this may result in excessive panting, inspiratory stridor, and exercise intolerance (Figure 12.8). There may be excessive skin folds and thickened skin around the head, neck, and distal extremities (Figures 12.9 and 12.10) and separation of the teeth with increased interdental spacing, particularly of the incisor teeth (Figure 12.11).



FIGURE 12.9 A 9-year-old Burmese cat with acromegaly showing enlargement of the paw.



FIGURE 12.10 A 12-year-old Collie-cross dog with acromegaly showing increased soft tissue around the head and neck.



FIGURE 12.11 A 12-year-old Labrador Retriever with acromegaly showing separation of incisor teeth with increased interdental spacing.

Differential Diagnosis

Hyperadrenocorticism, hypothyroidism, diabetes mellitus.

Diagnosis

Laboratory findings of uncontrolled or poorly regulated diabetes mellitus with hyperglycemia and glycosuria are found in most cases. A definitive diagnosis of acromegaly can be made by demonstrating elevated serum concentrations of GH or IGF-1.

CT or MRI of the cranium is required in the cat to demonstrate the size and the position of the pituitary tumor (Figure 12.12).

Management

Successful treatment of acromegaly in the bitch involves the withdrawal of progestogen therapy and ovariohysterectomy for estrus control. Insulin requirements may decrease dramatically or even cease completely following the withdrawal of progestogen therapy or after ovariohysterectomy. Patients should, therefore, be monitored very closely to avoid insulin over dosage and the development of hypoglycemia.

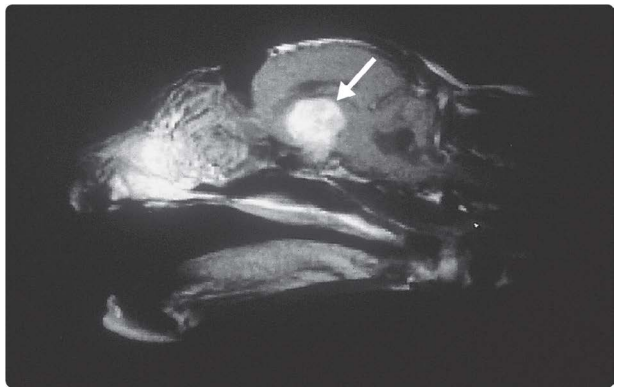


FIGURE 12.12 A T1-weighted MR image of the brain of a Domestic Shorthair cat with acromegaly showing a large pituitary mass (arrow) after gadolinium contrast.

In the cat, pituitary irradiation using a linear accelerator and transsphenoidal hypophysectomy have been successful in treating acromegaly and reducing the GH secretion to provide improved control or even resolution of the diabetes mellitus.

PITUITARY TUMORS

Definition/Overview

Primary and secondary tumors can involve the pituitary. Primary tumors may be functional or nonfunctional. Adenomas of the anterior lobe of the pituitary are the most common tumor, and many of these will secrete adrenocorticotropic hormone (ACTH), resulting in pituitary-dependent hyperadrenocorticism.

Pathophysiology

Functional pituitary tumors may produce signs associated with excess hormone production by the tropic endocrine glands. The space-occupying effects of large tumors may cause compression and destruction of surrounding pituitary tissue (Figure 12.13, arrows), leading to a reduction in the secretion of tropic hormones, which may result in clinical signs of hormone deficiency.

Clinical Presentation

Clinical signs may include those associated with endocrine upset such as polyuria and polydipsia due to excess secretion of ACTH by a functional corticotroph adenoma or impaired vasopressin synthesis or release by compression of the posterior pituitary, lethargy and weight gain due to secondary hypothyroidism, or atrophy of the sex organs due to reduced gonadotropin release.

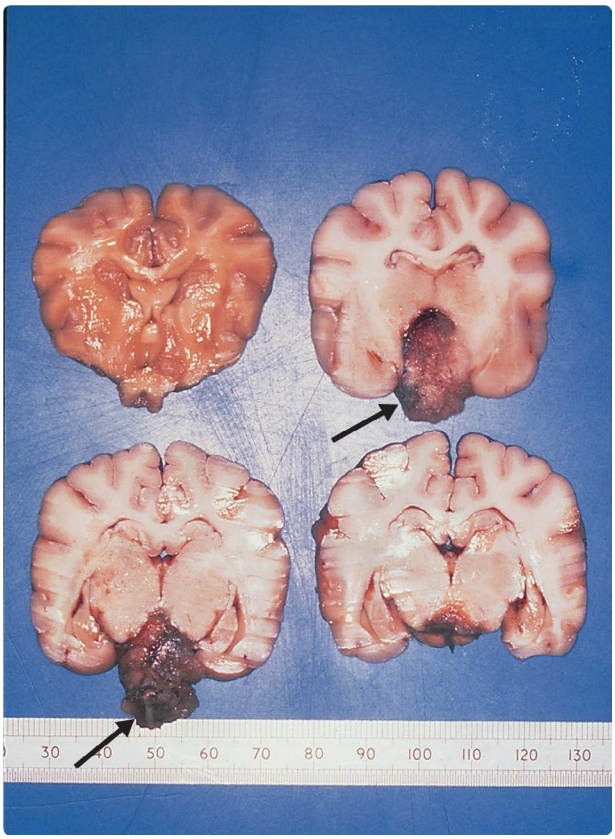


FIGURE 12.13 Postmortem specimen showing the effects of a large pituitary tumor (arrows).

Space-occupying effects of a pituitary tumor include listlessness, depression, anorexia, vomiting, adipsia, aimless wandering, head pressing, staring, apparent blindness, ataxia, incoordination, head tilt, circling, and seizures (Figure 12.14).

Pituitary apoplexy is occasionally recognized with pituitary tumors and is a clinical syndrome characterized by sudden onset of neurological signs and endocrine dysfunction resulting from acute hemorrhage or infarction of the pituitary.



FIGURE 12.14 A 5-year-old Chow Chow with signs of depression and circling due to a pituitary tumor.

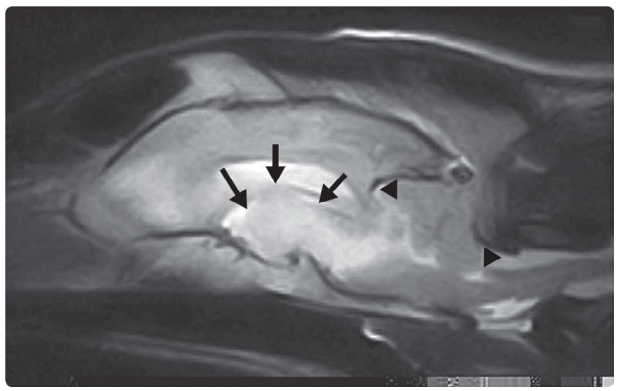


FIGURE 12.15 Sagittal T2-weighted MR image of a 12-year-old Dalmatian with a large pituitary mass (arrows) causing both caudal transtentorial and foramen magnum herniation (arrowheads).

Differential Diagnosis

Hyperadrenocorticism, acromegaly, hypothyroidism, diabetes insipidus, hypophysitis, neurologic conditions.

Diagnosis

Diagnosis of a pituitary mass can be confirmed by computed tomography (CT) or magnetic resonance imaging (MRI; Figure 12.15). Endocrine function tests will help demonstrate if the tumor is functional or not, or if hypopituitarism is present.

Management

If neurologic signs are present, radiotherapy using megavoltage radiation is the treatment of choice and has proved successful in reducing the size of the pituitary mass. Pituitary-dependent hyperadrenocorticism can be treated with trilostane or mitotane (see p. 430). Secondary hypothyroidism can be treated by replacement thyroxine (see p. 402).

DIABETES INSIPIDUS

Definition/Overview

Vasopressin (ADH) released from the posterior lobe of the pituitary increases the permeability of the distal convoluted tubules and collecting ducts of the kidney and thus controls water excretion. Diabetes insipidus results from a deficiency of vasopressin or a failure of vasopressin to act on the kidneys and is characterized by severe and uncontrolled polyuria, with resultant polydipsia.

Etiology

Diabetes insipidus can be caused by either a partial or total failure to synthesize or release vasopressin (central diabetes insipidus [CDI]) or a partial or total failure of the renal tubules to respond to vasopressin (nephrogenic diabetes insipidus [NDI]).

Both forms of diabetes insipidus may be congenital or acquired. CDI may result from neoplasia or head trauma but is usually idiopathic in the dog and cat. Rarely, inflammatory and parasitic lesions have been associated with CDI. NDI may be secondary to various drugs, a variety of renal and metabolic disorders, including chronic kidney disease, renal medullary fibrosis, tubular necrosis, hyperadrenocorticism, pyometra, and hypercalcemia, or it may be idiopathic.

Pathophysiology

Plasma osmolality is the major determinant of vasopressin release, but hypovolemia and hypotension can also stimulate ADH production. In total CDI, there is little increase in urine osmolality with increasing plasma osmolality. In partial CDI, vasopressin is released with increasing plasma osmolality, but concentrations and action are subnormal.

Clinical Presentation

Clinical signs of diabetes insipidus include marked polyuria, frequently with nocturia and incontinence, and severe polydipsia, with the animal often drinking more than 100 mL/kg per 24 hours. In acquired cases, the onset of clinical signs is usually sudden. Affected dogs and cats start searching for water and may become anorexic and lose weight as a result. Despite their increased thirst, affected animals remain mildly to moderately dehydrated. Affected animals generally show no other clinical signs, although neurologic signs may be noted, particularly if diabetes insipidus is associated with a space-occupying mass such as a pituitary tumor or if the animal becomes severely hypernatremic when deprived of water.

Differential Diagnosis

The differential diagnosis of polyuria and polydipsia is given in Table 12.4. Diabetes insipidus must be differentiated from primary polydipsia with resultant polyuria, so-called psychogenic polydipsia (PP), where there is a relative lack of vasopressin due to over hydration and, frequently, reduced renal concentrating power due to a decrease in medullary hypertonicity from the wash-out effect of handling large quantities of fluid.

Diagnosis

Hematologic, biochemical, and electrolyte profiles are generally unremarkable in animals with CDI or idiopathic NDI. When abnormalities are noted, they are usually secondary to dehydration. The most significant finding is very dilute urine of low specific gravity (SG), usually between 1.001 and 1.005. The urine SG is almost invariably less than that of glomerular filtrate (i.e., <1.010), indicating good renal tubular function with resorption of solute in excess of water.

TABLE 12.4 Differential diagnosis of polydipsia–polyuria

Polyuria with compensatory polydipsia
- Osmotic diuresis
  - Diabetes mellitus
  - Primary renal glycosuria/Fanconi's syndrome
  - Polyuric renal failure/postobstructive diuresis

Interference with ADH release and / or renal response to ADH
- Chronic kidney disease
- Glomerulopathy / nephrotic syndrome
- Pyelonephritis
- Pyometra
- Hyperadrenocorticism
- Chronic liver disease
- Hypercalcemia
- Hypoadrenocorticism
- Central diabetes insipidus
- Nephrogenic diabetes insipidus
- Hypokalemia
- Hyperthyroidism
- Drugs/diet

Primary polydipsia
- Psychogenic polydipsia

ADH, adrenal-dependent hyperadrenocorticism.

Urine osmolality is low and typically below that of plasma, which is often mildly or moderately elevated due to the concomitant dehydration (Table 12.5). In PP, the plasma osmolality is usually decreased due to the over hydration.

A carefully monitored water deprivation test (Table 12.6) will confirm the animal's inability to concentrate its urine in diabetes insipidus despite becoming dehydrated. Renal function must be assessed before undertaking this test, and the test must always be discontinued if the patient loses more than 5% of its body weight. Urine and plasma osmolality measurements

TABLE 12.5 Differentiation of central diabetes insipidus, nephrogenic diabetes insipidus, and psychogenic polydipsia

Parameter	Before water deprivation	After water deprivation		
		CDI	NDI	PP
Urine				
Specific gravity	<1.010	<1.010	<1.010	<1.025
Osmolality	<300	<300	<300	<700
Plasma				
Osmolality	>300 CDI or NDI <295 PP	>310	>310	±310
U:P osmolality	<1.0	<1.0	<1.0	2–3
ADH response test				
Urine specific gravity	<1.010	>1.015	<1.010	<1.025
U:P osmolality	<1.0	>1.0	<1.0	>1.0

Note: Osmolality measured in mOsm/kg.

TABLE 12.6 Protocol for water deprivation and antidiuretic hormone response testing

Water deprivation test
Indication – Used in the diagnosis of diabetes insipidus – Does not differentiate between the central and nephrogenic forms of the disease – The test should only be performed in animals with normal blood urea and creatinine concentrations
Method – Collect 5 mL of urine and plasma if osmolality is being measured; if specific gravity is to be measured, only urine is required – Weigh patient – Withhold all fluids and food – Collect urine and plasma after 8 hours and then at 2-hour intervals until the test is complete; it is rarely safe or necessary to continue this test for 24 hours – Weigh patient each time urine and plasma are collected – Stop test if patient demonstrates adequate concentrating ability (specific gravity >1.020) or if patient becomes dehydrated and loses 5% of its body weight or more
Interpretation – Cases of central or nephrogenic diabetes insipidus fail to concentrate urine (specific gravity <1.010), and urine osmolality remains low and does not exceed that of plasma – This test does not always give conclusive results, especially if plasma and urine osmolality are not measured
Vasopressin (ADH) response test
Indication – Used to differentiate between central and nephrogenic diabetes insipidus
Method – Collect 5 mL of urine and plasma if osmolality is being measured; only urine is required if specific gravity is to be measured – Inject desmopressin intramuscularly; use 2 µg for dogs <15 kg and 4 µg for dogs >15 kg – Collect urine and plasma samples every 2 hours
Interpretation – Dogs with nephrogenic diabetes insipidus will show very little or no response to exogenous vasopressin, and the urine specific gravity and osmolality will remain low – Dogs with central diabetes insipidus will concentrate their urine, usually within 6 hours (specific gravity >1.015); the urine osmolality will rise by 50% or more and will exceed the plasma osmolality

provide more definitive information than urine SG alone (Figure 12.16).

The ADH response test (Table 12.6) is used to distinguish CDI from NDI. Dogs and cats with CDI will concentrate their urine in response to the administration of exogenous ADH, whereas dogs with NDI will show no response.

Management

Successful treatment of CDI requires long-term replacement therapy using desmopressin, a vasopressin analog. Desmopressin is available in the form of an injection, intranasal drops, or tablets. It can provide antidiuretic activity for about 8 hours. One to four drops of the intranasal preparation placed in the conjunctival sac twice daily will control the polydipsia and polyuria in most dogs and cats with CDI. Oral therapy (5 µg/kg p.o. q.8–24 h. initially, up to a maximum dose 400 µg p.o. q.8 h.) has proved effective in some cases, but generally, the tablets appear to be less effective due to reduced bioavailability.



FIGURE 12.16 Urine samples from a dog with central diabetes insipidus taken during a water deprivation test. The specific gravity never increased above 1.008 despite the dog losing 5% of its body weight during the test.

Chlorpropamide, an oral sulfonylurea hypoglycemic agent, potentiates the effects of vasopressin on the renal tubules and, therefore, requires at least the presence of some endogenous vasopressin in order to be effective. Chlorpropamide has been shown to be effective in partial CDI in humans; however, the results in dogs with CDI have been inconsistent. In some cases, it may take several weeks to obtain an effect. Hypoglycemia is a potential adverse effect. A dose of 10–40 mg/kg p.o. q.24 h. has been suggested in dogs. Chlorpropamide is not recommended for use in cats.

Thiazide diuretics such as hydrochlorothiazide and chlorothiazide have a paradoxical effect in both CDI and NDI. Urine output may be decreased by up to 50%, although the urine is still dilute. The suggested doses for hydrochlorothiazide and chlorothiazide are 2–4 mg/kg q.12 h. and 20–40 mg/kg q.12 h., respectively. The precise dose should be tailored to each patient, and the effect may be enhanced by concurrent use of a sodium-restricted diet. Patients should be monitored periodically for electrolyte disturbances, particularly hypokalemia.

Idiopathic CDI has a favorable prognosis with treatment. Animals with an expanding hypothalamic or pituitary tumor have a more guarded prognosis, especially if neurologic signs are present. CDI following head trauma carries a variable prognosis; spontaneous recovery may occur within a few days or weeks in some cases, but in other cases the damage is permanent. NDI tends to have a more guarded prognosis, and a search for a primary cause should be undertaken in order to provide more appropriate therapy.

DISORDERS OF THE THYROID GLAND

The thyroid gland consists of two lobes, which are not normally palpable in healthy dogs or cats. Palpable enlargement of the thyroid from any cause is referred to as goiter. Two parathyroid glands are associated with each thyroid lobe. The internal parathyroids usually lie within the thyroid capsule at the caudal pole of each lobe.

The thyroid gland actively takes up inorganic iodide, resulting in concentrations that are 10–200 times that of serum. The inorganic iodide enters the thyroid follicular cells and is transformed into the metabolically active thyroid hormones thyroxine (T4) and triiodothyronine (T3). The synthesis and secretion of T4 and T3 are controlled by TSH secreted by the thyrotroph cells of the anterior pituitary. Secretion of TSH is stimulated by thyrotropin-releasing hormone (TRH), a hypothalamic tripeptide. A classic negative feedback system operates to maintain the plasma concentrations of T4 and T3 within close limits (Figure 12.17).

In plasma, more than 99% of T4 and T3 is bound to plasma proteins, mainly albumin and globulins. It is the free (unbound) hormones that are metabolically active. Although T4 is the major secretory product of the thyroid gland, the metabolic activity of T3 is much greater. About 80% of the plasma T3 concentration is produced by deiodination of T4 in peripheral tissues, mainly the liver, muscle, and kidneys. In catabolic states, such as those produced by starvation, anorexia, or debilitating disease, T4 is deiodinated to reverse T3 (rT3), an inactive metabolite, at the expense of T3 production.

Thyroid hormones play a dominant role in controlling metabolism. They increase basal metabolic rate, stimulate cellular oxygen consumption, promote carbohydrate absorption from the intestine, and regulate lipid metabolism. Thyroid hormones are also essential for normal growth and development, and they activate the anagen (growth) phase of the hair cycle. Some effects of thyroid hormones, such as stimulation of the nervous and cardiovascular systems, are mediated by increased sensitivity to catecholamines.

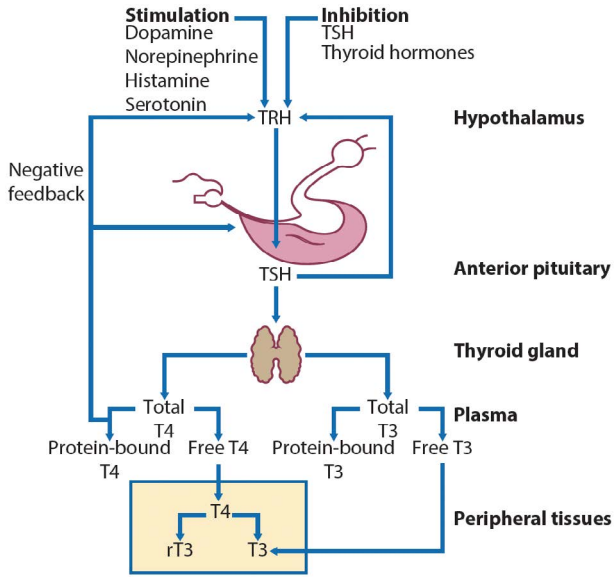


FIGURE 12.17 Physiology of thyroid function.

HYPOTHYROIDISM

Definition/Overview

Hypothyroidism is a multisystemic disorder resulting from inadequate circulating thyroid hormone concentrations. It is considered a common endocrinopathy in the dog and estimates of incidence range from 1 in 156 to 1 in 500 depending on the criteria for diagnosis. However, in the past, hypothyroidism may have been over diagnosed, as the clinical signs are vague and nonspecific, and diagnostic tests frequently give false positive results in euthyroid dogs.

Naturally occurring hypothyroidism is a rare clinical disorder in cats, but cases of both primary congenital and adult-onset hypothyroidism have been reported. However, iatrogenic hypothyroidism following any of the three common treatments for feline hyperthyroidism is well recognized.

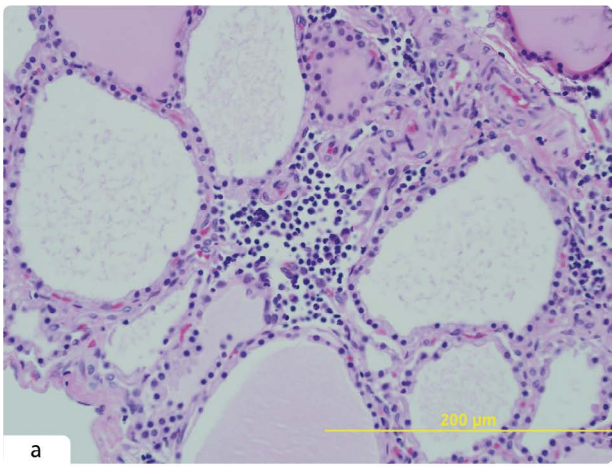
Etiology

Primary hypothyroidism is caused by an intrinsic disorder of the thyroid gland and is the most common type of hypothyroidism in the dog. Hypothyroidism usually results from lymphocytic thyroiditis or thyroid atrophy. Thyroid atrophy may be the end stage of lymphocytic thyroiditis (Figure 12.18a, b). Thyroid neoplasia can occasionally be associated with hypothyroidism, although most dogs with thyroid tumors have normal thyroid function. Congenital hypothyroidism is rare and may be caused by thyroid agenesis, dysgenesis, or dyshormonogenesis. Secondary hypothyroidism is usually associated with pituitary neoplasia, but it may also occur with congenital panhypopituitarism or following head trauma. Hypothalamic dysfunction, iodine deficiency, and serum transport defects are rare causes of hypothyroidism.

The most common cause of feline hypothyroidism is iatrogenic destruction or removal of the thyroid gland following radioiodine therapy or surgery for the treatment of hyperthyroidism. Spontaneous acquired hypothyroidism has been reported in a cat with lymphocytic thyroiditis. Congenital hypothyroidism has been reported in the cat and may be associated with goiter.

Pathophysiology

Hypothyroidism may result from dysfunction of any part of the hypothalamic–pituitary–thyroid axis. In lymphocytic thyroiditis, there is infiltration of the thyroid gland by lymphocytes, macrophages, and plasma cells. Leukocytes and degenerate follicular cells may be found within vacuolated colloid. The parenchyma becomes progressively destroyed and replaced by fibrous connective tissue. In follicular atrophy, the parenchyma



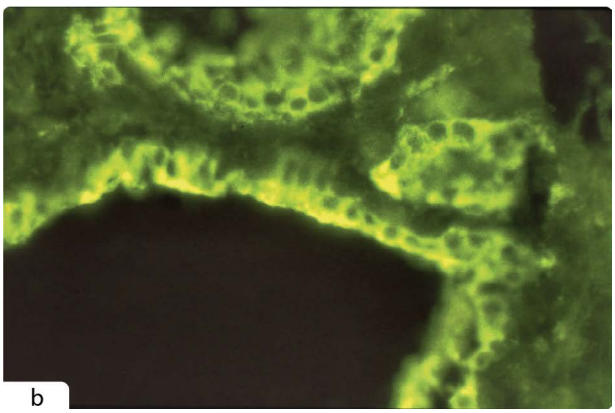


FIGURE 12.18 Hypothyroidism. **(a)** Histopathologic microscopic view of lymphocytic thyroiditis in a dog showing the infiltrating lymphocytes (hematoxylin and eosin [H&E] stain). **(b)** Histopathologic indirect immunofluorescent demonstration of autoimmune thyroiditis. The immunofluorescence represents antibodies that are bound to the thyroid epithelial cells. (*Courtesy of M. Schaer.*)

is replaced by adipose connective tissue. In secondary hypothyroidism, the follicular epithelial cells become flattened, and the follicles become distended with colloid.

Clinical Presentation

The clinical signs of hypothyroidism are very variable and often vague. Some cases present with a classic combination of clinical signs, whereas others may exhibit only one sign. Hypothyroidism usually affects young to middle-aged dogs of the larger breeds. Golden Retrievers, Dobermanns, Boxers, Great Danes, and Irish Setters appear to be overrepresented.

Lethargy, mental dullness, bradycardia, poor exercise tolerance, weight gain without an increase in food intake, intolerance to cold, and hypothermia are the most common clinical signs associated with hypothyroidism. Bilaterally symmetrical, nonpruritic alopecia affecting the flanks, thorax, ventral trunk, and neck is associated with failure to stimulate the anagen (growth) phase of the hair cycle (Figure 12.19). The remaining



FIGURE 12.19 A 6-year-old Dobermann with bilaterally symmetrical alopecia due to hypothyroidism.

hair coat is dry and dull. The skin is often thickened (myxedematous) and hyperpigmented. Myxedema of the skin is most evident on the head, resulting in a "tragic" facial expression (Figure 12.20). The skin, particularly on the ventral abdomen, may be cold and clammy to the touch. Comedones, seborrhea, and recurrent pyoderma may also be noted. Intact females often have abnormal estrous cycles and reduced fertility. Constipation and corneal lipidosis (Figure 12.21) may occasionally be noted.

Neurologic signs may be seen in some dogs with hypothyroidism and include neuromuscular dysfunction with cranial nerve abnormalities, laryngeal paralysis, megaesophagus, lower motor neuron disease, and encephalopathy (Figures 12.22 and 12.23). Clinical signs of lameness, dragging of the feet, quadriparesis, hearing impairment, and nystagmus have also been reported. Electromyography may reveal fibrillation potentials and positive sharp waves. Motor nerve conduction velocities may be decreased, and tendon reflexes appear sluggish.

Congenital hypothyroidism has been reported in a number of breeds, including the Boxer and the Giant Schnauzer. Clinical signs of congenital hypothyroidism include hypothermia, lethargy, disproportionate

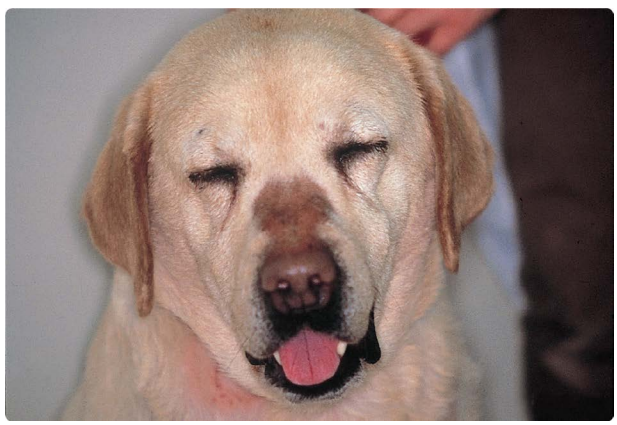


FIGURE 12.20 A 7-year-old Labrador Retriever with hypothyroidism showing a "tragic" expression.



FIGURE 12.21 An 8-year-old Golden Retriever with hypothyroidism showing corneal lipidosis around the limbal margin.



FIGURE 12.22 A young Labrador Retriever was referred to neurology for signs of tetraparesis and abnormal cranial nerve function. The diagnosis was hypothyroid neuropathy. The dog made a complete recovery with levothyroxine replacement treatment. (*Courtesy of M. Schaer.*)



FIGURE 12.23 The same dog as in **Figure 12.22** showing dysconjugate eye positioning. (*Courtesy of M. Schaer.*)



FIGURE 12.24 Two 7-month-old Boxer littermates. The puppy on the left has congenital hypothyroidism.

dwarfism with a short, broad skull, short thick limbs and kyphosis, delayed dental eruption, thickened skin, and a dry hair coat (**Figure 12.24**). Radiographic changes include delayed epiphyseal ossification and epiphyseal dysgenesis (**Figure 12.25**). Congenital hypothyroidism has also been seen in the cat (**Figure 12.26**).

Differential Diagnosis

Pituitary tumor or cyst, hypophysitis, surgery (thyroidectomy or hypophysectomy), drugs (particularly antithyroid drugs and glucocorticoids), diet/obesity, hyperadrenocorticism.

Diagnosis

Laboratory Findings

Hypercholesterolemia is found in about 70% of hypothyroid dogs. Thyroid hormones stimulate biliary excretion



FIGURE 12.25 Craniocaudal radiograph of the carpus of a 10-month-old Boxer with congenital hypothyroidism showing delayed ossification and epiphyseal dysgenesis.



FIGURE 12.26 This approximately 6-month-old kitten was the runt of the litter due to its congenital hypothyroid condition. (*Courtesy of A. Specht.*)

of cholesterol, and a deficiency of these hormones results in an increase in the cholesterol content of the liver. To prevent overloading the liver with cholesterol, the low-density lipoprotein receptors are downregulated to limit low-density and high-density lipoprotein uptake from the circulation. Plasma concentrations of these lipoproteins rise, causing hypercholesterolemia. Causes of hypercholesterolemia are listed in Table 12.7.

Mild normocytic, normochromic, nonregenerative anemia occurs in about 30% of hypothyroid dogs and represents a physiologic response to the lowered basal metabolic rate.

Mild-to-moderate increases in serum activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and creatinine kinase (CK) may be noted. Increased CK activity is particularly associated with myopathy in cases of hypothyroidism.

Thyroid Function Tests

The dynamic thyroid function tests and their protocols are listed in Table 12.8.

Serum Total and Free T4

Baseline serum T4 concentration using a validated assay is more accurate than serum T3 in assessing the status of thyroid gland function and is recommended for initial evaluation of the thyroid gland. Random fluctuations in serum T4 concentrations occur, but a true circadian rhythm has not been identified.

Serum T4 concentrations can be affected by breed, age, illness, and drug administration. Certain breeds, particularly sighthounds, have lower serum T4 concentrations than other breeds, and this is important when interpreting results from Greyhounds or Afghan Hounds, for example. Serum T4 concentrations tend to be higher in young growing puppies and lower in old dogs when compared with normal adult concentrations. Concurrent illness can suppress serum thyroid hormone concentrations (sick euthyroid syndrome). The degree of suppression is dependent on the severity of the illness or catabolic state rather than the specific disorder. Various drugs can alter thyroid hormone metabolism and serum binding, particularly glucocorticoids, anticonvulsants, NSAIDs, potentiated sulfonamides, furosemide, and anesthetic agents.

Serum free T4 concentrations measure metabolically active T4 and should not be influenced by the effects of serum binding. However, measurement of serum free T4 by most assays, which do not employ equilibrium dialysis, has not proved to be any more reliable than total T4 concentrations in the diagnosis of hypothyroidism. Serum free T4 measured by equilibrium dialysis

TABLE 12.7 Causes of hypercholesterolemia

Postprandial hyperlipidemia
Secondary hyperlipidemia – Hypothyroidism – Hyperadrenocorticism – Diabetes mellitus – Cholestatic liver disease – Nephrotic syndrome
Primary (idiopathic) hyperlipidemia

TABLE 12.8 Protocol and interpretation of the TSH and TRH stimulation tests

TSH stimulation test
Protocol – Collect plasma or serum sample for basal T4 concentration – Administer 50–100 μg per dog recombinant human TSH intravenously – Collect second sample for T4 concentration 6 hours later
Interpretation – A diagnosis of primary hypothyroidism can be confirmed if both the pre- and post-T4 samples are below the reference range for basal T4 concentration – In normal animals, the T4 concentration should be stimulated to well within or above the normal reference range for T4; in most animals, the T4 concentration should increase by at least 1.5 times the basal concentration – Interpretation of intermediate results is more difficult and may occur in association with nonthyroidal illness, treatment with certain drugs, secondary hypothyroidism, or possibly in the early stages of primary hypothyroidism
TRH stimulation test
Protocol – Collect plasma or serum sample for basal T4 concentration – Administer 200 μg per dog protirelin (TRH) intravenously; injection may cause salivation, vomiting, and tachycardia – Collect second sample for T4 concentration 4 hours later
Interpretation – Similar to TSH stimulation test, although stimulation of T4 concentrations is less than with TSH and the response to TRH shows greater individual variation

TRH, thyrotropin-releasing hormone (protirelin); TSH, thyroid-stimulating hormone.

can prove useful in differentiating genuine hypothyroidism when the total T4 concentration is in the reference range.

A low basal serum T4 concentration, with a history and clinical signs compatible with hypothyroidism, may be sufficient evidence to warrant a therapeutic trial. In one study, the predictive value of a positive test result was 0.75 and of a negative test result was 0.87 when using T4 concentrations to diagnose hypothyroidism. Serum T4 concentrations in the low normal or nondiagnostic range should have further tests performed (e.g., a canine TSH concentration and/or a TSH or TRH stimulation test) provided the index of suspicion is still high for hypothyroidism.

Serum T4 concentrations in the normal range are unlikely to be associated with hypothyroidism. However, antibodies to thyroid hormone can cause discordance between measured thyroid hormone concentrations and the clinical status of the dog. Depending on their concentration, binding affinity, and the assay method employed, thyroid antibodies can result in either falsely elevated or falsely low thyroid hormone concentrations. Autoantibodies to T4 and T3 can be measured in these cases.

Serum Total T3 and Free T3

Baseline serum T3 concentrations are less accurate for predicting hypothyroidism than serum T4. Random fluctuations in serum T3 concentrations are greater than with serum T4 and have a greater tendency to be misleading with respect to the status of thyroid gland function. Possible explanations for this discrepancy include the normal thyroid gland's preference for secreting T4, the intracellular formation and location of most T3, the preferential secretion of T3 compared with T4 as thyroid function progressively fails, and the development of anti-T3 antibodies. The diagnostic value of serum T3 concentrations in hypothyroidism is therefore inferior to serum T4.

Endogenous Canine TSH

Measurement of canine TSH (c-TSH) has revolutionized the testing for hypothyroidism, particularly in primary hypothyroidism where the concentrations should be high because of loss of the negative feedback effect of thyroid hormones. A validated c-TSH assay is now widely available, but unfortunately, it has been shown that not all cases of primary hypothyroidism exhibit elevated c-TSH concentrations and that some euthyroid dogs as well as some dogs with nonthyroidal illness may have elevated TSH concentrations. Studies have shown that a high serum c-TSH measurement together with a low serum total T4 or free T4 concentration has a high specificity (>90%) for the diagnosis of hypothyroidism; however, the sensitivity and specificity of the assay, particularly at lower concentrations, are insufficient to obviate the need for a dynamic test (TSH or TRH stimulation test) to confirm the diagnosis in some cases of hypothyroidism.

TSH Stimulation Test

The administration of exogenous TSH to measure thyroid secretory reserve is the most definitive method currently available for the diagnosis of hypothyroidism. Unfortunately, pharmaceutical grade bovine TSH has limited availability, but more recently, recombinant human TSH has become available. The protocol and interpretation criteria are given in Table 12.8. The use of this test is limited by the expense of the TSH injection.

Peak serum T4 responses are decreased by breed, nonthyroidal illness, and drug administration in the same way as basal T4 concentrations. Thyroid function testing is thus best performed after resolution of nonthyroidal illness and, if possible, with the patient off all medication.

TRH Stimulation Test

TRH is readily available and less expensive than TSH. However, the T4 response to TRH is less predictable, and peak concentrations tend to be lower than with TSH stimulation. Increasing the dose of TRH increases the duration but not the magnitude of the T4 response. TRH administration may cause cholinergic signs such as salivation, vomiting, and defecation. Responses are also affected by nonthyroidal illness and drug administration.

Reverse T3 (rT3)

Measurement of serum rT3 concentration can be useful in identifying cases with significant nonthyroidal illness and should be reserved for those cases with discordant or equivocal T4 concentrations. If the serum rT3 concentration is high in a dog with low or low-normal T4, hypothyroidism is unlikely to be the cause of the animal's clinical signs.

Thyroglobulin Autoantibodies (TgAA)

Lymphocytic thyroiditis is a major cause of canine hypothyroidism, and, as part of the inflammatory process, antibodies to thyroid antigens are released into the circulation. Thyroglobulin is the principal antigen for which measurable serum antibodies are present. Therefore, measurement of TgAA provides evidence of an active inflammatory process in the thyroid gland. However, the presence of TgAA does not provide information about thyroid function, since at least 60%–70% of the gland has to be destroyed before thyroid dysfunction occurs. Consequently, both lymphocytic thyroiditis and TgAA can be found in dogs that are not hypothyroid, and in dogs where hypothyroidism is caused by thyroid atrophy, circulating TgAA may not be present at all.

Thyroid Biopsy

Although not commonly performed, histologic examination of a thyroid gland biopsy provides an accurate method of differentiating between primary and

secondary hypothyroidism. In primary hypothyroidism, there is loss of thyroid follicles resulting from either lymphocytic thyroiditis or thyroid atrophy. In secondary hypothyroidism, the thyroid follicles become distended with colloid, and the follicular epithelial cells are flattened. Testing thyroid function is still required to make a diagnosis of hypothyroidism, since the degree of histologic change does not always relate to reduced hormone production and release.

Management

Thyroid hormone replacement is required for the treatment of hypothyroidism. Synthetic forms of T4 and T3 are available. Oral sodium levothyroxine (L-thyroxine) is the treatment of choice because it most closely resembles the preferential secretion of T4 by the normal thyroid gland. Synthetic T4 is readily deiodinated to T3 in peripheral tissues and, therefore, does not bypass the normal cellular regulatory processes that control the production of the more potent T3 in those tissues.

An initial replacement dose of L-thyroxine is 20–40 µg/kg p.o. daily in divided doses. Although it has been suggested that once-daily dosing is sufficient in many cases, the author has documented a number of cases where once-daily administration has failed to maintain adequate serum concentrations throughout the day, with a consequent failure of the clinical signs to resolve fully. Poor absorption and a shorter half-life for T4 explain why dogs require higher doses and more frequent administration than human patients with hypothyroidism.

Therapy should always be continued for a minimum of 3 months. Improved activity and mental alertness are usually seen within 2 weeks, but skin and hair coat changes may take up to 6 months to resolve.

The effect of treatment can be monitored by measurement of post-pill serum T4 concentrations. Sampling 4–6 hours after dosing will give a peak serum T4 concentration, and a sample taken just prior to dosing will give the lowest serum T4 concentration. The dose and frequency of administration should be adjusted to maintain the serum T4 concentration in the high end of the reference range throughout the day. Under dosage may lead to treatment failure, and over dosage can lead to iatrogenic hyperthyroidism. Replacement therapy is required for life.

Possible causes for cases failing to respond to replacement therapy include misdiagnosis, inadequate dose or frequency of administration, poor gastrointestinal (GI) absorption, and peripheral tissue resistance.

Congenital hypothyroidism should be treated as early as possible to achieve normal growth and development. The dose will require adjustment as the patient grows and becomes older, so post-pill assessments are required at monthly intervals during the first year of life.

HYPOTHYROID MYXEDEMA

Definition/Overview

Myxedema coma is an extreme form of hypothyroidism with an acute presentation that can prove life-threatening. It is considered to be a complication of chronic hypothyroidism and is manifest by impaired mental status, thermoregulation, respiratory and cardiovascular function.

Clinical Presentation

Affected dogs, mostly Dobermanns, are profoundly dull and present stuporous or comatose with hypothermia in the absence of shivering (Figure 12.27a–c). The skin can be myxedematous due to the accumulation of mucopolysaccharides and hyaluronic acid. Bradycardia, hypotension, and hypoventilation are also evident.

Diagnosis

Laboratory test results are characteristic of hypothyroidism.

Management

Treatment entails gradual warming, avoiding over hydration from IV fluids, monitoring ventilation and providing support if needed, and administration of glucocorticoids and L-thyroxine.

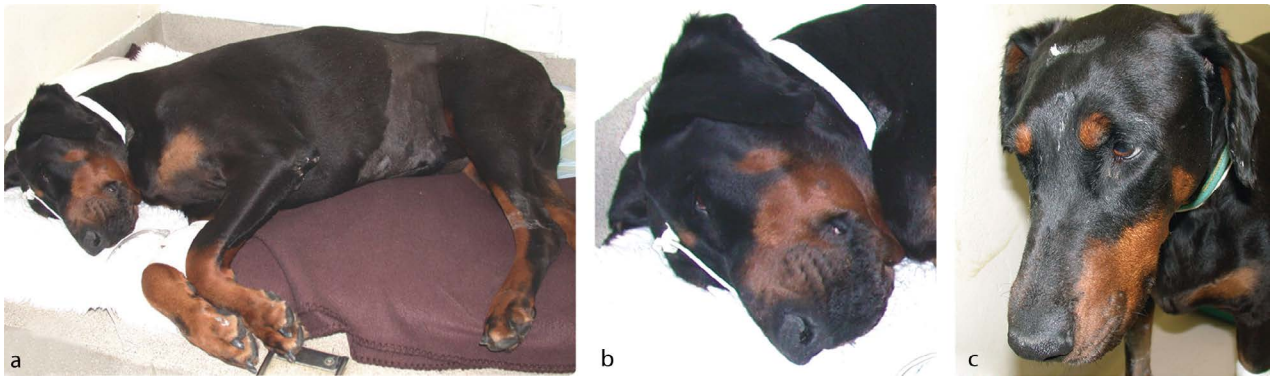


FIGURE 12.27 This Dobermann was referred to the neurology service to evaluate generalized weakness. The dog was profoundly mentally depressed and recumbent. Shown is the dog initially **(a, b)** and subsequently improved with treatment **(c)**.

HYPERTHYROIDISM

Definition/Overview

Hyperthyroidism (thyrotoxicosis) is a multisystemic disorder resulting from excessive circulating concentrations of T4 and/or T3. Hyperthyroidism is the most common endocrine disorder of the domestic cat but is rare in the dog.

Etiology

Functional adenomatous hyperplasia (adenoma) affecting one or, more commonly, both thyroid lobes is the most common cause of feline hyperthyroidism. Iatrogenic hyperthyroidism caused by excessive thyroid hormone supplementation is recognized occasionally. Thyroid carcinoma is a rare cause of hyperthyroidism in the cat. In the dog, although thyroid carcinoma is the most common thyroid tumor, it is rarely functional.

Pathophysiology

The pathogenesis is unknown, but the frequent involvement of both thyroid lobes would suggest a circulating factor may be involved. Recent epidemiologic studies suggest there is an increased risk of developing feline hyperthyroidism associated with indoor living and consumption of canned cat food, in particular fish flavors.

Clinical Presentation

Hyperthyroidism is a disease of middle-aged to older cats, with a mean age of 13 years and a range of 6–21 years. Only about 6% of hyperthyroid cats are younger than 10 years of age at the time of diagnosis. There is no breed or sex predisposition, but pure-bred cats, particularly Siamese and Himalayan cats, have a decreased risk of developing hyperthyroidism.

The clinical signs of hyperthyroidism relate to the excessive secretion of thyroid hormones and their general stimulatory effect on different body systems. The frequency and severity of the clinical signs are highly variable in cats with hyperthyroidism and are influenced by the duration of hyperthyroidism, the ability of the body systems to cope with the demands imposed by thyroid hormone excess, and the presence of concomitant disease in the older animal. In most cases, the clinical signs of hyperthyroidism are slowly progressive, with an insidious onset.

The major presenting sign, therefore, is progressive weight loss frequently accompanied by polyphagia (Figure 12.28). Since most cats maintain a good appetite and remain active for their age, owners frequently feel the cat is in good health until weight loss or other signs develop. Affected cats are often hyperactive and become irritable or aggressive, which can make clinical examination difficult (Figure 12.29). Polydipsia and polyuria are common. Intermittent GI signs such as vomiting, diarrhea, and the passage of voluminous fatty feces are also frequent clinical signs. Occasionally, systemic hypertension with retinal hemorrhages and/or detachment may occur, but generally, hypertension, if present, is only mild to moderate in severity.



FIGURE 12.28 A 13-year-old Domestic Shorthair cat with hyperthyroidism.



FIGURE 12.29 A 15-year-old Domestic Shorthair cat with hyperthyroidism showing irritation.

Cardiac abnormalities are frequently recognized in hyperthyroid cats. There is usually a tachycardia with a heart rate in excess of 240 bpm. Systolic murmurs, gallop rhythms, or dysrhythmias are frequently detected on auscultation. In severe cases, clinical signs of congestive heart failure (CHF) may develop, and these may include dyspnea resulting from pulmonary edema or accumulation of pleural fluid and ascites. The cardiac signs are associated with cardiomyopathy, usually the hypertrophic form, which develops secondarily to excessive thyroid hormone secretion. Electrocardiographic abnormalities may include tachycardia, increased R-wave amplitude, particularly in lead II, and various atrial and ventricular dysrhythmias and conduction disturbances (Figure 12.30).

Although there are no specific skin lesions, the coat of cats with hyperthyroidism is often matted and

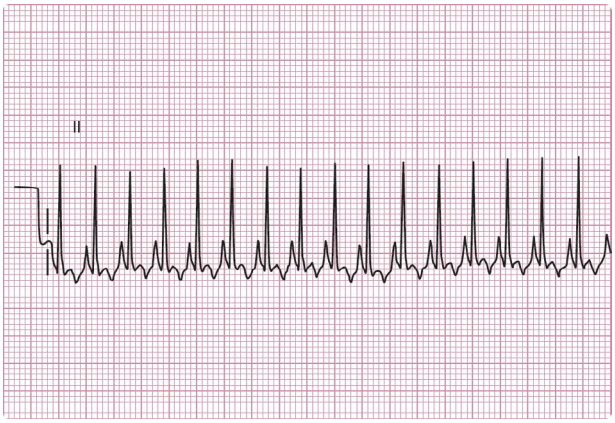


FIGURE 12.30 ECG from a 13-year-old Domestic Shorthair cat with hyperthyroidism showing sinus tachycardia. The heart rate is approximately 260 bpm.



FIGURE 12.31 Hyperthyroid cat showing its unkempt hair coat. (*Courtesy of M. Schaer.*)

unkempt (Figure 12.31). Affected cats may also develop heat intolerance with panting and dysphonia. Although most hyperthyroid cats are polyphagic and hyperactive, about 10% of cases are presented with severe depression and muscle weakness, which may result in ventroflexion of the neck. Weight loss remains a feature but is usually associated with anorexia rather than increased appetite. Cardiac abnormalities are also common. This clinical presentation is referred to as "apathetic" hyperthyroidism.

In most cases, there is palpable enlargement of one or both thyroid lobes (Figure 12.32). Thyroid palpation requires both skill and practice. The thyroid gland is not usually palpable in the normal cat. Enlarged lobes of the thyroid are usually located just distal to the larynx, but they can be quite mobile and descend down the neck and occasionally pass into the thoracic inlet. Ectopic thyroid tissue located anywhere from the base of tongue to the base of the heart is occasionally involved in the pathogenesis of the condition.

Differential Diagnosis

Chronic kidney disease, intestinal disorders (e.g., inflammatory bowel disease), lymphoma, diabetes mellitus, chronic liver disease, hypertrophic cardiomyopathy.

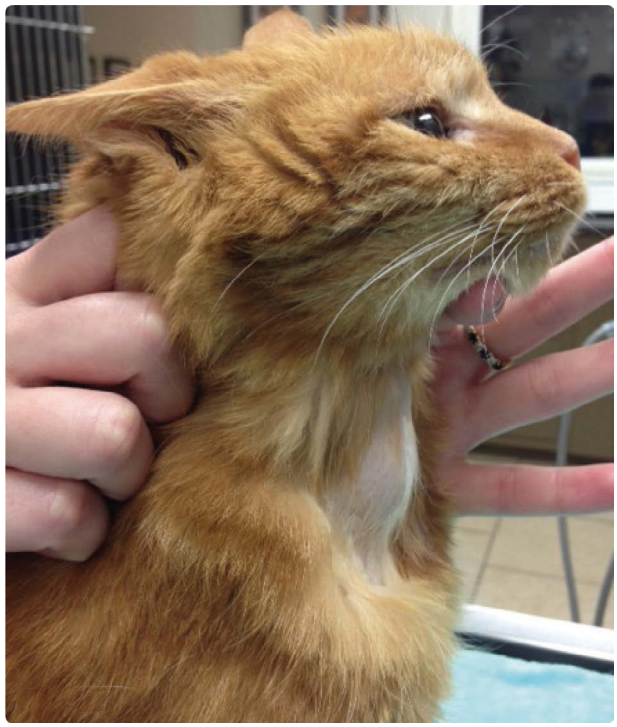


FIGURE 12.32 Hyperthyroid cat showing a large goiter. (*Courtesy of M. Schaer.*)

Diagnosis

Laboratory Findings

Routine hematologic and biochemical screening tests are useful not only because results may show alterations that support a diagnosis of hyperthyroidism, but because they may also indicate evidence of concurrent disease in the older cat. The most frequent hematologic change is a relative polycythemia with a mild-to-moderate increase in red cell parameters (red blood cell count, packed cell volume [PCV], and hemoglobin [Hgb] concentration). A mature neutrophilia with lymphopenia and eosinopenia is also common and probably reflects a stress response. However, eosinophilia and lymphocytosis are found in some cats with hyperthyroidism.

A mild-to-moderate increase in serum activity of the enzymes ALT, AST, ALP, and lactate dehydrogenase (LDH) is a frequent but nonspecific finding. The reason for the increase is not clear, but in some cases, it might be related to a relative hypoxemia in the portal circulation. Evidence of concurrent renal dysfunction in hyperthyroidism is common, with mild-to-moderate elevations in serum creatinine and urea. These increases may be related to increased protein catabolism and prerenal azotemia. Careful consideration should be given to the method of treatment selected for hyperthyroid cats with concomitant azotemia, since some of these cats may develop clinical signs of renal failure caused by a deterioration in renal function when the hyperthyroid state is corrected.

Thyroid Function Tests

Increased serum basal thyroid hormone concentrations are diagnostic of hyperthyroidism. In the majority of cases, both serum T4 and T3 concentrations are increased, often markedly; however, in a few cases, serum T3 concentrations are in the normal range despite obvious elevation of the serum T4 concentration. There is, therefore, usually no advantage in determining serum T3 concentrations, and in most cases, serum total or free T4 concentrations provide a reliable indication of hyperthyroidism. Measurement of TSH has limited utility in the diagnosis of hyperthyroidism. Most hyperthyroid cats will have barely detectable concentrations, but such low values are also found in normal cats and those with other diseases.

About 5% of cases of hyperthyroidism have serum thyroid hormone concentrations within the upper reference intervals at the time of examination, and this may be due to an early stage of the disease, significant daily fluctuations of thyroid hormone concentrations, or the effect of concurrent nonthyroidal illness. In cases where hyperthyroidism is still suspected on clinical grounds, a diagnostic T4 concentration may be obtained by retesting the animal in 3–6 weeks. Alternative diagnostic tests for equivocal cases of hyperthyroidism include the TRH stimulation test and the T3 suppression test.

Diagnostic Imaging

Hyperthyroid cats with secondary cardiomyopathy usually show cardiac enlargement, which is evident on both radiographic and echocardiographic examinations. However, it is important to recognize that significant concentric hypertrophy can occur without affecting the appearance of the cardiac silhouette on thoracic radiographs (Figure 12.33), and the diagnosis of cardiomyopathy in these cases can only be made on echocardiographic findings (Figure 12.34).

Thyroid imaging using radioactive iodine or Tc-99m pertechnetate is a useful diagnostic technique if gamma camera facilities are available. The technique determines whether there is unilateral or bilateral lobe involvement, which is valuable if surgical thyroidectomy is to be performed (Figure 12.35). The technique also determines any alteration in the position of the thyroid gland, the rare case of abnormal ectopic thyroid tissue within the thorax, or the presence of distant metastases from a functioning thyroid carcinoma. Thyroid scintigraphy can also be used to determine the dose of radioiodine for the treatment of hyperthyroidism.

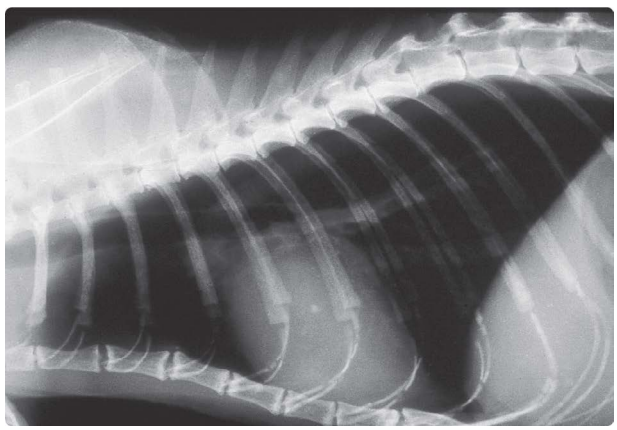


FIGURE 12.33 Lateral thoracic radiograph of a 12-year-old Domestic Shorthair cat with hyperthyroidism and hypertrophic cardiomyopathy. Note the cardiac silhouette is not enlarged.

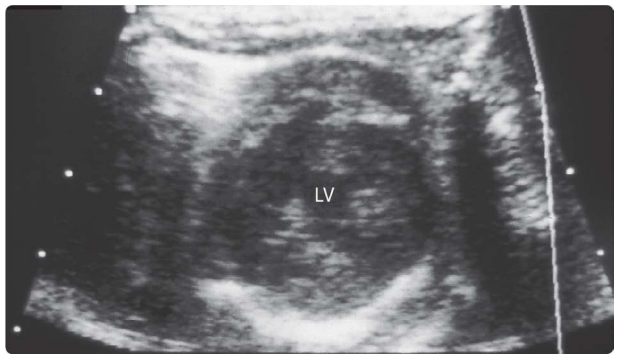


FIGURE 12.34 Short-axis 2D echocardiogram from the cat in Figure 12.33 showing the degree of concentric hypertrophy and the reduction in the size of the left ventricular lumen (LV).

Management

There are four options for treatment of hyperthyroidism: Dietary management, medical management (antithyroid medication), surgical thyroidectomy, and radioiodine. Each treatment modality has advantages and disadvantages which need to be considered when deciding on the most appropriate treatment for a case.

Dietary Management

The release of a prescription diet with ultra-low iodine content (Hills y/d) in 2011 provided an alternative option for the management of feline hyperthyroidism. The mechanism of action is simple. Without sufficient ingested iodine, the patient cannot synthesize and secrete the same amount of thyroid hormones. The diet must be used as the sole food source for the affected cat,

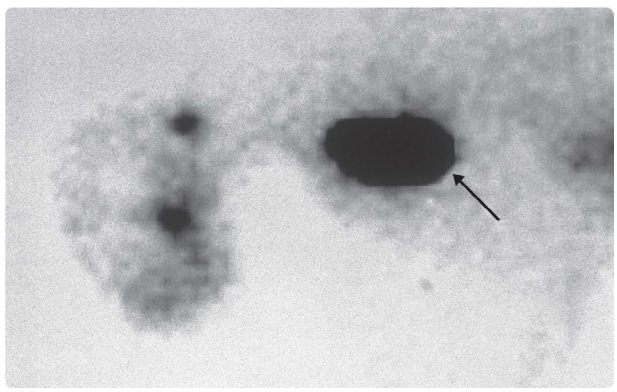


FIGURE 12.35 Thyroid scan using Tc-99m pertechnetate of a cat with hyperthyroidism. The head is seen to the left, with uptake in the salivary glands. The greatest uptake of technetium is by the thyroid adenoma (arrow).

as even small quantities of other foods (including milk) are likely to make the diet ineffective. The diet must not be used as the sole food source for healthy cats, which may restrict its use in multicat households. In addition, the diet must not be used at the same time as antithyroid medication or radioiodine as hypothyroidism may result. The diet needs up to 14 weeks to work, so for cats that are seriously ill with hyperthyroidism, other management options would be preferred.

The diet does not treat the underlying adenoma, which will continue to grow and become more able to produce thyroid hormone. Ultimately, the adenoma is likely to "break through," and conventional medical, surgical, or radioiodine treatment will be needed. However, for mildly affected animals, this may to be an effective treatment. Monitoring serum total T4 concentrations is essential to judge the effect of therapy.

Antithyroid Drugs

Medical management of hyperthyroidism using antithyroid drugs is indicated when preparing hyperthyroid cats for surgical thyroidectomy in order to improve their general condition and reduce the risk of complications arising during or following surgery. Antithyroid drugs are also recommended for the initial treatment of hyperthyroid cats with concurrent azotemia in order to ascertain whether significant deterioration in renal function is likely to occur after medical control of the hyperthyroid state. If there is no deterioration in renal function after 3–4 weeks of treatment, surgical thyroidectomy or radioiodine therapy for hyperthyroidism can be considered. Antithyroid drugs can also be used for long-term management of hyperthyroidism, particularly in cases where owners refuse surgical or radiative iodine treatment.

Methimazole and its pro-drug carbimazole inhibit thyroid hormone synthesis. Carbimazole is rapidly converted to methimazole after oral administration. They are a safe and effective form of treatment and are undoubtedly the treatment of choice for aged cats and those with concurrent disease.

Methimazole is initially administered at a dose of 2.5 mg p.o. q.12 h. and carbimazole at a dose of 5 mg p.o. q.8 h. and subsequently titrated to effect in order to obtain circulating total thyroxine concentrations in the lower half of the reference interval. Serum total thyroxine concentrations decrease to within the reference interval after 3–15 days. When euthyroidism has been achieved, monitoring is recommended at 1 month, 3 months, and biannually thereafter. These doses can usually be continued for the remainder of the cat's life. Adjustment of the dosage is required in some cases to maintain the euthyroid state. A sustained-release form of carbimazole is available in some countries, which only requires once daily administration. The sustained release form is initiated at a dose of 10–15 mg p.o. q.24 h. and titrated to effect. Monitoring of medical management should pay special attention to the possible development of azotemia, hypertension, and iatrogenic hypothyroidism.

Adverse reactions to methimazole and carbimazole include anorexia, vomiting, and lethargy, which are usually transient, but more serious reactions such as pruritus, self-induced excoriation, hepatopathy, jaundice, and bleeding diatheses have been reported and may necessitate withdrawal of these drugs.

Surgical Thyroidectomy

The aim of surgical thyroidectomy is to remove all of the abnormally functioning thyroid tissue. Surgical thyroidectomy is a highly effective treatment for feline hyperthyroidism, but it can be associated with significant morbidity and mortality if cats are not carefully assessed and stabilized prior to surgery. Preoperative treatment with carbimazole or methimazole and propranolol (2.5–5 mg p.o. q.8 h. for 7–14 days before surgery) will control the excessive thyroid hormone production and protect the heart against the effects of excess thyroid hormone.

The anesthetic protocol for the hyperthyroid cat should be carefully considered, using agents that have the minimum effect on cardiac rhythm. Techniques for unilateral and bilateral thyroidectomy have been reported for cats with hyperthyroidism. Both intracapsular and extracapsular techniques have been designed to preserve parathyroid function after removal of the abnormal thyroid tissue.

The potential complications associated with thyroidectomy include hypoparathyroidism, Horner's syndrome, and laryngeal paralysis. The most serious complication is hypocalcemia associated with damage to, or removal of, the parathyroid glands. Since only one parathyroid gland is required for maintenance of normocalcemia, hypoparathyroidism is mostly identified in cats treated by bilateral thyroidectomy. Hypocalcemia is usually transient and may be manifested by clinical signs, including anorexia, vocalization, lethargy, muscular tremors, tetany, and convulsions. The treatment of postoperative hypocalcemia is outlined in Table 12.9.

TABLE 12.9 Management of postoperative hypocalcemia

Immediate therapy
- Administer 1.0–1.5 mL/kg of 10% calcium gluconate or calcium glubionate by slow intravenous injection
- Stop injection if bradycardia develops; repeat as necessary

Maintenance therapy
- Begin oral supplementation as soon as possible using 50–75 mg/kg per day of calcium equivalent in three or four divided doses (equivalent to 500–750 mg/kg per day of calcium gluconate or 400–600 mg/kg per day of calcium lactate) and 0.03 mg/kg/day of dihydrotachysterol (unavailable in the United States) or 0.05 µg/kg per day of alfacalcidol calcitriol
- Monitor the serum calcium concentration and decrease the dihydrotachysterol by 0.01 mg/kg every other day or alfacalcidol calcitriol by 0.01 µg/kg every other day once serum calcium is within the reference range
  - Adjust doses of dihydrotachysterol, alfacalcidol, calcitriol, and calcium supplementation according to subsequent serum calcium concentrations; in most cases, hypocalcemia is temporary

Radioiodine Therapy

Radioiodine therapy is a safe and effective method of treating hyperthyroidism; however, it does require the cat to be housed in licensed premises with restricted access until the radiation dose rate has decreased to an acceptable level. This usually requires hospitalization for between 3 days and 3 weeks, depending on local regulations on the use of radioisotopes. The radioisotope used most commonly is iodine-131 (^{131}I), which has a half-life of 8 days and emits both beta particles and gamma radiation. The beta particles cause most of the required tissue damage. Radioiodine can be administered subcutaneously and is associated with few adverse reactions, although iatrogenic hypothyroidism and persistent hyperthyroidism can result from treatment.

Iatrogenic Hypothyroidism

Iatrogenic hypothyroidism is a recognized complication of all four treatment options for hyperthyroidism. Clinical signs of iatrogenic hypothyroidism include lethargy, inappetence, weight gain, and skin changes, particularly seborrhea sicca, alopecia of the pinnae, and an easily epilated, dull, dry, unkempt haircoat. However, a low total T4 concentration is not always associated with clinical signs in cats treated for hyperthyroidism. In one study, 37% of cats were classified as hypothyroid, defined as a decreased total T4 concentration and an elevated c-TSH concentration, 6 months after the start of treatment for hyperthyroidism. The importance of monitoring for iatrogenic hypothyroidism is that hypothyroidism can contribute to the development of azotemia and reduced survival times after treatment for hyperthyroidism and that restoration of euthyroidism by reducing antithyroid medication or by supplementation with L-thyroxine for those cats permanently treated by thyroidectomy or radioiodine can improve renal function.

DISORDERS OF THE PARATHYROID GLAND

The normal dog or cat usually has four small parathyroid glands. One pair of glands is generally found in the fascia cranial to each of the thyroid lobes. The caudal pair of parathyroid glands is embedded in the parenchyma of each thyroid lobe. The location and number of the parathyroid glands can vary. Each parathyroid gland contains chief cells, which synthesize and secrete parathyroid hormone (PTH).

PTH secretion is controlled by the serum-ionized calcium concentration in order to maintain the serum-ionized calcium within narrow limits. If the serum-ionized calcium concentration falls below the set point (reference range: dog, 1.2–1.5 mmol/L [4.8–6.0 mg/dL]; cat, 1.1–1.4 mmol/L [4.4–5.6 mg/dL]), PTH release is enhanced. Concentrations of serum-ionized calcium above the set point inhibit PTH secretion. Total serum calcium consists of ionized and protein-bound calcium. Although serum protein-bound calcium is affected by several factors, including the circulating albumin concentration and the acid–base status, it is only the ionized calcium that is physiologically active. It is important to appreciate this, since most laboratories only measure total serum calcium.

PTH tends to increase serum-ionized calcium concentrations through a number of integrated actions. In the kidney, PTH increases tubular reabsorption of calcium and enhances renal excretion of phosphate. PTH also activates 1-alpha-hydroxylase, the renal enzyme that converts 25-hydroxycholecalciferol to the active form of vitamin D, 1,25-dihydroxycholecalciferol (calcitriol). Increased circulating 1,25-dihydroxycholecalciferol enhances calcium and phosphate absorption by the intestine. In bone, PTH promotes the release of calcium and phosphate into the extracellular fluid by stimulating osteoclast and osteocyte activity and by suppressing osteoblastic activity. The combination of calcium mobilization from bone and retention of calcium by the kidneys causes the serum-ionized calcium concentration to rise.

Calcium plays an important role in neuromuscular excitability, membrane permeability, muscle contraction, enzyme activity, hormone release, and blood coagulation, as well as acting as an essential structural component of the skeleton.

HYPOPARATHYROIDISM

Definition/Overview

Hypoparathyroidism is caused by inadequate production and secretion of PTH (primary hypoparathyroidism) or, more rarely, by deficient end-organ responsiveness to circulating PTH (pseudohypoparathyroidism).

Etiology

The two most common causes of primary hypoparathyroidism are iatrogenic injury or removal of the parathyroid glands during thyroidectomy (see pp. XX) and idiopathic hypoparathyroidism due to destruction and atrophy of the parathyroid glands. Idiopathic hypoparathyroidism probably results from immune-mediated destruction of the parathyroid glands, and this is supported by the diffuse lymphocytic infiltration found in the parathyroid glands of some affected animals.

Pathophysiology

Cessation of parathyroid gland activity results in increased plasma phosphate concentrations and decreased serum calcium concentrations. Loss of PTH leads to changes in calcium and phosphate mobilization from bone, increased intestinal absorption of calcium and phosphate, and retention of calcium and enhanced renal excretion of phosphate. Neuronal membrane permeability is increased when extracellular calcium ion



FIGURE 12.36 Lenticular cataracts in a Springer Spaniel with primary hypoparathyroidism.

concentrations are below normal, and the nervous system becomes more excitable. Spontaneous discharge of nerve fibers initiates impulses to peripheral skeletal muscles, causing tetanic contractions.

Clinical Presentation

Idiopathic hypoparathyroidism is rare, but it has been reported in the dog and cat. The disease affects young to middle-aged animals of various breeds. A female bias has been reported in dogs. The clinical signs relate to neuromuscular abnormalities that develop secondary to hypocalcemia and include seizures, focal trembling or twitching, generalized muscle fasciculations, ataxia, stiff gait, weakness, panting, anorexia, and lethargy. The fact that the clinical signs tend to be intermittent, often precipitated by exercise, excitement, or stress, suggests a physiologic adaptation to severe hypocalcemia. Posterior lenticular cataract formation can occur secondary to hypocalcemia in dogs and cats (Figure 12.36). Electrocardiography may show prolongation of QT interval in some cases of hypoparathyroidism.

Differential Diagnosis

See Table 12.10 for the differential diagnosis list for hypocalcemia.

Diagnosis

Profound hypocalcemia (serum total calcium <2 mmol/L [<8 mg/dL]) and severe hyperphosphatemia (serum phosphate >1.3 mmol/L [>4 mg/dL]) with normal renal function (blood urea and serum creatinine) are found in cases of primary hypoparathyroidism.

PTH assays are available and have been validated for use in the dog and cat. Inappropriately low plasma PTH concentration in a hypocalcemic animal is diagnostic of primary hypoparathyroidism. Careful sample handling is essential to avoid erroneous results, since PTH is heat labile. Simultaneous measurement of serum calcium and PTH is essential in order to be able to interpret the PTH result.

TABLE 12.10 Differential diagnosis of hypocalcemia

- Primary hypoparathyroidism
- Chronic kidney disease*
- Hypoalbuminemia*
- Intestinal malabsorption*
- Hypovitaminosis D associated with inflammatory bowel disease and hypoalbuminemia
- Acute pancreatitis*
- Eclampsia
- Acute kidney injury
- Ethylene glycol toxicity
- Phosphate-containing enemas

* Not usually associated with clinical signs of tetany.

Management

The treatment protocol for hypocalcemia is outlined in Table 12.9; similar principles are used when treating dogs and cats. Parenteral calcium preparations should be used as emergency therapy to correct hypocalcemic tetany. Maintenance therapy using calcium and vitamin D supplementation must be tailored to the individual patient and the dose adjusted according to the serum calcium concentration. Dihydrotachysterol (commercial availability varies) supplementation can prove expensive in larger dogs. Vitamin D2 (1,000–6,000 IU/kg per day), alfacalcidol (0.05 µg/kg per day), or calcitriol (0.03–0.06 µg/kg per day) may be used as alternatives. These starting doses may need to be exceeded to bring the serum calcium into the reference range.

With adequate monitoring of the serum calcium concentration, the prognosis in cases of primary hypoparathyroidism is usually excellent, but supplementation is usually required for life.

Some cases with suspected lymphocytic parathyroiditis have responded to immunosuppressive treatment with cyclosporine. Glucocorticoids should not be used for immunosuppression due to their calciuretic action. Calcium and vitamin D supplementation is required initially but can be phased out in those cases that respond to cyclosporine.

HYPERPARATHYROIDISM

Definition/Overview

Hyperparathyroidism is caused by excess production and secretion of PTH, which can be primary or secondary. Primary hyperparathyroidism is an uncommon disease of older dogs and cats. There is no sex predisposition, but there is a breed predilection, as the Keeshond is overrepresented.



FIGURE 12.37 Necropsy specimen from a Dachshund that had several endocrinopathies. Shown are both thyroid glands, with one containing a parathyroid adenoma. (*Courtesy of M. Schaer.*)

Etiology

Primary hyperparathyroidism is a disorder resulting from autonomous and excessive secretion of PTH by one or more of the parathyroid glands. Secondary hyperparathyroidism is an adaptive increase in PTH secretion as a result of chronic stimulation from conditions that tend to reduce the concentration of ionized calcium in plasma. Secondary hyperparathyroidism may occur as a result of chronic kidney disease (see Chapter 12) and calcium deficiency during growth (see Chapter 14).

Primary hyperparathyroidism is most commonly caused by a small, solitary parathyroid adenoma (**Figure 12.37**). PTH excess may also be caused by nodular hyperplasia in one or more parathyroid glands. Very rarely, the disease is caused by a parathyroid carcinoma. The Keeshond has an autosomal dominant form of primary hyperparathyroidism that has partial age-dependent penetrance.

Pathophysiology

The normal negative feedback control regulating calcium concentration is lost by the entry of excess calcium into the extracellular fluid. The kidneys lose their ability to excrete the excess calcium and are unable efficiently to reabsorb sodium and water.

Clinical Presentation

The clinical signs in hyperparathyroidism are variable. The disease may be asymptomatic or may result in mild-to-severe systemic illness. The clinical signs relate to hypercalcemia and include polyuria, polydipsia, anorexia, vomiting, depression, muscle weakness, constipation, and weight loss. Urinary calculi can occur. Clinical examination may reveal bradycardia. The small size of the parathyroid lesions means that the nodules are rarely palpable.

TABLE 12.11 Differential diagnosis of hypercalcemia

– Cancer-associated hypercalcemia
  – Lymphoproliferative disease
  – Apocrine cell adenocarcinoma of the anal sac
  – Multiple myeloma
  – Other solid tumors

– Hypoadrenocorticism
– Chronic kidney disease (particularly in cats or as a result of familial nephropathies in dogs)
– Primary hyperparathyroidism
– Idiopathic hypercalcemia of cats
– Granulomatous diseases (e.g., the systemic mycoses)
– Vitamin D intoxication

Differential Diagnosis

See Table 12.11 for the differential diagnosis list for hypercalcemia.

Diagnosis

Laboratory Findings

Hypercalcemia (serum total calcium >3 mmol/L [>12 mg/dL]) and hypophosphatemia (serum phosphate concentration <1.3 mmol/L [<4 mg/dL]) are found in cases of primary hyperparathyroidism provided that renal function is normal. Prolonged increases in the circulating calcium concentration will facilitate calcium deposition in the kidneys, causing renal function to deteriorate and serum phosphate concentrations to rise. If renal failure develops, primary hyperparathyroidism is difficult to differentiate from secondary renal hyperparathyroidism.

Circulating PTH concentrations are inappropriately increased in animals with primary hyperparathyroidism. A PTH assay provides a useful differentiation in hypercalcemic patients because plasma PTH concentrations are low in dogs with cancer-associated hypercalcemia. Careful handling of the sample is essential to avoid erroneous results, since PTH is heat labile. Plasma PTH-related protein (PTH-rp) concentrations are elevated in most cases of cancer-associated hypercalcemia but are low in primary hyperparathyroidism.

Diagnostic Imaging

Ultrasonographic examination of the parathyroid glands is useful in the evaluation of hypercalcemic dogs and can be used to identify hyperplastic parathyroid glands and parathyroid adenomas (**Figures 12.38–12.40**). Ultrasound examination of the kidneys in the dog may also reveal the hyperechoic medullary band characteristic of nephrocalcinosis (**Figure 12.41**). This medullary band may be seen in normal cats.

Management

Treatment of the Hypercalcemic Crisis

The hypercalcemic crisis should be treated by aggressive IV fluid therapy using 0.9% sodium chloride solution. Saline will restore the circulating fluid volume and

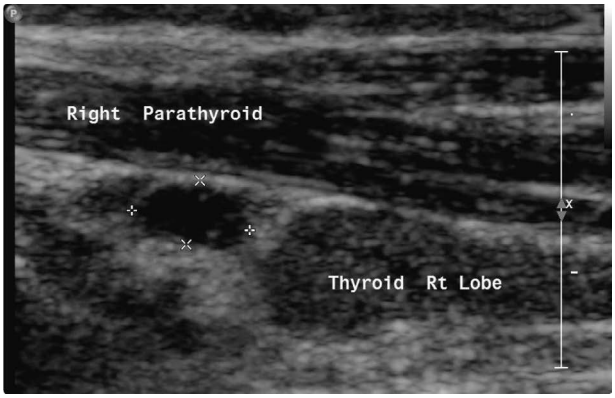


FIGURE 12.38 This ultrasound image shows a large parathyroid adenoma at the cranial aspect of the right thyroid gland. (*Courtesy of M. Schaer.*)

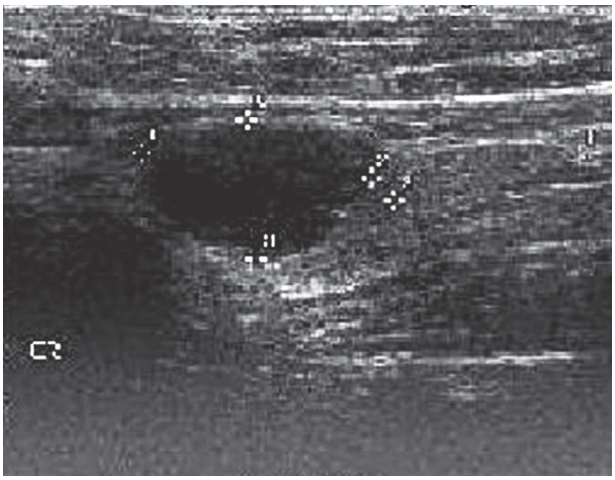


FIGURE 12.39 Ultrasonogram of the cervical region showing a large cystic parathyroid adenoma at the cranial pole of a thyroid lobe. (*Courtesy of M. Schaer.*)

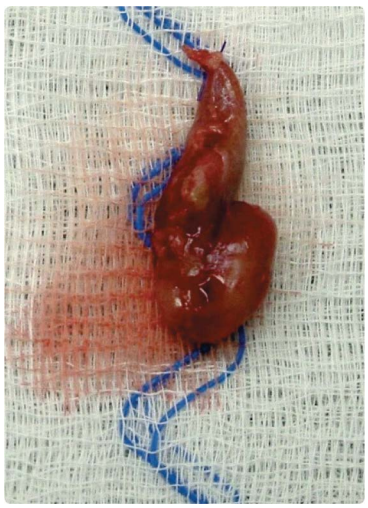


FIGURE 12.40 Excised parathyroid gland that was previously identified on cervical ultrasound (Figure 12.39). Note the cranial pole enlargement of the thyroid lobe which was previously identified on cervical ultrasound. (*Courtesy of M. Schaer.*)

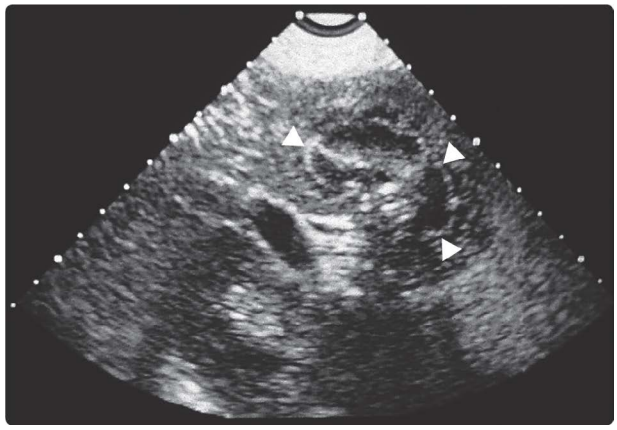


FIGURE 12.41 Ultrasonogram of the kidney of a Labrador Retriever with hypercalcemic nephropathy. Note the echogenic rim in the medulla (arrowheads).

promote calcium excretion. Furosemide (2–4 mg/kg IV q.12 h.) may also be administered to enhance calcium excretion. Bisphosphonates are osteoclast inhibitors and have also been used in dogs to control hypercalcemia. Clodronate, etidronate, alendronate, and pamidronate have been used. Pamidronate is the most commonly used parenteral preparation (1–2 mg/kg IV administered with 0.9% saline over 2 hours), and alendronate is the most commonly used oral preparation (0.5–1.0 mg/kg p.o. q.24 h. in dogs and 5–10 mg/cat per week in cats).

Surgical Treatment

Primary hyperparathyroidism should be resolved following parathyroidectomy. Parathyroid adenomas are usually easily identified and removed (Figure 12.42). Postoperative complications include hypocalcemia, since the remaining parathyroid glands may be atrophic and require a period of adaptation before control of circulating calcium is regained. For this reason, it is advisable to begin supplementation with vitamin D (dihydrotachysterol or alfacalcidol) and calcium gluconate at the time of surgery in those patients with calcium concentrations >3.75 mmol/L (>15 mg/dL).

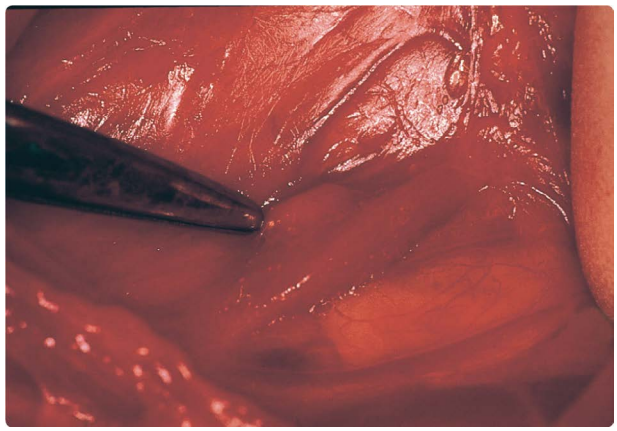


FIGURE 12.42 Parathyroid adenoma adjacent to the thyroid gland being pointed out at surgery.

DISORDERS OF THE ADRENAL GLANDS

The adrenal glands are located craniomedially to each kidney in retroperitoneal fat. Each gland consists of a cortex and a medulla. The cortex completely surrounds the medulla and consists of three distinct zones: The outer zona glomerulosa, the middle zona fasciculata, and the inner zona reticularis.

The adrenal cortex produces about 30 different hormones, many of which have little or no clinical significance. The hormones can be divided into three groups based on their predominant actions: Mineralocorticoids, which are important in electrolyte and water homeostasis; glucocorticoids, which promote gluconeogenesis and are potent inhibitors of inflammatory processes; and small quantities of sex hormones, particularly male hormones that have weak androgenic activity. Aldosterone is the most important mineralocorticoid and is produced by the zona glomerulosa. The principal glucocorticoid (cortisol) and the sex hormones are produced in the zonae fasciculata and reticularis.

Glucocorticoid and mineralocorticoid release are controlled by different mechanisms. Glucocorticoid release is controlled almost entirely by ACTH secreted by the anterior lobe of the pituitary, which in turn is regulated by corticotropin-releasing hormone (CRH) from the hypothalamus (Figure 12.43). CRH is secreted by the neurons in the anterior portion of the paraventricular nuclei within the hypothalamus, and it is transported to the anterior pituitary by the portal circulation, where it stimulates ACTH release. There is probably an internal or "short loop" negative feedback control by ACTH on CRH. ACTH secreted into the systemic circulation causes cortisol release, with concentrations rising almost immediately. Cortisol has direct negative feedback effects on the hypothalamus (decreases formation of CRH) and on the anterior lobe of the pituitary (decreases the formation of ACTH). These feedback mechanisms help regulate the plasma concentration of cortisol.

Secretion of CRH and ACTH is normally episodic and pulsatile, which results in fluctuating cortisol concentrations during the day. Diurnal variation is superimposed on this type of release. It is usually stated that in the dog CRH and ACTH, and thus cortisol concentrations, are highest in the early hours of the morning and that in the cat they are greatest in the evening. However, a true circadian rhythm of cortisol concentrations has been difficult to confirm in the dog and the cat. The episodic release of CRH and ACTH is perpetuated by the reciprocal effect of cortisol acting through negative feedback control. This reciprocal arrangement does not hold during periods of stress when both ACTH and cortisol are maintained at high concentrations because the effects of stress tend to override the normal negative feedback control.

Aldosterone release is influenced primarily by the renin–angiotensin system and by plasma potassium concentrations (Figure 12.44). Renin is secreted into the blood by the cells of the juxtaglomerular apparatus, which consists of specialized cells in the wall of the afferent arteriole immediately proximal to the glomerulus and the specialized epithelial cells of the distal convoluted tubule adjacent to that arteriole, the macula densa. Renin release may be stimulated by stretch receptors in the juxtaglomerular apparatus in response to hypotension or reduced renal blood flow or by sodium and chloride receptors in the macula densa. Renin is also released by sympathetic nerve stimulation and is

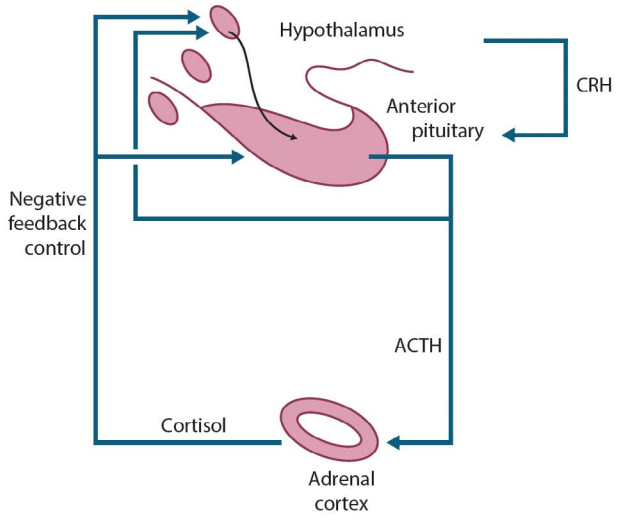


FIGURE 12.43 Physiology of the hypothalamic–pituitary–adrenal axis.

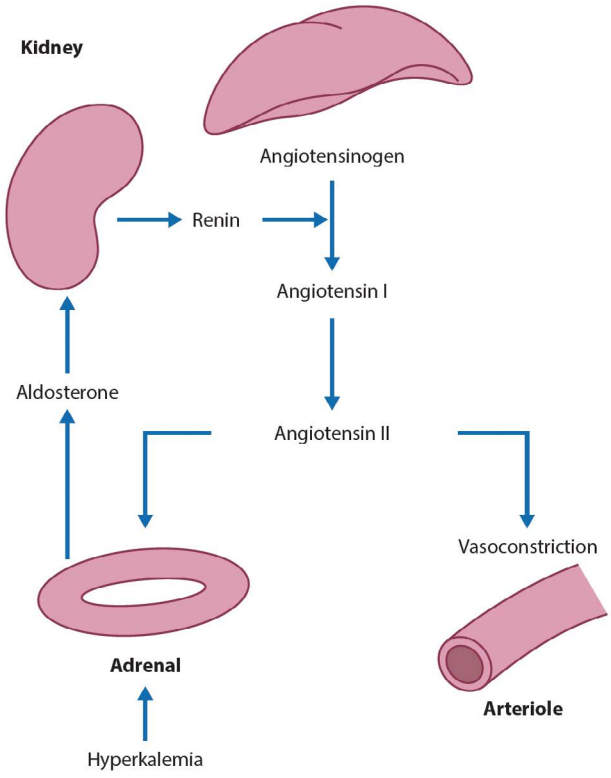


FIGURE 12.44 Physiology of the renin–angiotensin system.

inhibited by angiotensin II, ADH, hypertension, and increased reabsorption of sodium by the renal tubules.

Renin is an enzyme that splits circulating angiotensinogen, produced by the liver, into angiotensin I. Angiotensin I is converted to angiotensin II by angiotensin-converting enzyme, which is located almost entirely in the pulmonary capillary endothelium. Angiotensin II is a powerful vasoconstrictor, and it stimulates aldosterone secretion from the zona glomerulosa. Through its action on the distal convoluted tubule, aldosterone has a negative feedback effect on the juxtaglomerular apparatus.

Potassium has a direct stimulatory effect on the zona glomerulosa cells to release aldosterone. ACTH and sodium play a less significant role in aldosterone secretion. ACTH is necessary to maintain normal aldosterone output. In the absence of ACTH, the zona glomerulosa partially atrophies, causing mild-to-moderate aldosterone deficiency, whereas there is almost total loss of glucocorticoid synthesis and release.

The main function of aldosterone is to protect against hypotension and potassium intoxication. Aldosterone promotes sodium, chloride, and water reabsorption, as well as potassium excretion, in many epithelial tissues including the intestinal mucosa, salivary glands, sweat glands, and kidneys. Its main site of action is the renal tubule, where it promotes sodium and chloride reabsorption in the proximal convoluted tubule and sodium reabsorption by exchange with potassium in the distal convoluted tubule. It is one of the complex regulatory systems for the regulation of extracellular fluid electrolyte concentrations, extracellular fluid volume, blood volume, and arterial pressure.

HYPOADRENOCORTICISM

Hypoadrenocorticism is a syndrome that results from a deficiency of both glucocorticoid and mineralocorticoid secretion from the adrenal cortices. Destruction of more than 95% of both adrenal cortices causes a clinical deficiency of all adrenocortical hormones and is termed primary hypoadrenocorticism (Addison's disease). Secondary hypoadrenocorticism is caused by a deficiency in ACTH, which leads to atrophy of the adrenal cortices and impaired secretion of glucocorticoids. The production of mineralocorticoids, however, usually remains sufficient to maintain normal electrolyte concentrations.

PRIMARY HYPOADRENOCORTICISM (ADDISON'S DISEASE)

Definition/Overview

Primary hypoadrenocorticism is caused by the destruction or loss of the adrenal cortices. Addison's disease occurs more frequently in the dog than is recognized, but it is much less common than hyperadrenocorticism (Cushing's disease). Hypoadrenocorticism is rare in the cat. The clinical signs, diagnosis, and treatment of hypoadrenocorticism in the dog and cat are similar.

Etiology

Primary hypoadrenocorticism in the dog has been associated with the following conditions:

- *Idiopathic adrenocortical insufficiency:* This is the most common cause in the dog and is thought to result from immune-mediated destruction of the adrenal cortex. The presence of antiadrenal antibodies in two dogs and characteristic histopathologic findings in another support this hypothesis (Figures 12.45–12.47). In humans, hypoadrenocorticism has been found to be associated with other immune-mediated endocrine disorders such as lymphocytic thyroiditis, diabetes mellitus, hypoparathyroidism, primary gonadal failure, and atrophic gastritis. A similar autoimmune polyglandular disease has also been recognized in dogs.
- *Mitotane-induced adrenocortical necrosis:* Although mitotane usually spares the zona glomerulosa and,

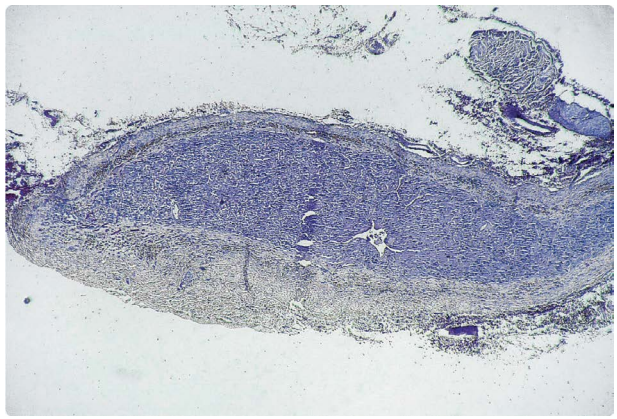


FIGURE 12.45 Histopathologic image of an adrenal specimen from a dog with Addison's disease. Noted is adrenocortical atrophy and lymphocytic and plasmacytic infiltrates within the cortex. (*Courtesy of M. Schaer.*)

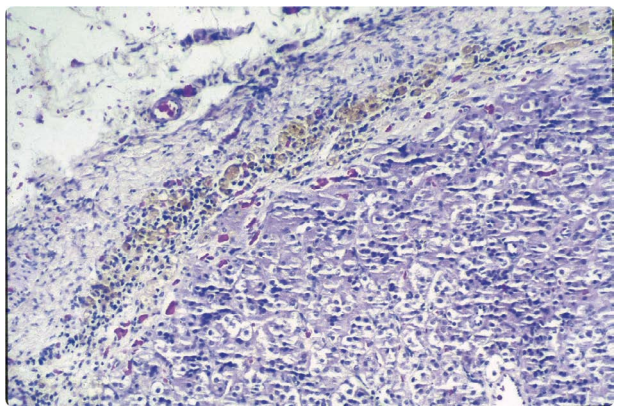


FIGURE 12.46 High power image of the same adrenal gland. Noted is adrenocortical atrophy and lymphocytic and plasmacytic infiltrates within the cortex. (*Courtesy of M. Schaer.*)

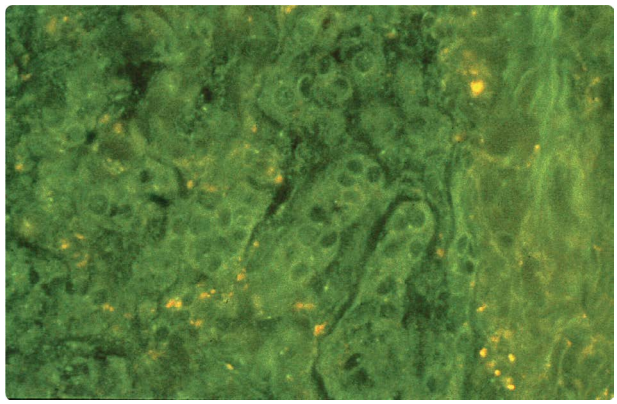


FIGURE 12.47 Indirect immunofluorescence stain of an adrenal cortex template showing the positive reaction for antiadrenal antibodies as illustrated with the bright yellow iridescence. (*Courtesy of M. Schaer.*)

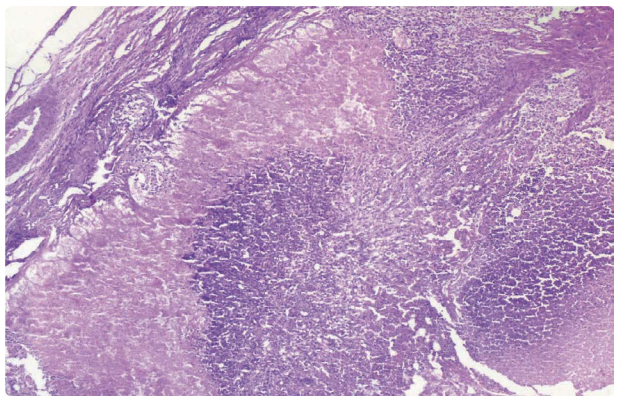


FIGURE 12.48 This histopathologic specimen is from a cushingoid dog that became toxic from mitotane therapy. Shown is widespread adrenocortical necrosis. (*Courtesy of M. Schaer.*)

therefore, mineralocorticoid secretion, cases of complete adrenocortical failure can occasionally occur (Figure 12.48) (see Hyperadrenocorticism).

- *Trilostane-associated adrenocortical necrosis:* Although trilostane is a competitive inhibitor of steroid synthesis, it can cause acute adrenal necrosis, which can lead occasionally to complete adrenocortical failure (see Hyperadrenocorticism).
- *Other causes:* Bilateral adrenalectomy, hemorrhage or infarction of the adrenal cortex, or mycotic or neoplastic involvement of the adrenal glands can also lead to adrenal insufficiency, but these are rare causes.

Pathophysiology

Loss of or damage to the adrenal cortex leads to mineralocorticoid and glucocorticoid deficiency. Aldosterone is the major mineralocorticoid, and deficiency causes impaired ability to conserve sodium and water and failure to excrete potassium, leading to hyponatremia and hyperkalemia. Hyponatremia induces lethargy, depression, and nausea and leads to the development of hypovolemia, hypotension, reduced cardiac output, and decreased renal perfusion. Hyperkalemia causes muscle weakness, hyporeflexia, and impaired cardiac conduction. Glucocorticoid deficiency causes decreased tolerance to stress, loss of appetite, and a mild normocytic normochromic anemia.

Clinical Presentation

There are no breed predilections, but the possibility of a hereditary factor has been suggested in some breeds, for example Standard Poodles, Bearded Collies, Portuguese Water Dogs, Nova Scotia Duck Tolling Retrievers, and Leonbergers. Hypoadrenocorticism appears to be a disease of the young and middle-aged dog, with an age range of 3 months to 14 years and a median age of 4–5 years. Approximately 70% of reported cases are female. The progression of adrenocortical insufficiency may be acute or chronic. Chronic hypoadrenocorticism is far more common than the acute disease in the dog.

Acute Primary Hypoadrenocorticism

The clinical appearance of the acute form is that of hypovolemic shock (adrenocortical crisis). The animal is usually found in a state of collapse or collapses when stressed. Other signs include a weak pulse, profound bradycardia, abdominal pain, vomiting, diarrhea, dehydration, hypotension, and hypothermia. Hypotension is present in approximately 90% of humans with primary hypoadrenocorticism and has certainly been documented in dogs with adrenal insufficiency and is likely to be common among the most severely affected cases. The condition is rapidly progressive and life-threatening. Aggressive fluid therapy will help most patients and allow more time to make a diagnosis.

Chronic Primary Hypoadrenocorticism

The clinical signs in the chronic form are often vague and nonspecific (Table 12.12). The diagnosis should be considered in any dog with a waxing and waning type of illness or who shows episodic weakness and collapse.

TABLE 12.12 Clinical signs of primary hypoadrenocorticism (in approximate decreasing order of frequency)

– Anorexia
– Lethargy/depression
– Vomiting
– Weakness
– Weight loss
– Waxing/waning course
– Dehydration
– Diarrhea
– Previous response to therapy
– Collapse
– Hypotension
– Hypothermia
– Slow capillary refill time
– Shaking
– Polyuria/polydipsia
– Melena
– Weak pulse
– Bradycardia (<60 bpm)

The most consistent clinical signs include anorexia, vomiting, lethargy, depression, and/or weakness. The severity of each sign can vary during the course of the disease and may be interspersed with periods of apparent good health, often following nonspecific veterinary therapy, usually consisting of corticosteroid medication and/or fluid administration. Other common clinical signs include dehydration, bradycardia, and weak femoral pulses. In a few cases, severe GI hemorrhage can occur resulting in profound anemia.

Differential Diagnosis

Chronic renal insufficiency, primary neuromuscular disorders, diseases that cause weight loss, weakness, anorexia, vomiting, and diarrhea.

Diagnosis

Laboratory Findings

The most common laboratory findings are listed in Table 12.13. Hematologic changes may include lymphocytosis, eosinophilia, and mild normocytic, normochromic nonregenerative anemia. However, these findings are not as consistent as those changes seen in hyperadrenocorticism. Normal or elevated eosinophil and lymphocyte counts in an ill animal with signs compatible with hypoadrenocorticism are significant because the expected response to stress is eosinopenia and lymphopenia. The mild anemia may not be obvious until the dog has been rehydrated, since dehydration may mask the anemia.

The most consistent laboratory findings in hypoadrenocorticism are prerenal azotemia, hypocholesterolemia, hyponatremia, and hyperkalemia. Blood urea and serum creatinine and phosphate concentrations are increased as a result of reduced renal perfusion and decreased glomerular filtration rate. Reduced renal perfusion results from hypovolemia, reduced cardiac output, and hypotension, which in turn result from chronic fluid loss through the kidneys, acute fluid loss through vomiting and/or diarrhea, and inadequate fluid intake.

TABLE 12.13 Laboratory findings in primary hypoadrenocorticism

Hematology
– Lymphocytosis
– Eosinophilia
– Relative neutropenia
– Anemia (usually a normocytic, normochromic, nonregenerative anemia but can be blood loss anemia associated with GI hemorrhage)
Biochemistry
– Azotemia
– Hyponatremia (<135 mmol/L [<135 mEq/L])
– Hyperkalemia (>5.5 mmol/L [5.5 mEq/L])
– Reduced sodium-to-potassium ratio (<25:1)
– Reduced bicarbonate and total CO_2 concentrations
– Hypochloremia
– Hypercalcemia
– Hypoglycemia
Urinalysis
– Specific gravity variable (but usually poorly concentrated 1.015–1.030)
Endocrine testing
– Low basal serum cortisol concentration with a failure to stimulate in response to ACTH administration
– Raised plasma ACTH concentration

Prerenal azotemia is usually associated with concentrated urine (SG >1.030), whereas the urine in primary renal failure is often isosthenuric or only mildly concentrated (1.008–1.025). However, some severe cases of hypoadrenocorticism may develop impaired concentrating ability because the chronic sodium loss reduces the renal medullary concentration gradient. Therefore, the laboratory findings may resemble those of chronic kidney disease. With adequate fluid therapy, the blood urea will return to normal in most cases of hypoadrenocorticism.

Sodium concentration is usually <135 mmol/L (<135 mEq/L) and potassium concentration >5.5 mmol/L (>5.5 mEq/L). The ratio of sodium to potassium may be more reliable than the absolute values. The normal ratio of sodium to potassium varies between 27:1 and 40:1, whereas in patients with hypoadrenocorticism, the ratio is commonly <25:1 and may be below 20:1; however, there are other medical disorders that can produce a similar serum electrolyte pattern. Blood samples must be collected before IV fluids are administered. Otherwise, the electrolyte concentrations can quickly return to normal. Despite this, approximately 10% of cases may have normal electrolyte concentrations (referred to by some authors as atypical hypoadrenocorticism) at the time of presentation, and these are usually thought to be early cases of hypoadrenocorticism.

Mild-to-moderate hypercalcemia is seen in about one-third of cases of hypoadrenocorticism, usually those dogs that are most severely affected by the disease. Hypercalcemia is caused by hemoconcentration, increased renal tubular reabsorption, and decreased glomerular filtration.

Cases of hypoadrenocorticism tend to develop hypoglycemia because glucocorticoid deficiency reduces glucose production by the liver and peripheral cell receptors become more sensitive to insulin. Severe hypoglycemia is uncommon, but the potential should remain a concern for the clinician.

Electrocardiographic Findings

Hyperkalemia impairs cardiac excitation and conduction, which can be assessed by an ECG examination (Figure 12.49). Although the ECG changes do not correlate directly with serum potassium levels, the guidelines shown in Table 12.14 have proved helpful. Changes in the ECG can also be used for monitoring the patient during treatment.

Radiographic Findings

Dogs with hypoadrenocorticism may show radiographic signs of hypovolemia, which include microcardia, decreased size of pulmonary vessels, and reduced size of

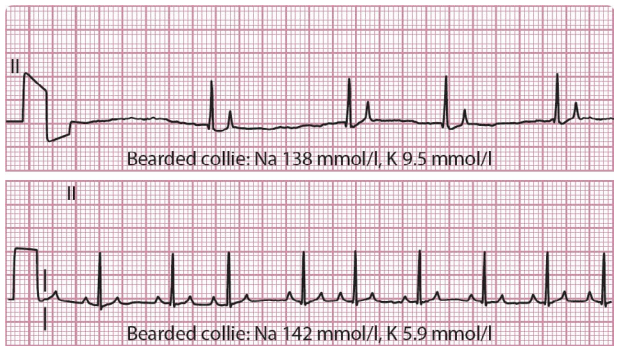


FIGURE 12.49 Electrocardiogram from a Bearded Collie in an Addisonian crisis. Note the slow ventricular rate and absence of P waves. The serum potassium was 9.5 mmol/L (9.5 mEq/L). Shown are the pre- and post-treatment electrocardiograms.

TABLE 12.14 ECG changes with hyperkalemia

>5.5 mmol/L (>5.5 mEq/L)—peaking of the T wave, shortening of the Q-T interval
>6.5 mmol/L (>6.5 mEq/L)—increased QRS duration
>7.0 mmol/L (>7.0 mEq/L)—P-wave amplitude decreased; P-R interval prolonged
>8.5 mmol/L (>8.5 mEq/L)—P wave absent, severe bradycardia (sinoventricular rhythm)

the caudal vena cava (Figure 12.50). The changes are not specific and only represent changes associated with hypovolemia and dehydration, irrespective of the cause. A few dogs with hypoadrenocorticism develop esophageal dilatation as a result of generalized muscle weakness, and this can be seen on thoracic radiographs (Figure 12.51).

Endocrine Testing

Basal cortisol has been shown to be a useful screening test for dogs with signs compatible with hypoadrenocorticism.

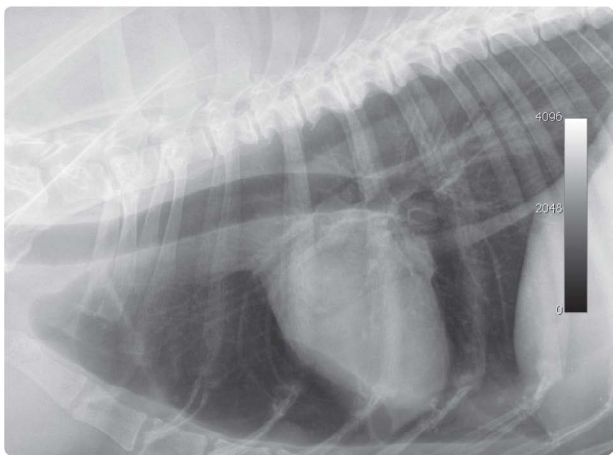


FIGURE 12.50 Lateral thoracic radiograph of a Bearded Collie with hypoadrenocorticism showing microcardia due to dehydration and hypovolemia.

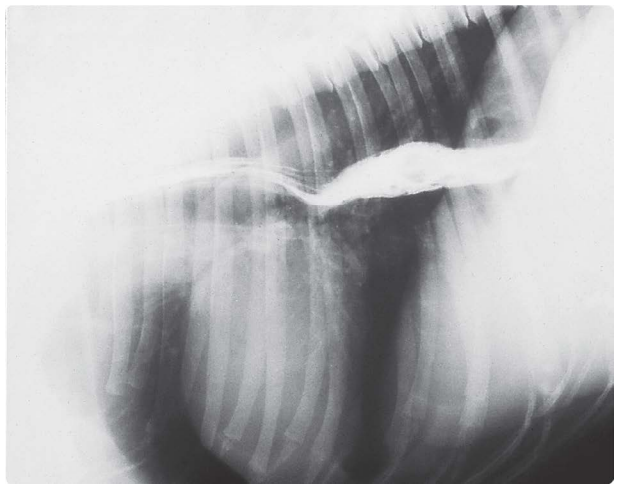


FIGURE 12.51 Lateral thoracic radiograph of a Dobermann with hypoadrenocorticism. A barium swallow has been performed to show a megaesophagus, which resolved following treatment of the hypoadrenocorticism.

The disease is unlikely when serum cortisol concentrations are >55 nmol/L. Basal cortisol concentrations <55 nmol/L cannot confirm a diagnosis of hypoadrenocorticism, and an ACTH stimulation test should be performed.

The ACTH stimulation test (Figure 12.52) is used to confirm the presence of hypoadrenocorticism; the protocol is described in Table 12.15. The IV preparation of ACTH (tetracosactin [cosyntropin in the United States]) should be used, as absorption by other routes cannot be relied on if the patient is collapsed or dehydrated. The ACTH stimulation test, however, does not distinguish

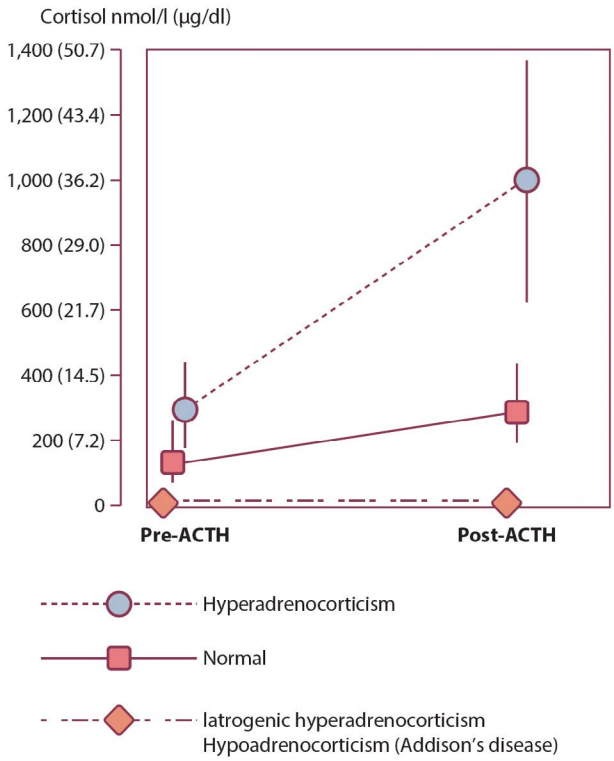


FIGURE 12.52 ACTH stimulation test.

TABLE 12.15 Protocol for endocrine testing for hypoadrenocorticism

ACTH stimulation test
Protocol – Collect 3 mL plasma or serum sample for basal cortisol concentration* – Inject 5 μg/kg of synthetic ACTH (tetracosactide [tetracosactrin]; Synacthen) IV in dogs and cats – Collect a second sample for cortisol concentration 30–60 minutes later
Interpretation – In normal dogs, pre-ACTH cortisol concentrations are usually between 20 and 250 nmol/L (0.7 and 9.1 μg/dL), with post-ACTH cortisol concentrations between 200 and 450 nmol/L (7.2 and 16.3 μg/dL) – Reduced responses to ACTH are also seen in primary hypoadrenocorticism (Addison's disease); usually both pre- and post-ACTH cortisol concentrations are <20 nmol/L (<0.7 μg/dL), but rarely the post-ACTH cortisol concentration may show some response up to 100 nmol/L (3.6 μg/dL)

* The recent administration of glucocorticoids, such as hydrocortisone, prednisolone, or prednisone, may result in elevated cortisol concentrations due to cross-reactivity in many cortisol assays. For this reason, these glucocorticoids should be withheld for at least 24 hours before testing. There is no cross-reactivity with dexamethasone, although dexamethasone will suppress cortisol concentrations in patients with an intact hypothalamic–pituitary–adrenal axis.

between primary and secondary hypoadrenocorticism. While aldosterone concentrations pre- and post-ACTH are not routinely measured, they may be useful in addition to cortisol concentrations in those cases with normal electrolyte concentrations (so-called atypical hypoadrenocorticism) to determine whether mineralocorticoid supplementation is likely to be indicated.

Plasma ACTH concentrations are required to differentiate primary and secondary hypoadrenocorticism. Plasma ACTH concentrations are usually below the detection range of the assay in secondary hypoadrenocorticism and markedly increased in primary hypoadrenocorticism.

Management

Acute Primary Hypoadrenocorticism

Aggressive IV fluid therapy using 0.9% saline should be used in the acute crisis to treat the hyperkalemia, which is life-threatening. Once stabilized, 0.45% saline may be used, since the serum sodium should not be increased by more than 8–12 mmol/L (8–12 mEq/L) per 24 hours in order to avoid causing central pontine myelinosis (osmotic demyelination). This is particularly important when the serum sodium level is <120 mmol/L (<120 mEq/L). The response to treatment is predictable and often dramatic, while acute kidney injury will slow down the improvement process. Glucose and insulin therapy or calcium administration are, therefore, not usually required for the treatment of hyperkalemia due to hypoadrenocorticism unless there are life-threatening ECG abnormalities such as atrial standstill or the appearance of sine waves. The serum potassium falls because of the dilution effect of the saline and the improvement in renal perfusion. The increased renal blood flow allows further excretion of potassium into the urine.

Glucocorticoid therapy should be used early in the treatment of the acute crisis. Once the animal has improved with saline and glucocorticoids, maintenance therapy with mineralocorticoids can be instigated (see ahead given in the text). Glucocorticoids of choice in the acute crisis include:

- Hydrocortisone sodium succinate (10 mg/kg IV repeated every 3–6 hours or a CRI of 0.5 mg/kg per hour)
- Prednisolone sodium succinate (5 mg/kg IV repeated every 3–6 hours)
- Dexamethasone sodium phosphate (0.5–1.0 mg/kg IV given once)

If plasma cortisol concentrations are to be measured for the diagnosis of hypoadrenocorticism, dexamethasone should be used, as the other preparations cross-react with cortisol in the assay.

Chronic Primary Hypoadrenocorticism (Maintenance Therapy)

Desoxycorticosterone pivalate, a long-acting ester of desoxycorticosterone, can be used for the replacement of mineralocorticoid deficiency in dogs and cats with primary hypoadrenocorticism. It only replaces mineralocorticoid hormones and, therefore, must be combined with glucocorticoid replacement therapy. The dose recommended starting dose is 2 mg/kg IM or SC every 28–30 days (lower doses and longer treatment intervals have been efficacious in some dogs). Fludrocortisone acetate is an oral synthetic adrenocortical steroid with mineralocorticoid effects. An initial dose of 15 μg/kg per day of fludrocortisone is given and serum electrolytes measured after 5–7 days. The dose rate should then be adjusted until the sodium and potassium concentrations are within the reference range. The daily maintenance dose required is usually between 15 and 30 μg/kg. The dose may have to be increased during the first 6–18 months of therapy, and the drug may need to be administered twice daily in some cases.

Prednisolone at a dose of 0.1–0.2 mg/kg daily should be sufficient for physiologic glucocorticoid replacement, although the dose may need to be tailored to the individual patient. Daily glucocorticoid supplementation is required when using desoxycorticosterone pivalate but not required after initial treatment with fludrocortisone acetate in the majority of cases, as fludrocortisone has some glucocorticoid activity. However, the owners of animals with hypoadrenocorticism treated with fludrocortisone should be given a supply of prednisolone tablets to be administered if the patient appears unwell.

Salt supplementation using salt tablets or salting the food may be instigated initially to help correct hyponatremia, but this can be gradually reduced and phased out as it is not usually required long term. However, dogs requiring unusually high doses of fludrocortisone may respond to oral salt and fewer fludrocortisone tablets.

The prognosis for primary hypoadrenocorticism is generally excellent providing owner education is adequate. Hypoadrenocorticism can occur in conjunction with other endocrine deficiencies, such as hypothyroidism, diabetes mellitus, and hypoparathyroidism or with other immune-mediated diseases, such as immune-mediated hemolytic anemia or thrombocytopenia.

SECONDARY HYPOADRENOCORTICISM

Definition/Overview

Secondary hypoadrenocorticism is associated with a deficiency of glucocorticoids caused by a deficiency in ACTH production and/or release. The production of mineralocorticoids, although reduced, generally remains adequate. Secondary hypoadrenocorticism occurs in both dogs and cats.

Etiology

Secondary hypoadrenocorticism can be associated with congenital panhypopituitarism (q.v.) or destructive lesions (e.g., nonfunctional tumors, hemorrhage, trauma, or hypophysitis) affecting the hypothalamus or anterior pituitary. More commonly, however, the condition is iatrogenic, with clinical signs occurring after the cessation of glucocorticoid therapy. In these cases, secondary hypoadrenocorticism is caused by prolonged suppression of ACTH secretion from glucocorticoid therapy. In the cat, secondary hypoadrenocorticism is also seen following prolonged megestrol acetate therapy.

Pathophysiology

Destructive lesions in the pituitary or hypothalamus may result in deficiencies of several pituitary hormones, including ACTH. Alternatively, exogenous glucocorticoid administration may suppress ACTH production and release. Both situations result in atrophy of the adrenal cortices and decreased glucocorticoid synthesis and release.

Clinical Presentation

The clinical signs are variable and may include depression, anorexia, occasional vomiting or diarrhea, a weak pulse, and sudden collapse when stressed. If the secondary hypoadrenocorticism is associated with cessation of glucocorticoid therapy, clinical signs of iatrogenic hyperadrenocorticism (Cushing's disease) are usually present.

Differential Diagnosis

Diabetic ketoacidosis, septic peritonitis, acute necrotizing pancreatitis.

Diagnosis

Diagnosis of secondary hypoadrenocorticism is based on a failure of the animal's cortisol concentrations to respond to ACTH stimulation and an endogenous plasma ACTH concentration below the detection range of the assay.

Management

Glucocorticoid replacement using prednisolone (0.1–0.2 mg/kg q.24 h.) is indicated for immediate correction of the clinical signs. Further treatment and the prognosis depend on the cause and whether glucocorticoid therapy can be eliminated.

HYPERADRENOCORTICISM (CUSHING'S DISEASE)

Definition/Overview

Hyperadrenocorticism is associated with excessive production or administration of glucocorticoids and is one of the most commonly diagnosed endocrinopathies in the dog. Hyperadrenocorticism is rare in the cat.

Etiology

Hyperadrenocorticism can be spontaneous or iatrogenic. Spontaneously occurring hyperadrenocorticism may be associated with inappropriate secretion of ACTH by the pituitary (pituitary-dependent hyperadrenocorticism [PDH]) or with a primary adrenal disorder (adrenal-dependent hyperadrenocorticism) (Figure 12.53a–c).

Pathophysiology

Pituitary-Dependent Hyperadrenocorticism

PDH accounts for 80%–85% of dogs and the majority of cats with naturally occurring hyperadrenocorticism. Excessive ACTH secretion results in bilateral adrenocortical hyperplasia and increased cortisol secretion. There is a failure of the negative feedback mechanism of cortisol on ACTH. However, episodic secretion of ACTH results in fluctuating cortisol concentrations that may at times be within the normal range. The presence of excessive cortisol secretion can be confirmed by measuring urine cortisol excretion over a 24-hour period.

Pathologic changes in PDH include microadenomas and macroadenomas of the corticotroph cells and a primary failure of the negative feedback response. Microadenomas are <1 cm in diameter. The incidence of corticotroph adenomas associated with PDH varies widely, probably because detection of small tumors requires careful microdissection, experience, and special stains. In one study using immunocytochemical staining, more than 80% of dogs with PDH were positive for pituitary adenomas. Macroadenomas are >1 cm in diameter, and only a small percentage of dogs have large corticotroph adenomas (Figure 12.54). These may compress the remaining pituitary and extend dorsally into the hypothalamus. However, they are generally slow growing and do not always

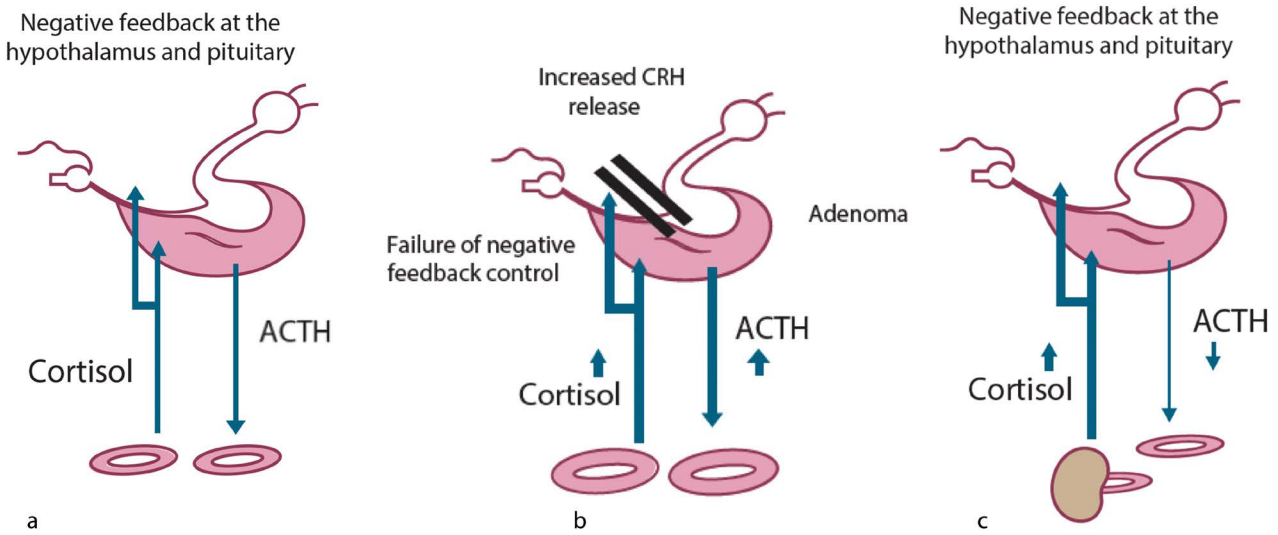


FIGURE 12.53 (a) Physiology of the hypothalamic–pituitary–adrenal axis. Corticotropin-releasing hormone (CRH) is released from the hypothalamus into the portal circulation which stimulates the release of adrenocorticotropic hormone (ACTH) from the corticotrophs in the anterior lobe of the pituitary. ACTH stimulates the release of cortisol from the adrenal cortex, which has a negative feedback control at the hypothalamus and pituitary level to regulate glucocorticoid release. **(b)** The hypothalamic–pituitary–adrenal axis in pituitary-dependent hyperadrenocorticism. Increased ACTH release, usually from a pituitary adenoma, results in symmetric enlargement of the adrenal cortices and increased capacity to release cortisol in response to the ACTH release. **(c)** The hypothalamic–pituitary–adrenal axis in adrenal-dependent hyperadrenocorticism. The adrenocortical tumor autonomously secretes cortisol, which has a negative feedback control at the hypothalamus and pituitary level halting the release of CRH and ACTH. The reduced release of ACTH leads to adrenocortical atrophy of the contralateral adrenal cortex as well as any remaining cortex in the affected adrenal gland.

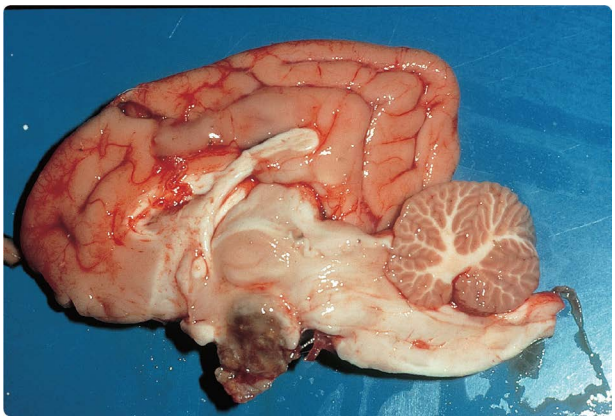


FIGURE 12.54 A large corticotroph adenoma associated with pituitary-dependent hyperadrenocorticism. The dog was successfully treated for 5 years while the tumor was gradually enlarging.

produce neurologic signs. Malignant pituitary tumors are rare.

The defect responsible for PDH unassociated with pituitary neoplasia is unknown. A primary failure of the negative feedback response by cortisol has been proposed. Others suspect an overproduction of CRH from the hypothalamus, which may cause diffuse hyperplasia of ACTH-producing cells in the anterior pituitary. From a clinical point of view, the precise pituitary pathology is not of great importance unless neurologic signs are present at the time of diagnosis or become apparent during the initial treatment.

Adrenal-Dependent Hyperadrenocorticism

The remaining 15%–20% of spontaneous cases of hyperadrenocorticism in dogs and cats are caused by unilateral or, occasionally, bilateral adrenal tumors, which can be benign or malignant. Adrenocortical adenomas are small (usually <4 cm in diameter), well-circumscribed tumors that do not metastasize and are not locally invasive. Approximately 50% are partially calcified. Adrenocortical carcinomas are usually larger, locally invasive, hemorrhagic, and necrotic. Tumor calcification also occurs in about 50% of dogs. The tumors frequently invade the phrenicoabdominal vein and caudal vena cava and metastasize to the liver, lung, and kidney.

In dogs, adrenocortical adenomas and carcinomas occur in approximately equal proportions. The cortex contiguous to the tumor and that of the contralateral gland will tend to become atrophied in the presence of functional adenomas and carcinomas (Figure 12.55). This is important if the tumor is removed surgically, as postoperatively the animal may not be able to secrete sufficient glucocorticoids. Function of the zona glomerulosa should not be affected.

Clinical Presentation

Any breed of dog can develop hyperadrenocorticism, but Poodles, Dachshunds, Bichon Frise, Spaniels, and small terriers (e.g., Yorkshire Terrier, Jack Russell Terrier, and Staffordshire Bull Terrier) appear more at risk of developing PDH. Adrenocortical tumors occur more frequently in larger breeds of dog, with approximately



FIGURE 12.55 A large adrenal tumor invading the kidney from a dog with adrenal-dependent hyperadrenocorticism.



FIGURE 12.56 A 10-year-old Yorkshire Terrier with hyperadrenocorticism showing a pot-bellied appearance and bilaterally symmetrical alopecia.

50% of affected dogs weighing >20 kg. No breed predisposition has been recorded in cats.

PDH is usually a disease of the middle-aged to older dog, with an age range of 2–16 years and a median age of 7–9 years. Dogs with adrenal-dependent hyperadrenocorticism tend to be older, with a range of 6–16 years and a median age of 10–11 years. There is no significant difference in sex distribution in PDH; however, female dogs are three times more likely to develop adrenal tumors than males. Affected dogs usually develop a classic combination of clinical signs associated with increased glucocorticoid levels. These are listed in Table 12.16 in approximate decreasing order of frequency. Some dogs, however, may only show a few characteristic signs rather than the classic array of clinical signs. Hyperadrenocorticism has an insidious onset and is slowly progressive over many months or even years. Many owners consider the early signs as part of the normal aging process of their dog. In a few cases, clinical signs may be intermittent with periods of remission and relapse, and in other cases, there may be rapid onset and progression of clinical signs.

Polydipsia, defined as water intake in excess of 100 mL/kg body weight per day, and polyuria, defined as urine production in excess of 50 mL/kg body weight per day, are seen in virtually all cases of hyperadrenocorticism. Excessive thirst, nocturia, and/or urination in the house are usually noted by owners. The polydipsia occurs secondary to the polyuria, which is only partially responsive to water deprivation.

TABLE 12.16 Clinical signs of hyperadrenocorticism (in approximate decreasing order of frequency)

- Polydipsia and polyuria
- Polyphagia
- Abdominal distension
- Liver enlargement
- Muscle wasting/weakness
- Lethargy, poor exercise tolerance
- Skin changes
- Alopecia
- Panting
- Hypertension
- Persistent anestrus or testicular atrophy
- Calcinosis cutis
- Myotonia neurologic signs

Increased appetite is common, but most owners often assess this as a sign of good health. However, a voracious appetite and scavenging or stealing food may give rise to concern, especially if the dog previously had a poor appetite. Polyphagia is assumed to be a direct effect of glucocorticoids.

A pendulous abdomen or pot-bellied appearance is very common in hyperadrenocorticism, but it may be so gradual that owners fail to recognize its significance (Figure 12.56). The abdominal distension is associated with redistribution of fat to the abdomen, liver enlargement, and abdominal muscle wasting and weakness.

The gradual onset of lethargy and poor exercise tolerance are usually considered by most owners to be compatible with aging. Only when muscle weakness is severe, as reflected by an inability to climb stairs or jump into the car, does the owner become concerned. Lethargy, excessive panting, and poor exercise tolerance are probably an expression of muscle wasting and weakness. Apart from the development of a pendulous abdomen, decreased muscle mass may be noted around the limbs, over the spine, or over the temporal region. Muscle weakness is the result of muscle wasting caused by protein catabolism.

Occasionally, dogs with hyperadrenocorticism develop myotonia, characterized by persistent active muscle contractions that continue after voluntary or involuntary stimuli (Figure 12.57). All limbs may be affected, but the signs are usually more severe in the hind limbs. Animals with myotonia walk with a stiff, stilted gait. The affected limbs are rigid and rapidly return to extension after being passively flexed. Spinal reflexes are difficult to elicit because of the rigidity, but pain sensation is normal. The muscles are usually slightly hypertrophied rather than being atrophied, and a myotonic dimple can be elicited by percussion of the affected muscle. Bizarre high-frequency discharges are noted on electromyography.



FIGURE 12.57 An 11-year-old Poodle with hyperadrenocorticism showing rigidity associated with myotonia.



FIGURE 12.59 A close-up of comedones around the nipple of a Poodle with hyperadrenocorticism.



FIGURE 12.58 Thin, inelastic skin on the ventral abdomen of a Dachshund with hyperadrenocorticism.



FIGURE 12.60 Stretching of an abdominal scar and striae on the ventral abdomen of a Boxer with hyperadrenocorticism.

The skin, particularly over the ventral abdomen, becomes thin and inelastic (Figure 12.58). Elasticity can be assessed clinically by tenting the skin between the thumb and forefinger. In the normal dog, the skin will flow back to a smooth contour, but in hyperadrenocorticism, it remains tented. Striae can form as a result of this inelasticity. The abdominal veins are prominent and easily visible through the thin skin. There is often excessive surface scale and comedones, caused by follicular plugging, are seen, especially around the nipples (Figure 12.59). Hyperpigmentation of the skin is rare in canine hyperadrenocorticism.

Protein catabolism, causing atrophic collagen, also leads to excessive bruising following either venipuncture or other minor trauma. Wound healing is extraordinarily slow, presumably because of inhibition of fibroblast proliferation and collagen synthesis. Healing wounds often undergo dehiscence, and even old scars may start to break down (Figure 12.60).

Calcinosis cutis is a frequent finding in biopsy material from the skin; however, clinical evidence of calcinosis cutis is less common. The gross appearance can vary, but the predilection sites are the neck, axilla, ventral abdomen, and inguinal areas (Figure 12.61). Calcinosis cutis usually appears as a firm, slightly elevated, white or cream plaque surrounded by a ring of erythema. Large plaques tend to crack, become secondarily infected, and develop a crust containing white powdery material. The exact pathogenesis is unknown, but plasma calcium and phosphorus concentrations are usually normal. Mineralization of the soft tissues may be seen at other



FIGURE 12.61 Calcinosis cutis (arrow) and comedones on the ventral abdomen of a Poodle with hyperadrenocorticism.



FIGURE 12.62 Bilaterally symmetrical alopecia in a Wirehaired Dachshund with hyperadrenocorticism.

sites (e.g., the bronchial walls and kidneys) on radiographic examination.

Thinning of the hair coat, leading to bilaterally symmetrical alopecia, is frequently seen with hyperadrenocorticism and occurs because of the inhibitory effect of cortisol on the anagen or growth phase of the hair cycle. The remaining hair is dull and dry because it is in the telogen or resting phase of the hair cycle. The alopecia is nonpruritic and affects mainly the flanks, ventral abdomen and chest, perineum, and neck. The head, feet, and tail are usually the last areas to be affected (Figure 12.62). The coat color is often lighter than normal.

Systemic hypertension and associated proteinuria may be found in >80% of cases with untreated hyperadrenocorticism, with 46% of classified as severe hypertension (>180 mmHg). In the majority of cases, the degree of hypertension is moderate and not associated with clinical signs; however, hypertension-induced blindness due to intraocular hemorrhage and retinal detachment and ischemic arterial infarcts have occasionally been reported.

Entire bitches with hyperadrenocorticism usually cease to cycle. The length of anestrus (often years) indicates the duration of the disease process. In the intact male, both testes become soft and flabby. Anestrus and testicular atrophy occur due to the negative feedback effect of high concentrations of cortisol on the pituitary, which also suppresses secretion of gonadotropic hormones.

Although uncommon at the time of presentation, a few cases develop neurologic signs associated with large, expanding functional pituitary tumors. The most common manifestations of a pituitary tumor are vague neurological signs such as lethargy, mental dullness, depression, disorientation, loss of learned behavior, and anorexia rather than more specific neurological signs such as aimless wandering, head pressing, circling, ataxia, blindness, anisocoria, and seizures. More often, however, neurologic signs develop during initial treatment of PDH with trilostane or mitotane. This is thought to involve removal of the negative feedback of cortisol, which can cause some pituitary tumors to enlarge rapidly, resulting in edema and increased intracranial pressure.

Differential Diagnosis

Causes of polydipsia/polyuria (Table 12.4), liver disease, hypothyroidism, Sertoli cell tumor, ovarian imbalance.

Diagnosis

Laboratory Findings

The main hematologic, biochemical, and urinalysis findings are listed in Table 12.17. The most consistent hematologic finding is a stress leukogram with a relative and absolute lymphopenia (<1.5 × 10^9/L [<1.5 × 10^3/μL]) and eosinopenia (<0.2 × 10^9/L [<0.2 × 10^3/μL]). Lymphopenia is most likely the result of steroid lymphocytolysis and/or redistribution of T cells to lymphoid tissues, and the eosinopenia results from bone marrow sequestration of eosinophils. A mild-to-moderate neutrophilia and monocytosis may be present, and it is thought that excessive glucocorticoids result in decreased capillary margination and diapedesis and increased release from the bone marrow. The red cell count is usually normal, although mild polycythemia may occasionally be noted. Platelet counts may also be elevated. These findings are thought to result from stimulatory effects of glucocorticoids on the bone marrow.

Glucocorticoids, both endogenous and exogenous, induce a specific hepatic isoenzyme of ALP in the dog. The increase in serum ALP is commonly 5–40 times the normal level and is perhaps one of the most reliable indicators of hyperadrenocorticism. Measurement of the specific steroid-induced isoenzyme of ALP has been used for more accurate assessment of elevated serum ALP activity. A marked increase in serum ALP is rarely seen in cats with hyperadrenocorticism because they do not

TABLE 12.17 Laboratory findings in hyperadrenocorticism

Hematology
– Lymphopenia (<1.5 × 10^9/L [<1.5 × 10^3/μL])
– Eosinopenia (<0.2 × 10^9/L [<0.2 × 10^3/μL])
– Neutrophilia
– Monocytosis
– Erythrocytosis
Biochemistry
– Increased ALP (often markedly elevated); dog only
– Increased ALT
– High normal fasting blood glucose; rarely diabetic except for the cat where the majority of the cases are diabetic
– Decreased blood urea nitrogen
– Increased cholesterol (>8 mmol/L [>309 mg/dL])
– Hypertriglyceridemia
– Lipemia
– Increased bile acid
Urinalysis
– Urine SG <1.015
– Urinary tract infection
– Increased urine protein-to-creatinine ratio
– Glycosuria (<10% of canine cases)
Other findings
– Low T4 concentrations
– Subnormal T4 response to TSH or TRH stimulation
– Increased parathyroid hormone concentrations

possess a steroid-induced isoenzyme and have the ability to clear serum of excess ALP. ALT is commonly elevated in hyperadrenocorticism, but the increase is usually only mild and is believed to result from liver damage caused by swollen hepatocytes due to glycogen storage. Blood glucose is usually in the high normal range, but about 10% of canine cases will develop overt diabetes mellitus. The gluconeogenic effect of glucocorticoids results in insulin antagonism and subsequent development of pancreatic islet cell exhaustion. Cats appear to be more prone to developing hyperglycemia and overt diabetes. In contrast to the dog, where polydipsia and polyuria are among the earliest clinical signs of hyperadrenocorticism, the onset of polydipsia and polyuria is delayed in the cat and coincides with the development of moderate-to-severe hyperglycemia and glycosuria. Hyperadrenocorticism should be suspected in any cat that requires high daily insulin doses to control the hyperglycemia and glycosuria.

Blood urea is usually below normal due to the continual urinary loss associated with glucocorticoid-induced diuresis. Serum creatinine concentrations also tend to be in the low to normal range. Cholesterol and lipid concentrations are usually increased due to glucocorticoid stimulation of lipolysis. Cholesterol is usually >8 mmol/L (>309 mg/dL), but this is not a specific finding as cholesterol is also raised in hypothyroidism, diabetes mellitus, chronic liver disease, and chronic renal disease, all of which may be differential diagnoses. Lipemia is important as it can interfere with the accurate assessment of a number of laboratory parameters. Resting and postprandial bile acid concentrations may show a mild-to-moderate increase in some cases of hyperadrenocorticism due to steroid hepatopathy.

The SG of the urine is usually <1.015 and is often hyposthenuric (<1.010) provided water has not been withheld. Dogs with hyperadrenocorticism can concentrate their urine if deprived of water, but their concentrating ability is usually reduced. Urinary tract infection is common and occurs in about half the cases of hyperadrenocorticism; however, it does not result in typical signs of cystitis due to the anti-inflammatory effects of excess glucocorticoids. Proteinuria, defined as a urine protein-to-creatinine ratio of ≥1.0, is present in over 40% of untreated cases of hyperadrenocorticism. Glycosuria is present in the 10% of cases with diabetes mellitus.

Basal thyroxine concentrations are decreased in about 70% of dogs with hyperadrenocorticism. This is, in part, due to inhibition of TRH and reduced pituitary secretion of TSH. Excess cortisol, however, may also alter thyroid hormone binding to plasma proteins and enhance the metabolism of thyroid hormone. The response to stimulation by TSH usually parallels that of normal dogs, but thyroxine concentrations both before and after stimulation with TSH are subnormal. Endogenous canine TSH concentrations are usually low but may be increased in some cases, mimicking the changes seen in hypothyroidism.

Glucocorticoids are known to increase urinary calcium excretion in canine hyperadrenocorticism. In order to maintain normal circulating concentrations of calcium, parathyroid hormone (PTH; parathormone) concentrations are increased in >80% of cases of hyperadrenocorticism.

TABLE 12.18 Radiologic signs of hyperadrenocorticism

Abdominal radiographs
- Liver enlargement
- Good radiographic contrast
- Pendulous abdomen or pot-bellied appearance
- Calcinosis cutis/soft tissue mineralization
- Distended bladder
- Cystic or renal calculi
- Adrenal enlargement/calcification
- Osteopenia

Thoracic radiographs
- Tracheal and bronchial wall calcification
- Pulmonary metastasis from adrenocortical carcinoma
- Osteopenia
- Pulmonary interstitial mineralization (rare)
- Congestive heart failure (rare)
- Pulmonary thromboembolism (rare)

Diagnostic Imaging

Radiography

Radiographic examination of the thorax and abdomen is advisable in all cases of suspected or proven hyperadrenocorticism. Although positive diagnostic information is only obtained in the small number of cases in which adrenal enlargement can be detected, the number and the frequency of radiologic changes consistent with hyperadrenocorticism provide a useful aid to diagnosis. In addition, survey radiographs may reveal significant concurrent disease. The most common radiologic signs of hyperadrenocorticism are listed in Table 12.18.

Hepatomegaly is the most consistent radiographic finding in hyperadrenocorticism. Good radiographic contrast permits easy identification of the abdominal structures because of the large deposits of intra-abdominal fat. Hepatomegaly may be mild to severe, and the ventral lobe borders vary in shape between distinctly rounded and sharply wedge shaped. Abdominal distension and a pendulous abdomen are usually very obvious on the recumbent lateral projection (Figure 12.63). Hepatomegaly

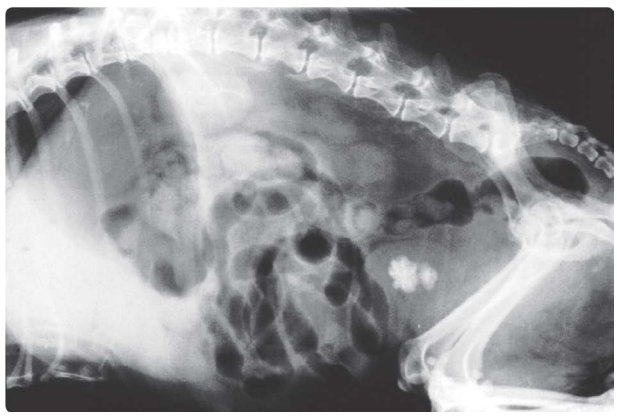


FIGURE 12.63 Lateral abdominal radiograph of a case of hyperadrenocorticism. Cystic calculi are also present.

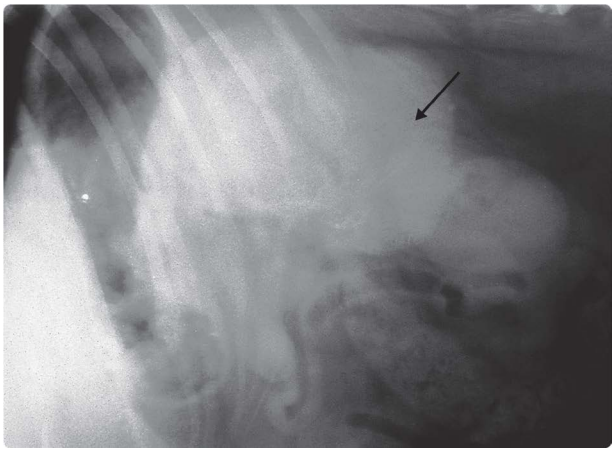


FIGURE 12.64 Lateral abdominal radiograph of a 9-year-old German Shepherd Dog with a right adrenal tumor (arrow).

and a pendulous abdomen are the most consistent radiographic findings in cats with hyperadrenocorticism.

Adrenal enlargement is the least common finding on abdominal radiographs. Gross enlargement is suggestive, although not diagnostic, of an adrenocortical carcinoma. Unilateral mineralization in the region of an adrenal gland suggests the possibility of an adrenal tumor (Figure 12.64). Both adrenocortical adenomas and carcinomas can become calcified. Radiography of the abdomen not infrequently demonstrates calcification of the adrenal glands in normal older cats and is not associated with any functional abnormality.

Calcinosis cutis tends to have a nodular mineralization pattern, whereas calcification in the fascial planes (e.g., just dorsal to the thoracolumbar spine) tends to be linear. Mineralization may also be seen in the renal pelvis, liver, gastric mucosa, and abdominal aorta.

A grossly distended urinary bladder may be seen radiographically even when the animal has been allowed to urinate prior to the radiographic examination. Cystic calculi may also be present and are usually associated with urinary tract infection. Occasionally, the impression of osteopenia is gained from a distinct reduction in radiographic density of the lumbar vertebral bodies relative to the vertebral endplates. Tracheal and bronchial wall calcification is frequently seen radiographically in cases of hyperadrenocorticism. However, calcification of these structures can be seen in animals as part of the normal aging process and is not considered to be a highly significant finding.

The thoracic radiographs should also be examined for evidence of pulmonary metastases from an adrenocortical carcinoma, CHF, osteoporosis of the thoracic spine, or pulmonary thromboembolism. The latter is a rare complication of hyperadrenocorticism and may be suspected when the radiographic signs include pleural effusion, increased diameter and blunting of pulmonary arteries, decreased vascularity of the affected lobes, and overperfusion of the unobstructed pulmonary vasculature. However, in some cases of pulmonary thromboembolism, the radiographs may reveal no abnormalities.



FIGURE 12.65 Ultrasonogram of a Boxer with adrenal hyperplasia due to PDH.

Ultrasonography

Abdominal ultrasonography is frequently used to examine the adrenal glands. The challenge for the ultrasonographer is to distinguish consistently between normal and hyperplastic adrenal glands, since the diagnosis of adrenal hyperplasia is somewhat subjective. Measurement of the thickness (ventrodorsal dimension) of the adrenal gland has been shown to be more sensitive than either the length or width of the gland. A thickness of >7.5 mm for the left adrenal gland would be suggestive of adrenal hyperplasia (Figures 12.65 and 12.66). If both adrenal glands are of similar size and normal shape in a dog or cat with hyperadrenocorticism, it confirms the disease is PDH.

Abdominal ultrasonography can also detect adrenocortical tumors (Figure 12.67). Adrenal masses are diagnosed by the location of the mass and the clinical signs exhibited by the animal. However, the appearance of adrenal nodules and masses is not specific for the underlying pathology. The differential diagnosis for solid nodules or masses within the adrenal gland includes adrenocortical adenoma, adrenocortical carcinoma, pheochromocytoma, myelolipoma, metastasis, nodular hyperplasia, and granuloma. Adrenal masses exceeding 2 cm in diameter generally predict benign or malignant neoplasia rather than hyperplasia.

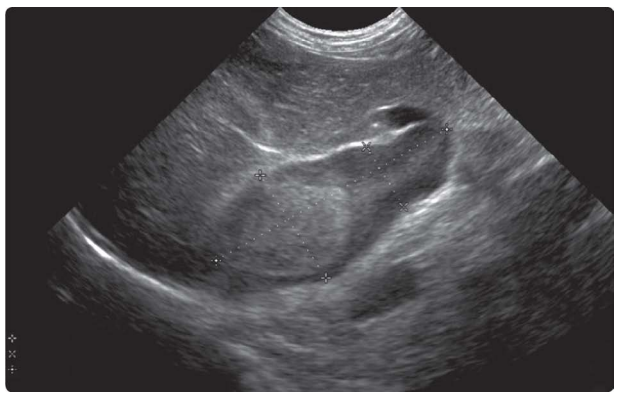


FIGURE 12.66 Ultrasonogram showing right-sided adrenal enlargement with nodular hyperplasia. The dog was being treated with trilostane, which can cause treatment-associated adrenomegaly.

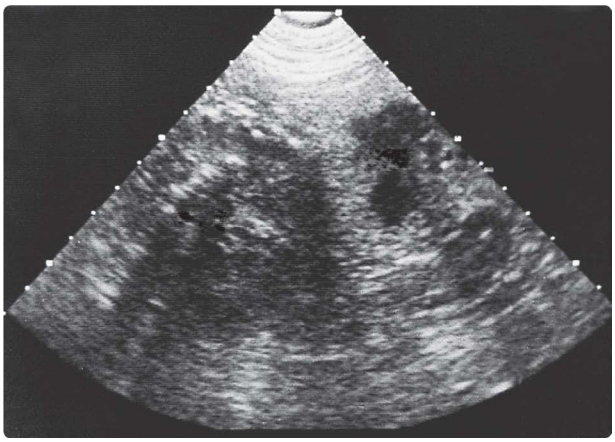


FIGURE 12.67 Ultrasonogram of a large adrenal tumor adjacent to the left kidney in a Rottweiler with adrenal-dependent hyperadrenocorticism.

Percutaneous ultrasound-guided fine-needle aspiration of adrenal masses is relatively safe and provides useful cytological information regarding the origin of the tumor (cortical or medullary), although it cannot distinguish between benign or malignant lesions. There is a propensity for malignant adrenal tumors to invade nearby vessels and surrounding tissues; therefore, a thorough ultrasonographic examination of adjacent vessels and tissues should be performed (Figures 12.68 and 12.69a, b). Mineralization is frequently associated with benign and malignant adrenocortical tumors in the dog, and acoustic shadowing may aid in localizing the adrenal tumor. If an adrenal mass is identified, the liver should also be examined ultrasonographically for evidence of hepatic metastases.

CT and MR Imaging

Cross-sectional imaging using CT and MR imaging has proved helpful in the diagnosis of adrenal tumors, adrenal hyperplasia, and pituitary tumors (Figure 12.70), but these techniques are more expensive.

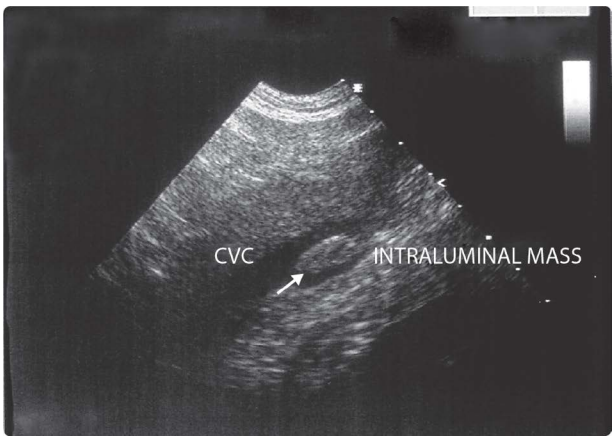


FIGURE 12.68 Ultrasonogram of an adrenal tumor (arrow) invading the caudal vena cava in a Labrador Retriever with adrenal-dependent hyperadrenocorticism.



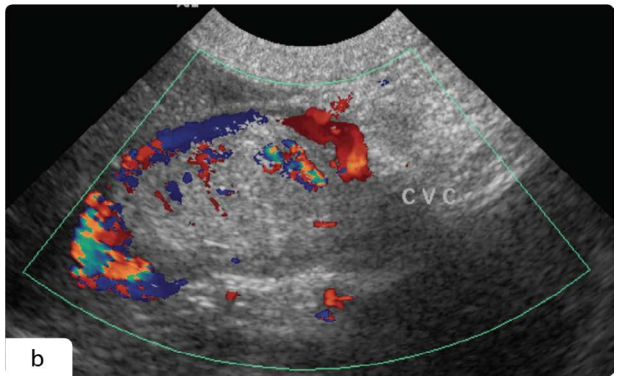


FIGURE 12.69 A plain abdominal ultrasound examination **(a)** and a flow Doppler evaluation **(b)** showing invasion of the caudal vena cava by a malignant adrenocortical carcinoma.

Abdominal and thoracic CT with contrast should be performed before adrenalectomy, as the presence of vascular or tissue invasion and distant metastasis can be more readily identified with CT than with any other imaging modality.

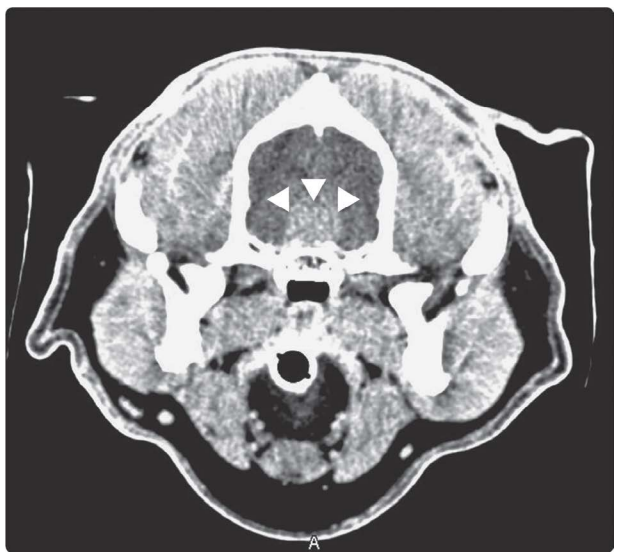


FIGURE 12.70 A contrast CT scan of a cushingoid dog showing a large pituitary macroadenoma (arrowheads) expanding deep into the diencephalon. (*Courtesy of M. Schaer.*)

Endocrine Screening Tests

A presumptive diagnosis of hyperadrenocorticism can be made from clinical signs, physical examination, routine laboratory tests, and diagnostic imaging findings, but the diagnosis must be confirmed by either an ACTH stimulation test or a low-dose dexamethasone suppression test (LDDST); however, the urinary corticoid-to-creatinine ratio has also proved useful in certain situations (see Table 12.19). A single resting or basal plasma or serum cortisol determination is of limited diagnostic value because of the overlap in cortisol concentrations obtained from normal and abnormal disease states.

ACTH Stimulation Test

The ACTH stimulation test (see Figure 12.52) is the best screening test for distinguishing spontaneous from iatrogenic hyperadrenocorticism. It reliably identifies about 85% of dogs with PDH but only about 50% of those dogs with adrenal-dependent hyperadrenocorticism. It is a simple test to perform and the only one that directly documents excessive production of glucocorticoids by the adrenal cortex. The information gained also provides a baseline for monitoring trilostane or mitotane therapy. However, the ACTH stimulation test does not reliably differentiate adrenal-dependent hyperadrenocorticism from PDH. A diagnosis of hyperadrenocorticism should not be excluded on the basis of a normal ACTH response if the clinical signs are compatible with the disease. Occasionally, an animal under chronic stress may develop some degree of adrenal hyperplasia, which produces an abnormal or equivocal ACTH response result. The author has seen this in a

TABLE 12.19 Protocols for endocrine screening tests for hyperadrenocorticism

ACTH stimulation test
Protocol – Collect 3 mL plasma or serum sample for basal cortisol concentration* – Inject 5 µg/kg of synthetic ACTH (tetracosactide [tetracosactrin]; Synacthen**) IV in dogs and cats – Collect a second sample for cortisol concentration 30–60 minutes later
Interpretation – In normal dogs, pre-ACTH cortisol concentrations are usually between 20 and 250 nmol/L (0.7 and 9.1 µg/dL), with post-ACTH cortisol concentrations between 200 and 450 nmol/L (7.2 and 16.3 µg/dL) – An exaggerated response (post-ACTH cortisol concentrations >600 nmol/L [>21.7 µg/dL]) is expected in dogs and cats with hyperadrenocorticism. The ACTH stimulation test reliably identifies more than 50% of dogs with adrenal-dependent hyperadrenocorticism and about 85% of dogs with PDH. Exaggerated responses to ACTH may also be seen in chronic illness (e.g., uncontrolled diabetes mellitus). – The ACTH stimulation test is the best screening test for distinguishing spontaneous hyperadrenocorticism from iatrogenic Cushing's disease where reduced responses to ACTH are recorded due to adrenocortical suppression as a result of long-term or high-dose glucocorticoid administration
Low-dose dexamethasone suppression test (LDDST)
Protocol – Collect 3 mL plasma or serum sample for cortisol determination – Inject 0.01 mg/kg of dexamethasone IV – Collect a second sample for cortisol concentration 4 hours later and a third sample 8 hours after dexamethasone administration
Interpretation – A plasma or serum cortisol concentration exceeding 40 nmol/L (1.5 µg/dL) at 8 hours is regarded as diagnostic for hyperadrenocorticism. The LDDST reliably identifies all dogs with adrenal-dependent hyperadrenocorticism and about 90% of PDH. However, stress during therapy may cause animals without hyperadrenocorticism to break the suppressive effect of dexamethasone. – Cortisol concentrations at 0 and 4 hours are not required for the diagnosis of hyperadrenocorticism but may be informative in the differential diagnosis. Suppression of the cortisol concentration to <30 nmol/L (<1.1 µg/dL) at 4 hours with a rebound escape of suppression at 8 hours would be suggestive of PDH. Cases of adrenal-dependent hyperadrenocorticism do not show significant suppression of cortisol at 4 hours; however, up to 40% of dogs with PDH will not show suppression at 4 hours either.
Urine cortisol-to-creatinine ratio
Protocol – Urine (5 mL) is collected in the morning for cortisol and creatinine measurements. It is preferable for the dog to be at home for this test so that it is as little stressed as possible. The urine cortisol-to-creatinine ratio is determined by dividing the urine cortisol concentration (in nmol/L) by the urine creatinine concentration (in µmol/L).
Interpretation – The reference ratio for normal dogs is $<10 \times 10^6$. The urine cortisol-to-creatinine ratio is increased above the normal ($>10 \times 10^6$) in dogs with hyperadrenocorticism. However, the ratio is also increased in many dogs with nonadrenal illness. Therefore, while this simple test appears highly sensitive in detecting hyperadrenocorticism in dogs, it is not specific. The test does provide a good screening test for hyperadrenocorticism, and values in the normal range make a diagnosis of hyperadrenocorticism highly unlikely.

* The recent administration of glucocorticoids, such as hydrocortisone, prednisolone, or prednisone, may result in elevated cortisol concentrations due to cross-reactivity in many cortisol assays. For this reason, glucocorticoids should be withheld for at least 24 hours before testing. There is no cross-reactivity with dexamethasone, but dexamethasone will suppress cortisol concentrations in patients with an intact hypothalamic–pituitary–adrenal axis.

** Sold in the United States as cosyntropin (Cortrosyn, Amphastar Pharmaceuticals).

number of severe systemic diseases (e.g., uncontrolled diabetes mellitus and pyometra) and has documented a normal ACTH response after treatment in each case. The ACTH response test is not as reliable for diagnosing this disorder in the cat.

Low-Dose Dexamethasone Suppression Test

The LDDST (Figure 12.71) is more reliable than the ACTH stimulation test in confirming hyperadrenocorticism, since the results are diagnostic in most adrenal-dependent cases and in 90% of dogs with PDH. However, it is not as useful as the ACTH stimulation test for the detection of iatrogenic hyperadrenocorticism. It is also affected by more variables, takes 8 hours to complete, and does not provide pretreatment information that may aid in monitoring the effects of trilostane or mitotane therapy. The LDDST, like the ACTH stimulation test, does not reliably differentiate PDH from adrenal-dependent hyperadrenocorticism.

Interpretation of the results of a LDDST must be based on the laboratory's normal range of cortisol values for the dose and preparation of dexamethasone administered. If the dose of dexamethasone fails to suppress adequately circulating cortisol concentrations in a dog with compatible clinical signs, a diagnosis of hyperadrenocorticism is confirmed. While basal and 8-hour post-dexamethasone samples are most important for interpretation of the test, one or more samples taken at intermediate times (for example, 2, 4, or 6 hours) during the test period may also prove helpful. If a plasma cortisol concentration determined 2–6 hours after dexamethasone injection is suppressed to <40 nmol/L (<1.5 µg/dL), while the 8-hour sample shows escape from cortisol suppression, then a diagnosis of PDH can be made. While some cases of PDH will not suppress at any stage during a LDDST, any suppression during the 8-hour period essentially rules out a diagnosis of adrenal-dependent hyperadrenocorticism. This test is variable and thus not always reliable for diagnosing hyperadrenocorticism in the cat.

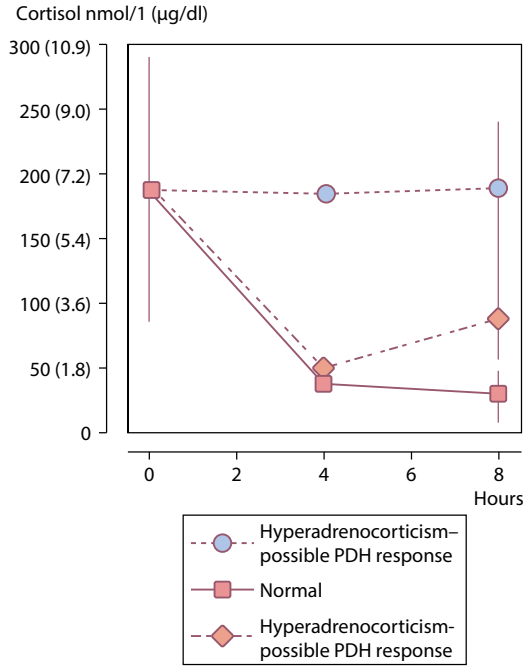


FIGURE 12.71 Low-dose dexamethasone suppression test.

Other Screening Tests

Evaluation of urinary corticoid-to-creatinine ratio rather than the more laborious 24-hour urinary corticoid excretion has been shown to be a simple and valuable screening test that is highly sensitive in detecting hyperadrenocorticism; however, it lacks specificity and is affected by many variables. The test does provide useful information in that values within the reference range make a diagnosis of hyperadrenocorticism highly unlikely.

Endocrine Tests to Differentiate the Cause of Hyperadrenocorticism

The ability to differentiate between PDH and adrenal-dependent hyperadrenocorticism is important in order to provide a better prognosis and the most effective method of management for the disease. An accurate test is therefore required to differentiate pituitary from adrenal causes of hyperadrenocorticism. The protocols for such tests are listed in Table 12.20.

Plasma ACTH Concentration

The determination of plasma ACTH concentrations in the dog provides a reliable test for differentiating pituitary and adrenal causes of hyperadrenocorticism providing sample handling is meticulous. Dogs with adrenal tumors have undetectably low endogenous ACTH concentrations, whereas cases of PDH have normal or high concentrations.

TABLE 12.20 Protocols for endocrine tests to differentiate the cause of hyperadrenocorticism

High-dose dexamethasone suppression test
– Collect 3 mL serum or plasma sample for cortisol determination
– Inject 0.1 mg/kg (although some authors recommend 1.0 mg/kg, especially for cats; see ahead given in the text) of dexamethasone IV
– Collect two post-dexamethasone samples, one at 4 hours and a second at 8 hours after the dexamethasone
Plasma endogenous ACTH concentration
– Blood (5 mL) is collected into a cooled plastic EDTA tube and centrifuged at 4°C immediately
– The plasma should then be harvested and stored frozen (at < –20°C) in a plastic tube
– Samples must be transported to the laboratory frozen and kept frozen until assayed (best not send over the weekend or holiday because of inherent delays)
– Stringent and meticulous sample handling is crucial, since hormone activity in the plasma will reduce rapidly, resulting in falsely low values and incorrect interpretation
– The endogenous ACTH assay must be validated for use in dogs, otherwise the test may provide spurious results that could be misleading

High-Dose Dexamethasone Suppression Test

The high-dose dexamethasone suppression test was the most commonly used test for differentiating the cause of hyperadrenocorticism, but it is less accurate than abdominal ultrasonography or plasma ACTH measurements. This test may be indicated in cases where the diagnosis of hyperadrenocorticism has been established by a screening test, but the differentiation between adrenal-dependent hyperadrenocorticism and PDH has not been determined. The high dose of dexamethasone inhibits pituitary ACTH secretion through negative feedback in PDH, thus suppressing serum cortisol concentrations by 50% or more by 4 hours. Adrenocortical tumors are autonomous; therefore, serum cortisol is not suppressed at 4 hours if an adrenocortical tumor is present. However, approximately 20%–30% of PDH cases will not suppress with this test, which limits the utility of the test for distinguishing PDH from ADH cases. In addition, the test does not differentiate adrenocortical adenomas from adrenocortical carcinomas. This test has been recommended for diagnosing hyperadrenocorticism in the cat, but the high dose of dexamethasone can cause or worsen concurrent diabetes mellitus.

Management

Treatment of Pituitary-Dependent Hyperadrenocorticism

Trilostane Therapy

Trilostane (Vetoryl, Dechra) is a short-acting, synthetic steroid analog that competitively inhibits 3 beta-hydroxysteroid dehydrogenase, thus interfering with adrenal steroid biosynthesis. It has been successfully used to treat hyperadrenocorticism in dogs with relatively few adverse effects.

Treatment is initiated at 2–6 mg/kg once daily with food. Although this once-daily treatment regimen is usually effective, there is an increasing body of evidence and experience that starting treatment with lower doses given twice daily results in faster control, a lower rate of adverse events, and lower total daily doses.

The dosage should be adjusted on basis of the clinical signs and the results of the ACTH stimulation test carried out 4 hours after the administration of trilostane. Following the introduction of trilostane therapy, patients should be re-examined, and an ACTH stimulation performed at 10 days and then at 4 weeks, 12 weeks, and thereafter every 3 months or more frequently if problems occur. If the post-ACTH cortisol concentration is <20 nmol/L (<0.7 μg/dL), trilostane should be stopped for 5–7 days and then restarted at a lower dose. If the post-ACTH cortisol concentration is >120 nmol/L (>4.3 μg/dL), the dose of trilostane should be increased. If the post-ACTH cortisol concentration is between 20 and 120 nmol/L (0.7 and 4.3 μg/dL) and the patient appears clinically well controlled, the dose should remain unchanged. If, however, the patient's clinical signs appear poorly or only partially controlled, trilostane may need to be given twice daily.

Minor adverse effects such as mild lethargy, diarrhea, or decreased appetite may occur soon after starting therapy and are usually transient and respond to a reduction in dose. If more serious adverse effects such as vomiting, severe or hemorrhagic diarrhea, or severe depression develop, trilostane should be stopped and prednisolone replacement therapy instigated. Acute adrenal necrosis has been associated with death in a few cases. Hypoadrenocorticism has also been associated with trilostane therapy. The median survival time for dogs with PDH treated with trilostane is 22 months. Trilostane is effective for treating cats with PDH. The starting dose for cats is 1.0 mg/kg per day, and this is subsequently titrated to effect.

Mitotane Therapy

Mitotane (o'p'DDD; Lysodren, Bristol Laboratories) was formerly the treatment of choice for PDH, but many clinicians have since switched to trilostane as their preferred treatment. During its evaluation as an insecticide, mitotane was discovered to have adrenocorticolytic effects. It selectively destroys the zona fasciculata and zona reticularis while tending to preserve the zona glomerulosa.

Mitotane (Bristol Meyers-Squibb) therapy should only be considered once the diagnosis of hyperadrenocorticism has been confirmed. Because of its powerful effects, it should never be used empirically. Before treatment is instigated, the patient's daily water consumption should be measured over at least two consecutive 24-hour periods. If the water intake and appetite are not increased, baseline lymphocyte and eosinophil counts and an ACTH stimulation test are required to monitor the response to therapy.

The author prefers to hospitalize the patient for the initial course of treatment, although many clinicians have dogs treated by their owners at home, with the owners doing the necessary monitoring. Mitotane is given orally with food at a dose rate of 50 mg/kg per day. Concomitant glucocorticoid treatment is not advised, although if the dog is being treated at home, the owner should be given a small supply of prednisolone tablets. Daily mitotane therapy should be continued until any of the following changes are noted:

- The water intake of a polydipsic dog drops to below 60 mL/kg per day.
- The dog takes longer to consume its meal than before treatment or stops eating completely.
- The dog vomits or has diarrhea.
- The dog becomes listless and depressed.

The initial course of mitotane is then stopped and the dog put on maintenance therapy (see ahead given in the text). The importance of close monitoring of the patient during this period cannot be overemphasized.

Mitotane therapy is comparatively safe, and the side effects that commonly occur (e.g., anorexia, vomiting, or diarrhea) are rarely serious providing they are noticed early so that the mitotane can be withheld. Some of the problems occasionally encountered during

treatment are summarized in Table 12.21, together with their suggested management. Mitotane is ineffective in dogs being treated with phenobarbital because the latter drug will enhance mitotane hepatic metabolism.

The majority of dogs with PDH require between 7 and 14 days of treatment, with an average of 10 days, before water consumption drops to below 60 mL/kg per day. If the dog is not polydipsic or polyphagic, treatment should continue until the lymphocyte count is above 1.0×10^9 cells per liter or the eosinophil count is above 0.3×10^9 cells per liter. However, the best method of evaluating treatment is by use of the ACTH stimulation test. In adequately treated cases, the basal and ACTH stimulated serum cortisol concentrations should be <120 nmol/L (<4.3 µg/dL). If the serum cortisol concentrations exceed 200 nmol/L (7.2 µg/dL) with ACTH stimulation, further mitotane should be administered until the cortisol concentrations are adequately suppressed. A few dogs respond in 2–3 days, and occasionally others require more than 60 consecutive days of treatment. It is important to emphasize that each dog must be treated as an individual if treatment is to be successful.

Having produced sufficient adrenocortical damage with daily mitotane treatment, it is important to continue therapy, albeit at a lower dose. Otherwise, the zona glomerulosa will regenerate a hyperplastic zona fasciculata and zona reticularis, and the clinical signs will recur. Mitotane is given at a dose of 50 mg/kg per week with food. Cases that are well controlled may sleep for a few hours after the weekly dose, and for that reason, it is often recommended that the treatment is given in the evening. More profound depression or weakness requires re-evaluation and possibly a reduction of the maintenance dose. Failure to control the polydipsia may require an increased dose of mitotane (Table 12.21).

Treated dogs should be re-examined 6–8 weeks after completion of the initial therapy, unless there are any problems. Marked improvement should be noted at this time. The most obvious response is a rapid reduction in water intake, urine output, and appetite, and this is usually obvious at the end of the initial course of therapy. Muscle strength and exercise tolerance improve over the first 3–4 weeks. Skin and hair coat changes take longer, and the progress is variable. The skin and alopecia may deteriorate markedly before improving; alternatively, there may be a gradual and noticeable resolution of the dermatologic signs. Although improvement should be noted at 8 weeks, the skin and hair coat may not return to normal for 3–6 months (Figures 12.72 and 12.73). A few dogs have dramatic changes in coat color following successful therapy.

Re-examination every 3–6 months is recommended for the remainder of the animal's life. Relapses and episodes of overdosage do occur, and reassessment of adrenal reserve by ACTH stimulation testing is indicated. Relapses may require a short course of daily mitotane therapy or an increase in the maintenance dosage. Overdosage requires reassessment by an ACTH stimulation test and a reduction of the maintenance dose. The median survival time of treated dogs is 30 months with a range of a few days to over 7 years.

TABLE 12.21 Possible problems arising from mitotane therapy and their management

Problem	Management
Vomiting or anorexia within the first 3 days of treatment (gastric irritation)	– Discontinue mitotane and reassess patient – Divide dose and give 2–4 times per day
Profound weakness, depression, and anorexia usually around 4th or 5th day of treatment	– Discontinue mitotane and reassess patient – Check sodium and potassium levels and institute prednisolone (0.2 mg/kg per day) – Reassess ACTH stimulation test – Start maintenance therapy with mitotane
Acute onset of neurologic signs (due to sudden expansion of the pituitary tumor)	– Reassess patient – Continue mitotane unless the dog is anorexic, vomiting, or depressed – Give prednisolone (2.0 mg/kg per day) or dexamethasone (0.1 mg/kg per day) and decrease dose slowly once neurologic signs have resolved
Failure to resume normal water intake	– Recheck urinalysis and blood urea – Reassess ACTH stimulation test – Increase mitotane by 50% if post-ACTH cortisol level is >200 nmol/L (>7.2 µg/dL)
Failure to regrow hair	– Reassess ACTH stimulation test – Determine baseline T4 – Increase mitotane by 50% if post-ACTH cortisol level is >200 nmol/L (>7.2 µg/dL) – If <120 nmol/L (<4.3 µg/dL), perform a TRH/TSH stimulation test
Excessive depression or weakness related to weekly maintenance therapy	– Reassess patient – Check sodium and potassium levels – Repeat ACTH stimulation test – If cortisol level post-ACTH is <15 nmol/L (<0.5 µg/dL), reduce maintenance dose or give every other week



FIGURE 12.72 Uncontrolled hyperadrenocorticism prior to mitotane therapy. An 8-year-old Cocker Spaniel before medical treatment.



FIGURE 12.73 Response to mitotane therapy. Four months post-mitotane treatment in the same 8-year-old Cocker Spaniel.

Mitotane has been shown to be ineffective in the cat because of its rapid hepatic metabolism.

Other Therapeutic Options for Pituitary-Dependent Hyperadrenocorticism

- L-deprenyl (selegiline hydrochloride [Somerset Pharmaceuticals]) is a monoamine oxidase inhibitor that inhibits ACTH secretion by increasing dopaminergic tone to the hypothalamic–pituitary axis. The use of L-deprenyl for treatment of hyperadrenocorticism has been evaluated in dogs. Although the effectiveness of treatment is variable, one major advantage of L-deprenyl is the lack of any severe adverse effects, including iatrogenic hypoadrenocorticism. Treatment is initiated at a dosage of 1 mg/kg daily. If an inadequate response is seen after 2 months, the dosage is increased to 2 mg/kg per day. If this dosage also proves ineffective, alternative treatment is required. However, if the treatment with L-deprenyl is effective, daily treatment should be continued for the remainder of the dog's life. Response to treatment is evaluated by the resolution of clinical signs, since there is minimal measurable endocrinological improvement. More than 50% of dogs fail to respond adequately to L-deprenyl.
- Ketoconazole (LGM Pharma) has a reversible inhibitory effect on glucocorticoid synthesis while having minimal effects on mineralocorticoid production. Ketoconazole has been used effectively to control hyperadrenocorticism in dogs, but it is not effective in cats. However, ketoconazole is not uniformly efficacious in dogs, and between one-third and one-half of all dogs treated fail to respond adequately. The initial recommended dosage of ketoconazole is 10 mg/kg q.12 h. for 14 days. Alternatively, treatment is initiated at 5 mg/kg q.12 h. for the first 7 days to assess drug tolerance, then increased to 10 mg/kg. The efficacy of the initial 14-day course of treatment is determined by an ACTH stimulation test. To ensure adequate control of hyperadrenocorticism, both the pre- and post-ACTH serum cortisol concentrations must be lowered into the basal reference range. If the serum cortisol concentrations remain above this range, the dosage is increased to 15 mg/kg q.12 h., and an ACTH response test repeated in 14 days.
- Bilateral adrenalectomy has been employed successfully, but it involves the risk of putting an ill animal with a compromised immune system and poor wound healing through a difficult surgical procedure. Bilateral adrenalectomy used to be the recommended treatment for feline hyperadrenocorticism despite its accompanying postoperative morbidity. Patients treated by this approach require lifelong treatment for hypoadrenocorticism. More recently, trilostane has been found to be an effective treatment option for treating PDH in the cat.
- Pituitary irradiation is indicated for dogs with neurological signs associated with pituitary tumors. CT or MRI of the brain is required to plan the treatment protocol. Radiotherapy using megavoltage irradiation from a linear accelerator is required to penetrate to the depth of the pituitary gland without seriously injuring overlying soft tissues. Most treatment protocols involve the administration of 40–50 Gy in 3–4 Gy fractions, since it has been shown that increasing the number of fractions and reducing the dose per fraction, whilst keeping the total dose at the low end of the range, can give increased survival times. There is often a dramatic response, although in some cases improvement takes several weeks. The resolution of neurological signs parallels the reduction in size of the tumor, which can continue to decrease for a year or more after the completion of the radiotherapy. Reduction in ACTH secretion by the tumor is less predictable, occurring in only about 20% of cases and, if it does occur, may not be evident for 6–12 months after therapy. Therefore, medical management of hyperadrenocorticism with trilostane or mitotane is indicated, at least initially.
- Hypophysectomy has been successfully performed in the dog for the treatment of PDH using the transsphenoidal approach. The operation is technically difficult and should only be carried out by a surgeon with considerable skill and experience of the technique and the immediate aftercare. Otherwise, it is associated with high morbidity and mortality.

Treatment of Adrenal-Dependent Hyperadrenocorticism

Dogs diagnosed as having adrenal-dependent hyperadrenocorticism carry the best prognosis if the tumor can be completely removed surgically, although mitotane (for dogs) or trilostane (for dogs and cats) therapy is also recommended.

Unilateral Adrenalectomy

This procedure requires considerable expertise because of the complex anatomy. Preoperative staging using ultrasonography and radiography or CT is essential. Adrenalectomy is best performed via a ventral midline laparotomy (Figure 12.74). It should only be performed by experienced surgeons, as perioperative mortality is high. Postoperative support is important, as the contralateral adrenal cortex will be atrophic and unable to respond to the stress. Replacement glucocorticoid and mineralocorticoid therapy may, therefore, be required

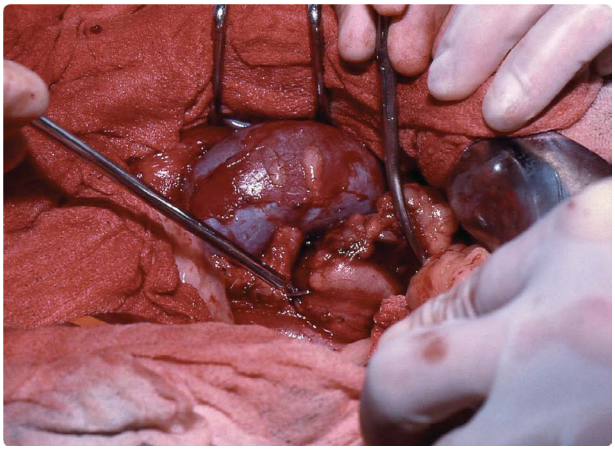


FIGURE 12.74 Surgical view of an adrenocortical carcinoma that had a spontaneous bleed into the retroperitoneal space. (*Courtesy of M. Schaer.*)

for 7–10 days postoperatively. Even with experienced surgeons, there is a high morbidity and mortality rate, and perioperative mortality can be as high as 30%. The median survival time is around 2 years, with some dogs surviving for longer than 4 years. Heparin has been recommended for some dogs in the perioperative period because of hypercoagulability.

Mitotane Therapy

Mitotane is effective and relatively safe in dogs with adrenal-dependent hyperadrenocorticism. Dogs with adrenal tumors, however, tend to be more resistant to mitotane than dogs with PDH. Generally, dogs with adrenal-dependent hyperadrenocorticism require higher daily induction doses (50–75 mg/kg per day) and a longer period of induction (>14 days) than dogs with PDH. Frequent monitoring of treatment by ACTH stimulation testing is important to ensure adequate control of the hyperadrenocorticism. Maintenance doses are also generally higher (75–100 mg/kg per week) and, again, frequent monitoring of the cortisol response to ACTH stimulation is required to maintain optimal control of the disease. Adverse effects of treatment are similar to those described for PDH. Those dogs requiring higher dose rates tend to be more prone to adverse effects. The adrenal tumor and metastatic mass will often reduce in size due to the cytotoxic effects of mitotane, but in other cases, the tumor will continue to grow despite increasing doses of mitotane. The median survival time is 11 months, with a range from a few weeks to more than 5 years.

Trilostane Therapy

Trilostane is also effective and relatively safe in dogs and cats with adrenal-dependent hyperadrenocorticism. The dose of trilostane needs to be tailored to the individual patient with an adrenal tumor on the basis of the results of regular ACTH stimulation testing. There is a tendency for the dose to increase as the tumor continues to grow. Survival times similar to mitotane therapy (in dogs) for adrenal tumors have been reported.

PRIMARY HYPERALDOSTERONISM

Definition/Overview

Primary hyperaldosteronism is characterized by excessive autonomous secretion of aldosterone from one or both adrenal glands resulting in clinical signs relating to hypertension and/or hypokalemia. It is a disease of middle-aged to old-aged cats, with a mean age of 12 years. There is no breed or sex predisposition. The condition is rare in dogs.

Etiology

Adrenocortical tumors are the most common cause of primary hyperaldosteronism in cats. There is an approximately equal incidence of adenomas and carcinomas, with the right and left adrenal glands being affected with almost equal frequency. Rarely, bilateral tumors have been reported. More recently, primary hyperaldosteronism has been recognized in association with adrenocortical hyperplasia.

Pathophysiology

Increased autonomous secretion of aldosterone leads to excessive sodium and water retention, with resultant hypertension, and excessive potassium secretion leading to hypokalemia. The elevated plasma aldosterone and increased circulating blood volume have a negative feedback effect on renin release, resulting in reduced plasma renin activity.

Clinical Presentation

The most common presenting sign is muscular weakness due to the hypokalemia. This can range from mild weakness and lethargy to severe generalized weakness, ataxia, depressed spinal reflexes, and flaccidity. Ventroflexion of the neck may be noted (Figure 12.75). Blindness, which may be sudden or gradual in onset, is due to systemic hypertension and usually results from retinal detachment and intraocular hemorrhage. Systemic hypertension can also lead to left ventricular hypertrophy and cardiac murmurs. Impaired renal function is common, and many cats also exhibit polydipsia and polyuria.



FIGURE 12.75 A Burmese cat showing ventroflexion of the neck due to hypokalemia.

TABLE 12.22 Differential diagnosis of feline hypokalemia

Decreased intake
– Anorexia
– Potassium-deficient intravenous fluids
– Potassium-deficient diet
Potassium translocation
– Metabolic alkalosis
– Insulin administration
– Diabetic ketoacidosis
– Periodic hypokalemia (Burmese cats)
Increased gastrointestinal loss
– Vomiting
– Diarrhea
Increased renal loss
– Polyuria/osmotic diuresis
– Chronic kidney disease
– Acute kidney injury (polyuric phase)
– Diuretic administration (loop or thiazide diuretics)
– Renal tubular acidosis
– Primary hyperaldosteronism
– Liver failure
– Congestive heart failure

Note: Hypokalemia in some diseases may have more than one mechanism.

Differential Diagnosis

The differential diagnoses of hypokalemia and hypertension are given in Tables 12.22 and 12.23, respectively.

Diagnosis

The most consistent routine laboratory finding in primary hyperaldosteronism is hypokalemia. Some cases may also have an increased plasma creatine kinase concentration caused by hypokalemic myopathy with rhabdomyolysis. The diagnosis of primary hyperaldosteronism is based on demonstrating the presence of an adrenal tumor or bilateral adrenal hyperplasia together with an elevated plasma aldosterone concentration with a concomitant decreased plasma renin activity.

Adrenal tumors can usually be identified using ultrasonography (Figure 12.76). Abdominal ultrasonography can also be used to identify metastases and evidence of invasion of surrounding structures, particularly the caudal vena cava. CT and MRI have also been used to identify these changes.

Plasma aldosterone concentrations are usually raised to between 2 and 30 times the reference range. Although ACTH stimulation has been described when measuring plasma aldosterone, there is no clear evidence of improved diagnostic performance following ACTH stimulation. It should be noted, however, that raised aldosterone concentrations are not pathognomonic for primary hyperaldosteronism and that diseases that activate the renin–angiotensin–aldosterone system (RAAS), especially chronic kidney disease and CHF, will cause secondary hyperaldosteronism.

TABLE 12.23 Differential diagnosis of feline hypertension

– Chronic kidney disease
– Hyperthyroidism
– Diabetes mellitus
– Hyperaldosteronism
– Hyperadrenocorticism
– Pheochromocytoma
– Chronic anemia
– Liver disease

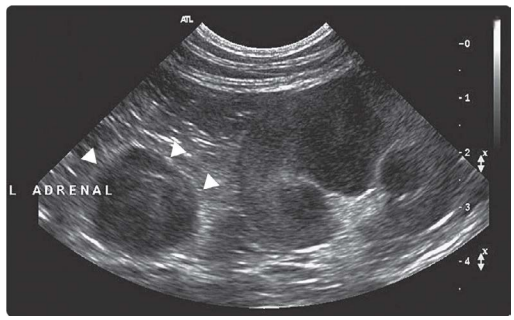


FIGURE 12.76 Ultrasonogram of an adrenal tumor (arrowheads) in a Domestic Longhair cat with primary hyperaldosteronism.

In primary hyperaldosteronism, plasma aldosterone is raised, which exerts a negative feedback effect on renin, resulting in reduced plasma renin activity, resulting in a raised plasma aldosterone-to-renin ratio as distinct from secondary hyperaldosteronism where the RAAS has been activated resulting in a lowered plasma aldosterone-to-renin ratio. Adrenal hyperplasia can only be diagnosed by demonstrating a raised plasma aldosterone-to-plasma renin activity ratio. When renin assays are unavailable, the combination of clinical signs and elevated serum aldosterone concentration in the absence of any demonstrable adrenal mass is highly suggestive of adrenocortical hyperplasia as the cause of the hyperaldosteronism.

Management

Initial therapy should be aimed at controlling hypokalemia and hypertension. Hypokalemia can be treated with potassium supplementation and the competitive aldosterone antagonist spironolactone. Hypertension can usually be controlled with amlodipine, telmisartan, and beta-blockers. Treatment with these drugs can be continued for life, and survival times from 4 months to 2.5 years have been reported. Medical management is the recommended treatment for cases associated with adrenal hyperplasia.

Although unilateral adrenalectomy is the treatment of choice for adrenal tumors, perioperative mortality is relatively high, with intraoperative and postoperative hemorrhage the most common cause of death. However, those patients who survive surgery frequently live for more than a year.

PHEOCHROMOCYTOMA

Definition/Overview

Tumors of the adrenal medulla (pheochromocytomas) are rare in dogs and have only been reported rarely in cats. They are usually unilateral, benign, slow-growing

tumors that may reach a considerable size. Rarely, they are malignant and may invade the caudal vena cava or metastasize to lung, liver, or bone. Pheochromocytomas may secrete excessive amounts of catecholamines.

Pathophysiology

The physiologic effects of catecholamines secreted by pheochromocytomas account for many of the diverse clinical signs. The presence of the tumor mass may also contribute to the clinical presentation.

Clinical Presentation

Clinical signs of a pheochromocytoma may relate to an abdominal mass compressing adjacent structures or to the secretion of catecholamines. Clinical signs related to tumor size might include a palpable abdominal mass, ascites, and hindlimb weakness. Secretion of catecholamines may be intermittent or persistent and can cause hypotension or hypertension, tachycardia, tachyarrhythmias with episodic weakness and trembling, head pressing, or seizures. Epistaxis and retinal hemorrhages may also be noted. The clinical signs vary depending on whether an excess of epinephrine or norepinephrine is predominant. In some cases, there may be no reported clinical signs, and an adrenal mass is found incidentally, usually during abdominal ultrasonography.

Differential Diagnosis

Causes of episodic weakness (Table 12.24).

TABLE 12.24 Differential diagnosis of episodic weakness

Cardiovascular disorders
- Bradyarrhythmia
- Tachyarrhythmia
- Congenital heart disease (e.g., aortic or pulmonic stenosis, tetralogy of Fallot, reverse shunting PDA)
- Acquired heart disease (e.g., valvular, myocardial, pericardial)
- Heartworm disease (dirofilariasis, angiostrongylosis)
- Vasovagal syncope
- Vasodilation
- (Aortic) thromboembolism

Respiratory disorders
- Laryngeal paralysis
- Brachycephalic airway disease
- Tracheal collapse
- Severe coughing
- *Filaroides osleri*
- Pulmonary disease
- Pleural effusions
- Thoracic masses
- Hematologic disorders

Anemia
- Myeloproliferative disorders
- Polycythemia
- Hyperviscosity syndrome
- Hemoglobinopathies
- Pyrexia of unknown origin
- Orthopedic disorders

TABLE 12.24 (*Continued*)

Degenerative joint disease, particularly hips or stifles
- Polyarthritis—various types

Neuromuscular disorders
- Myasthenia gravis
- Polymyositis
- Hereditary myopathy of Labrador Retrievers
- Sex-linked muscular dystrophy—Irish Terriers, Golden
- Retrievers
- Myotonia in Chow Chows, Staffordshire Terriers
- Malignant hyperthermia
- Mitochondrial myopathies
- Exertional myopathy (rhabdomyolysis)

Neurologic disorders
- Congenital or acquired spinal disorders, including wobbler syndrome
- Epilepsy (various causes)
- Vestibular disease
- Cerebellar disorders
- Thiamine deficiency
- Congenital disorders (e.g., hydrocephalus)
- Acquired disorders (e.g., old dog encephalitis, cerebral vascular accident, tumors)
- Lysosomal storage diseases
- Giant axonal neuropathy
- Progressive axonopathy—Boxer
- Tetanus
- Botulism
- Narcolepsy/cataplexy—Dobermann, Poodle, Labrador Retriever
- Generalized tremor
- Jack Russell Terrier ataxia
- Scottie cramp—also in the Norwich and Jack Russell Terrier, Dalmatian
- Episodic falling in the Cavalier King Charles Spaniel

Metabolic disorders
- Hepatic encephalopathy
- Uremic encephalopathy
- Hyperglycemia
- Hypoglycemia
- Hyponatremia
- Hyperkalemia
- Hypokalemia
- Hypercalcemia
- Hypocalcemia
- Hypermagnesemia
- Hypomagnesemia
- Acidosis
- Hyperthermia (heatstroke)
- Hypoxia
- Shock

Endocrine disorders
- Insulinoma
- Hyperadrenocorticism—myotonia
- Hypoadrenocorticism
- Diabetic ketoacidosis
- Hypoparathyroidism
- Hypothyroidism
- Pheochromocytoma
- Primary hyperaldosteronism
- Diabetic ketoacidosis

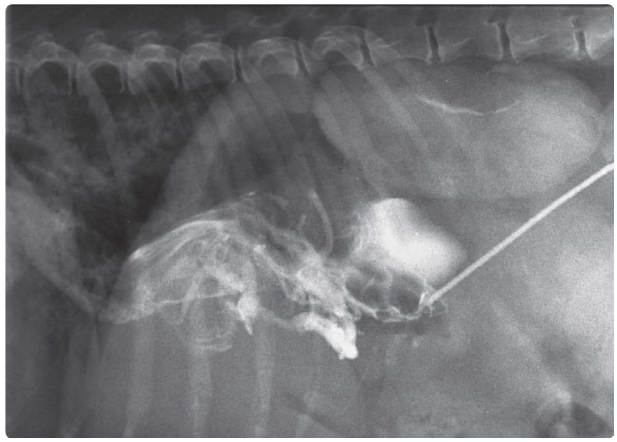


FIGURE 12.77 Contrast venogram radiographic study showing abnormal dispersion of the contrast medium in the posterior vena cava. This was caused by a pheochromocytoma invading the vessel. (*Courtesy of M. Schaer.*)

Diagnosis

A diagnosis of pheochromocytoma should be suspected in any unexplained case of episodic weakness. Radiographic and ultrasonographic examinations will often reveal a mass in the adrenal area, although cross-sectional imaging with CT or MRI have also been used (Figures 12.77–12.79). Confirmation of functionality requires quantification of plasma catecholamines and their metabolites or urinary excretion of catecholamines and their metabolites, but these tests are not widely available, and the results can be unreliable, if the tumor only intermittently secretes catecholamines.

Abdominal and thoracic CT with contrast should be performed before adrenalectomy, as the presence of vascular or tissue invasion and distant metastasis can be more readily identified with CT than with any other imaging modality.

Management

Surgical removal (Figures 12.80 and 12.81) is the treatment of choice, but this should only be performed by

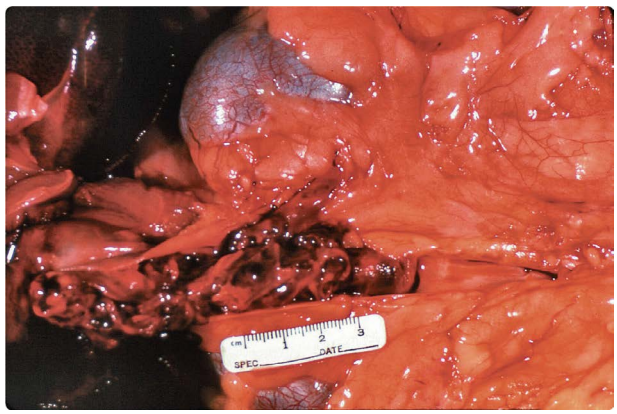


FIGURE 12.78 The pathology at postmortem is shown. (*Courtesy of M. Schaer.*)

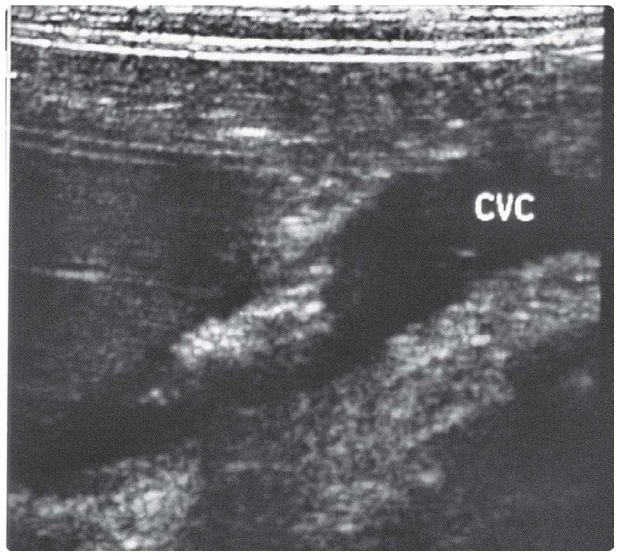


FIGURE 12.79 Ultrasonogram of a dog with a pheochromocytoma invading the postcava. (*Courtesy of M. Schaer.*)

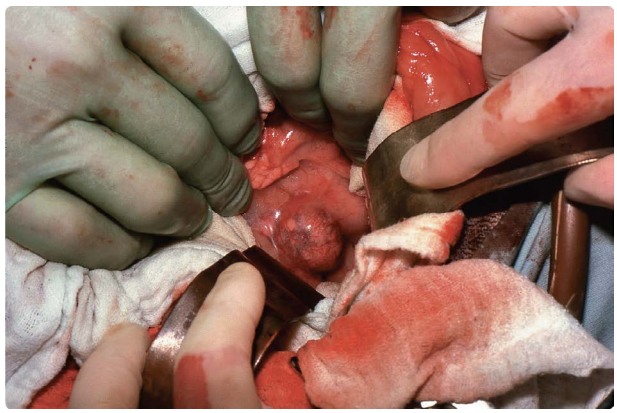


FIGURE 12.80 Surgical view of a well-localized and noninvasive pheochromocytoma. (*Courtesy of M. Schaer.*)

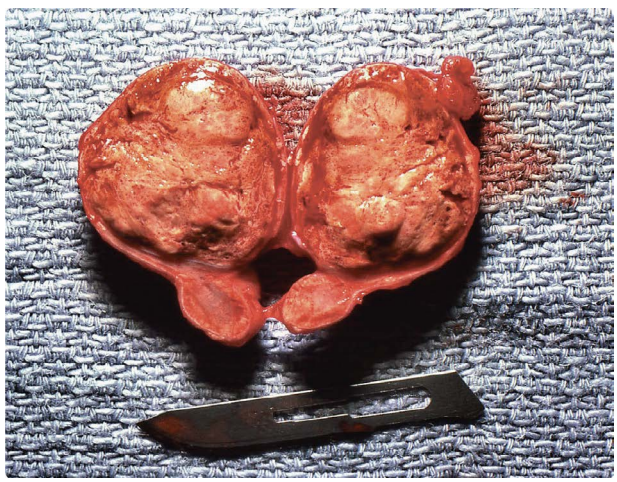


FIGURE 12.81 Excised noninvasive pheochromocytoma from Figure 12.80. (*Courtesy of M. Schaer.*)

experienced surgeons, since excessive handling of the tumor during surgery may provoke massive secretion of catecholamines, and the tumors tend to be invasive. Phentolamine, an alpha-adrenergic antagonist for IV use, can be used at a dose of 0.02–0.1 mg/kg to lower blood pressure while manipulating the tumor. However, phenoxybenzamine (0.2–1.5 mg/kg p.o. q.12 h.) may be the drug of choice due to its long duration of action. Improved surgical survival has been associated with the use of oral phenoxybenzamine treatment for 2 weeks prior to surgery. Lidocaine or propranolol can be administered intravenously as necessary during surgery to control tachycardia or tachyarrhythmias.

DIABETES MELLITUS

Definition/Overview

Diabetes mellitus is a heterogeneous syndrome in the dog and cat rather than a single disease entity. It is characterized by a relative or absolute deficiency of insulin secretion by the beta cells of the islets of Langerhans in the pancreas.

Etiology

Carbohydrate metabolism, and in particular blood glucose concentration, is controlled by the balance between the action of catabolic hormones (e.g., glucagon, cortisol, catecholamines, and GH) on the one hand and the principal anabolic hormone, insulin, on the other.

Pathophysiology

A relative or absolute deficiency of insulin results in decreased utilization of glucose, amino acids, and fatty acids by peripheral tissues, particularly liver, muscle, and adipose tissue. Failure of glucose uptake by these cells leads to hyperglycemia. Once the renal threshold for glucose reabsorption is exceeded, an osmotic diuresis ensues with loss of glucose, electrolytes, and water in the urine. A compensatory polydipsia prevents the animal becoming dehydrated. The loss of glucose leads to catabolism of the body's reserves, especially of fats. Excessive fat catabolism leads to the production and accumulation of ketone bodies and the onset of diabetic ketoacidosis (Figure 12.82). In diabetic ketoacidosis, the patient is unable to maintain an adequate fluid intake and becomes rapidly dehydrated due to the uncontrolled osmotic diuresis. The dehydration and acidosis require emergency care if the animal is to survive.

In humans, diabetes is classified as type 1 insulin-dependent diabetes mellitus and type 2 noninsulin-dependent diabetes mellitus. This classification has not proved very useful in veterinary medicine, since nearly all dogs with diabetes mellitus require insulin therapy regardless of the underlying etiology. However, in cats, type 2 diabetes mellitus is the most common form of the disease and is characterized by variable loss of insulin secretory capacity and insulin resistance. Classifying diabetes mellitus into primary and secondary causes is of more use clinically in the dog and cat (Table 12.25). In secondary diabetes, which is caused by peripheral insulin resistance, there is initially a compensatory increase in insulin secretion, but after a period of time, the islet cells become exhausted, the beta cells are destroyed, and their function is permanently lost.

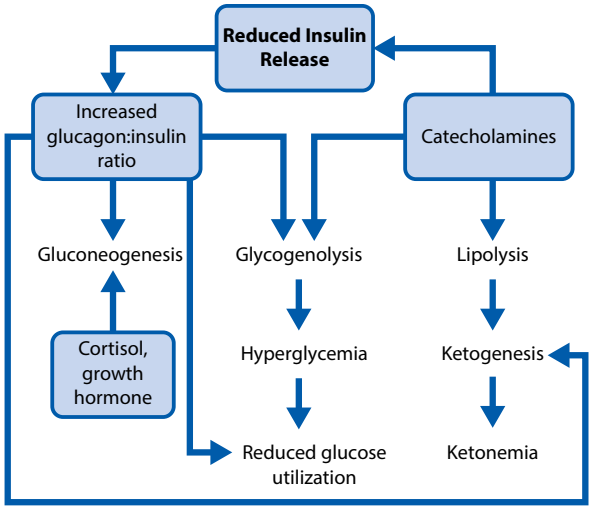


FIGURE 12.82 Etiology of diabetic ketoacidosis.

Clinical Presentation

Diabetes mellitus is a disease of middle-aged dogs, with a peak incidence around 8 years of age. Genetic predisposition to diabetes has been found in Keeshonds and Samoyeds. Cairn Terriers, Tibetan Terriers, Poodles, and Dachshunds may also be overrepresented and certain breeds, e.g., Boxers appear to be underrepresented. Entire bitches are more frequently affected than male dogs due to diestrus diabetes, which is due mainly to the induction of GH by progesterone but can also be associated with the use of progestogens.

Diabetes mellitus is the second most common endocrine disorder in cats after hyperthyroidism. Its incidence

TABLE 12.25 Etiology of diabetes mellitus in the dog and cat

Primary islet cell degeneration (insulin-deficient diabetes mellitus)
– Islet cell destruction (? autoimmune)
– Chronic pancreatitis (beta-cell loss)
– Glucotoxicity
– Amyloidosis
Secondary diabetes mellitus (insulin-resistant diabetes mellitus)
Obesity—causing downregulation of insulin receptors
Antagonism to insulin by counterregulatory hormones
– Hyperadrenocorticism
– Diestrus diabetes (progesterone-induced GH excess [dogs only])
– Acromegaly
– Antagonism to insulin by drug therapy
– Glucocorticoids
– Progestogens



FIGURE 12.83 A 12-year-old Labrador Retriever with diabetes mellitus. Note the weight loss.

appears to be increasing, probably due to an increase in obesity in the cat population. Several risk factors have been identified, including age, obesity, neutering, and sex. The disease is seen in middle-aged to older cats and appears to be more common in males than females and in neutered cats rather than entire cats.

Polyuria, polydipsia, increased appetite, and weight loss develop over a few weeks in uncomplicated cases (Figure 12.83). In entire bitches, this usually occurs in the diestrus phase of the estrous cycle. Hepatomegaly, muscle wasting, and infections of the urinary or respiratory tract may be noted on clinical examination. Ulcerative skin lesions and cutaneous xanthomata have occasionally been reported. If the diabetes remains uncontrolled, an accumulation of ketone bodies may occur, which causes metabolic acidosis and leads to depression, anorexia, vomiting, and rapid dehydration (Figure 12.84). Coma and death may result from severe hypovolemia and circulatory collapse.

Differential Diagnosis

Primary renal glycosuria, stress, hyperadrenocorticism, pancreatitis, renal insufficiency, exocrine pancreatic neoplasia, acromegaly, diestrus, pheochromocytoma, postprandial hyperglycemia.



FIGURE 12.84 A 3-year-old Cavalier King Charles Spaniel in a diabetic ketoacidotic coma.

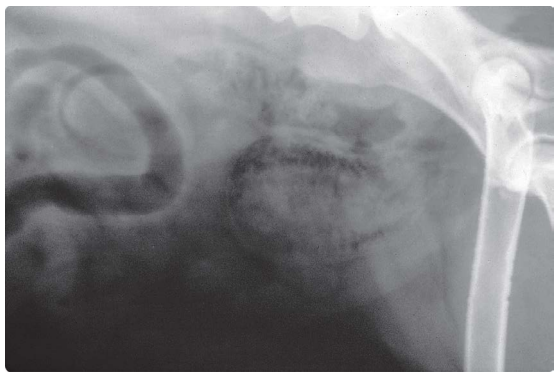


FIGURE 12.85 Abdominal radiograph of a diabetic dog showing emphysematous cystitis. (*Courtesy of M. Schaer.*)

Diagnosis

Urinalysis reveals persistent glycosuria and often ketonuria. Despite the high solute load in the urine, which would tend to increase the SG of the urine, many older dogs and cats may have impaired renal concentrating power, and thus, the SG of the urine is variable, typically between 1.015 and 1.045. Bacterial cystitis is common and occasionally may involve Gram negative gas-producing organisms, which can cause emphysematous cystitis (Figure 12.85).

Plasma biochemistry reveals hyperglycemia (>9 mmol/L [>162 mg/dL]) and hyperlipidemia. In some patients, the blood will be lactescent due to lipemia. Liver enzymes are usually raised, and liver function tests such as bile acid concentrations may be abnormal. In cases where diabetes is associated with pancreatitis, canine or feline-specific pancreatic lipase immunoreactivity may be elevated.

Diabetic ketoacidosis is often triggered by an underlying condition such as systemic inflammatory disease (pancreatitis, urinary tract infection, pyometra, or pneumonia) or a condition that causes dehydration. In diabetic ketoacidosis, there are serious derangements in fluid, electrolyte, and acid–base status. The most frequent abnormalities are prerenal azotemia, hyponatremia, hypokalemia, and acidosis.

Management

Treatment can be divided into the acute management of diabetic ketoacidosis and the stabilization of the uncomplicated diabetic. The ketoacidotic dog can be stabilized as for the uncomplicated case, once it has started to feed normally.

Acute Management of Diabetic Ketoacidosis

Although the healthy (still eating and drinking) ketotic diabetic can usually be managed conservatively without fluid therapy or intensive care, diabetic ketoacidosis characterized by hyperglycemia, ketonemia, metabolic acidosis, dehydration, and electrolyte imbalance is a medical emergency that is associated with a high mortality. Treatment should consist of replacement of fluid and electrolytes, reduction of blood glucose concentrations, correction of acidosis, and identification

of precipitating causes. A treatment protocol is given in Table 12.26, but diagnosis and treatment of the underlying trigger is also important.

Fluid Therapy

IV replacement of fluid and electrolytes is essential for the successful management of diabetic ketoacidosis. Unless serum electrolytes suggest otherwise, 0.9% sodium chloride or lactated Ringer's solution is the initial fluid of choice. The fluid deficit is usually about 10% of body weight and this should be replaced over a period of 24–48 hours. Sodium chloride may be alternated with lactated Ringer's solution or, if the blood glucose falls below 10 mmol/L (180 mg/dL), a solution containing 0.18% sodium chloride and 4% glucose (or some other comparable isotonic crystalloid–glucose solution). Urine output should be measured and, if possible, a central venous catheter used so that central venous pressure can be monitored during fluid therapy.

TABLE 12.26 Treatment protocol for diabetic ketoacidosis in the dog

Intravenous fluid and electrolyte replacement
- 0.9% sodium chloride initially then alternate with lactated Ringer's solution
- Monitor urine output and, if possible, central venous pressure

Insulin therapy
- *Low-dose insulin infusion:* Add 25 units soluble (regular) insulin or lispro to 500 mL 0.9% sodium chloride solution or 2.5 units in a 50 mL syringe (0.05 U/mL) and infuse at a rate of 0.1 U/kg/h through a separate IV catheter
- Use of an infusion pump, syringe driver, or pediatric burette is helpful in controlling the rate of infusion
- Monitor blood glucose concentration every 2 hours
- *Soluble insulin injection:* A dose of 1 U/kg is divided, and one-quarter of the dose is given IV and three-quarters IM
- The dose is repeated every 4–6 hours
- Monitor blood glucose concentration every 2 hours

Continue intravenous fluid and electrolyte replacement
- Continue alternating 0.9% sodium chloride with lactated Ringer's solution while blood glucose remains >10 mmol/L (>180 mg/dL)
- Use 0.18% sodium chloride with 4% glucose solution when blood glucose falls to <10 mmol/L (<180 mg/dL)

Potassium supplementation
- Ideally, supplementation with potassium should be based on serum potassium concentrations, in the absence of serum potassium measurements, add 20 mmol/L (20 mEq/L) of potassium chloride to each 500 mL bag of IV fluid solution
- Two to three times more potassium will be necessary with potassium concentrations <3.0 mmol/L. The rate of administration should not exceed 0.5 mmol/kg/h, although in dire circumstances (potassium <2.0 mmol/L), the rate can be increased to 1.5 mmol/kg/h with simultaneous ECG monitoring
- This treatment will be safe providing the patient has adequate urine production

Phosphate supplementation
- Phosphate shifts in the same way as potassium
- Hypophosphatemia is only likely to occur in severe diabetic ketoacidosis but can be severe (<0.5 mmol/L [0.5 mEq/L])
- Dose of 0.01–0.03 mmol/kg/h of potassium phosphate in calcium-free fluid (e.g., normal saline) is required if hypophosphatemia is detected
- In cases of severe hypophosphatemia, the dose may be increased to 0.12 mmol/kg/h

Correction of acidosis
- Bicarbonate therapy is not necessary provided renal function has been re-established
- It is only indicated in life-threatening (pH <7.0) acidosis, and only one-third of the calculated replacement dose should be used to prevent excessive blood HCO_3^- concentrations

Antibiotic therapy
- If indicated

Insulin Therapy

Soluble insulin ("regular") or lispro (a genetically engineered human analog insulin) should be used in the treatment of diabetic ketoacidosis. Although intermittent administration using the IV and IM routes has been used, low-dose IV insulin infusion (0.1 U/kg/h) is effective and appears to be associated with fewer side effects, such as hypokalemia and hypoglycemia. Low-dose IV insulin infusion provides a steady, gradual reduction in blood glucose and ketone concentrations and is less likely to cause the increases in glucagon, cortisol, and GH that can occur with intermittent bolus administration of insulin.

Blood glucose should be monitored every 2 hours. Glucose-containing fluids should be introduced when the blood glucose concentration falls below 10 mmol/L (180 mg/dL), and the insulin infusion should be stopped when the blood glucose reaches 6 mmol/L (108 mg/dL). Once the insulin infusion is halted, blood glucose concentrations will increase, so that further infusion of insulin may be required if the patient is not eating, or a longer-acting insulin preparation may be introduced if its appetite has returned.

Potassium Supplementation

A deficit in total body potassium is usually masked by the acidosis, which sometimes causes potassium to move extracellularly. Serum potassium concentration can decrease rapidly as renal function improves and insulin therapy causes potassium to move back into the cells. Although hypokalemia is less likely to occur with low-dose insulin infusion, replacement therapy should be started within a few hours of instigating fluid and insulin therapy. In the absence of serum potassium measurements, 20 mmol of potassium chloride should be added to every 500 mL of IV fluid solution. Insulin treatment is best delayed for several hours if the patient is initially hypokalemic in order to avoid a further lowering of the serum potassium concentration (see Table 12.26).

Phosphate Supplementation

Phosphate moves between the intracellular and extracellular compartments in the same way as potassium. Hypophosphatemia can cause hemolytic anemia, weakness, ataxia, and seizures. Phosphate supplementation is only usually required in dogs and cats with severe diabetic ketoacidosis. Potassium phosphate

(0.01–0.03 mmol/kg/h IV) is recommended to correct hypophosphatemia.

Bicarbonate Therapy

The use of sodium bicarbonate to correct the acidosis in diabetic ketoacidosis is controversial. Rapid correction of the acidosis with bicarbonate can lead to metabolic alkalosis, tissue anoxia due to a shift to the left of the hemoglobin–oxygen dissociation curve, and paradoxical cerebral acidosis because carbon dioxide crosses the blood–brain barrier more rapidly than bicarbonate ions. For these reasons, bicarbonate should be used only in life-threatening acidosis (arterial pH <7.0). Provided normal renal function is restored and adequate fluid therapy is given, the acidosis will resolve without bicarbonate administration.

Antibiotic Therapy

Initially, broad-spectrum antibiotic therapy might be preferred by some clinicians because bacterial infection is a common precipitating factor for diabetic ketoacidosis, and the use of IV and urinary catheters may predispose the patient to infection.

Concurrent Problems

Other common concurrent illnesses in the dog and cat with diabetic ketoacidosis include pancreatitis, renal failure, CHF, hyperadrenocorticism, and pyometra. Entire bitches may be resistant to insulin therapy during the diestrus phase of their estrous cycle, thus requiring ovariohysterectomy as soon as the patient is physiologically stable during the first 2–3 days of hospitalization.

Stabilization of Uncomplicated Diabetes Mellitus

The primary goal of diabetes therapy is to maintain normoglycemia and thereby control the signs that occur secondary to hyperglycemia and glycosuria and result in the development of complications (Table 12.27). The essentials of good stabilization of diabetes mellitus require understanding by the owner and adherence to a regular daily routine that involves diet, insulin administration, and regular controlled exercise. Stabilization can be carried out satisfactorily at home, but, particularly if the patient is ketotic, it may be preferable to hospitalize the animal during stabilization, since it is easier to monitor blood glucose more closely.

TABLE 12.27 Complications associated with diabetes mellitus

- Hypoglycemia
- Ketoacidosis
- Cataract formation
- Hepatic lipidosis
- Pancreatitis
- Infections
- Retinopathy
- Diabetic neuropathy
- Diabetic nephropathy
- Skin disease

Most diabetic dogs are presented with complete islet cell degeneration and atrophy. Therefore, diabetes mellitus in dogs is insulin dependent. Rarely, bitches may be presented during the diestrus phase of the estrous cycle before islet cell exhaustion has occurred. If ovariohysterectomy is performed in these patients immediately when the signs of diabetes become apparent, there can be complete resolution of the disease. However, in the majority of bitches, this opportunity is missed or goes unnoticed, and permanent damage to the islet cells occurs.

While a small percentage of cats may respond to diet and oral hypoglycemic agents, principally glipizide (a sulfonylurea), it is generally considered that insulin provides better glycemic control and, therefore, more chance of attaining diabetic remission. Remission of diabetes in cats usually occurs within 1 month of beginning insulin therapy but can occur as late as 6–8 months after the start of treatment.

Dietary Therapy

Appropriate dietary therapy is an essential part of the management of diabetes. The diet must be well balanced and constant in both composition and the amount fed at each meal. It is, therefore, most convenient to use a commercial diet. Canned or dry foods that contain digestible complex carbohydrates should be fed, as slow digestion minimizes the fluctuations in postprandial blood glucose concentrations. Semi-moist foods containing a predominance of easily assimilated carbohydrates in the form of disaccharides and propylene glycol should be avoided because of marked postprandial hyperglycemia. There is evidence that diets with a high-fiber content improve glycemic control by delaying starch hydrolysis and glucose absorption, thereby reducing postprandial fluctuations in blood glucose. High-fiber diets are also beneficial in correcting obesity. However, there may be disadvantages in using high-fiber diets (e.g., reduced palatability and the fact that the low-caloric density may cause patients to lose excessive weight or fail to gain weight if already below ideal body weight). The author tends to reserve high-fiber diets for those patients that are difficult to stabilize and/or are obese.

Correction of obesity and minimizing the impact of the diet on postprandial blood glucose concentrations are also important dietary considerations in diabetic cats. Following weight reduction, glycemic control often improves, and, in some cats, remission of diabetes may occur. Although high-fiber diets have been used in cats with diabetes, palatability can prove a problem. More recently, high-protein, low-carbohydrate diets have been used in the management of feline diabetes. Since cats are strict carnivores and maintain their blood glucose mainly through gluconeogenesis from amino acids, these diets produce a more stable blood glucose level, and insulin requirements are reduced.

Finally, the feeding schedule should be designed to enhance the action of insulin and minimize postprandial hyperglycemia. The daily caloric intake should

occur when insulin is present in the circulation and capable of handling glucose absorbed from the intestine. Several small meals are preferable to one large feed, as these will help minimize postprandial hyperglycemia and thus help to control fluctuations in blood glucose. The author routinely recommends two equal meals fed at times to coincide with insulin activity. In cases that prove difficult to stabilize, 3–4 smaller meals are fed during the day. Titbits and scavenging must be avoided as they tend to destabilize diabetic patients.

Insulin Therapy

For routine stabilization in the dog, insulin zinc suspension (lente), which contains a mixture of 30% insulin zinc suspension (amorphous) and 70% insulin zinc suspension (crystalline), is the preparation of choice in the UK (Vetsulin® in the United States). When given by subcutaneous injection, it is an intermediate-acting insulin with an onset of activity at 1–2 hours, peak activity around 6–12 hours, and a duration of action of between 18 and 26 hours in the dog. The times for peak activity and duration of action vary with the individual, but in some dogs, once-daily administration is adequate, although in the majority of cases, twice-daily administration is required to maintain good glycemic control. In the United States, clinicians also use NPH insulin, which has a shorter duration of action, and administer it to diabetic dogs in a divided twice-daily dosage.

Cats tend to metabolize insulin more quickly than dogs; therefore, a long-acting insulin such as protamine zinc insulin is often recommended if once-daily dosing is to be tried, although PZI is often administered twice daily as with other intermediate- to long-acting insulins. However, many clinicians use twice-daily dosing with lente insulin to gain good glycemic control. Insulin glargine, a long-acting insulin analog, has been used in cats with encouraging results (a dose of 0.25–0.5 U/kg q.24 h. or q.12 h. has been recommended). Insulin glargine forms microprecipitates at the site of injection from which small amounts of insulin are slowly released.

Lente insulin can be given as a single morning injection at the same time as or just before the first meal, with the second meal given 6–8 hours later to coincide with peak insulin activity. However, because of the frequency of hypoglycemia associated with once-daily treatment, the lente insulin can also be given in a divided twice-daily treatment protocol (see ahead given in the text). An initial dose of between 0.5 and 1.0 U/kg is used. Insulin is probably best dosed on body surface area rather than a simple weight basis. Thus, small dogs (<15 kg) tend to require 1.0 U/kg, and larger dogs (>25 kg) receive 0.5 U/kg. Although the subcutaneous route is ideal for long-term use, the intramuscular route may be used initially, especially in dehydrated or "healthy" ketotic animals because absorption from subcutaneous depots in these patients may be slow and erratic. Regular insulin can also be given by the intramuscular or intravenous route.

Insulin should be administered using specific 0.3, 0.5, or 1.0 mL syringes calibrated in units (100 U/mL or 40 U/mL depending on the concentration of the preparation). Insulin preparations should be stored in a refrigerator at 2–8°C (35.6–46.4°F) because they are adversely affected by heat or freezing. Preparations should be rolled gently to resuspend the particles before use. A diabetic patient will usually take 2–4 days to respond fully to a dose of insulin or a change in preparation. It is important to avoid increasing the dose too quickly before equilibration has occurred, as this can lead to a sudden and precipitous fall in blood glucose due to overdosage with insulin. In most cases, adjustments in the insulin dose should be made in small changes of 1–4 units per injection, depending on the size of the patient and the severity of the hyperglycemia. The type of preparation and frequency of administration may require alteration in those patients that prove difficult to stabilize with this standard routine. However, it is good for the clinician to become familiar with one type of insulin preparation and only change from that preparation if the insulin is the cause of the instability.

The standard routine for a dog would be:

8:00 a.m.: Give lente insulin injection SC
8:30 a.m.: Feed half of the measured daily ration
2:30 p.m.: Feed second half of the daily ration

for once-daily treatment (although administering the insulin in divided doses SC is recommended) and:

8:00 a.m.: Give lente insulin injection subcutaneously
8:30 a.m.: Feed half of the measured daily ration
8:00 p.m.: Give lente insulin injection subcutaneously
8:30 p.m.: Feed second half of the measured daily ration for twice-daily treatment

Keep the daily routine constant, including exercise; avoid titbits and scavenging.

Monitoring Therapy

Ideally, monitoring should consist of serial blood glucose concentrations, as tighter diabetic control can be gained than with urine glucose estimations. Initially, at least two blood glucose estimations should be made, one before insulin is administered and the second just before the second feed. Once the patient appears fairly stable, more frequent blood samples should be taken throughout the day to assess the degree of stabilization. An assessment of daily water intake can also provide useful information about the degree of diabetic control.

Blood glucose concentrations should ideally be maintained at between 5 and 9 mmol/L (90 and 162 mg/dL) (**Figure 12.86**). The blood glucose concentration will usually be highest in the morning before insulin is administered and lowest just before the second feed. A trace of glucose in the morning urine sample may be acceptable, but the urine should be negative at other times in the day. However, it is important to remember that urine glucose may not reflect the blood glucose concentration at the same point in time, and if the urine glucose is negative, the blood glucose concentration could

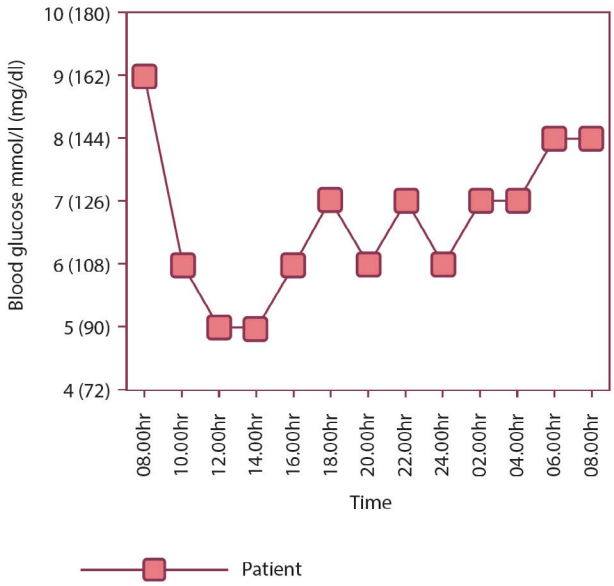


FIGURE 12.86 Ideal blood glucose curve.

be hypoglycemic (<3.0 mmol/L [<54 mg/dL]), normoglycemic, or hyperglycemic (>5.5 mmol/L [>99 mg/dL]). Although the author's clients monitor urine for glucose and ketones regularly, he does not advocate adjusting daily insulin dosages on the basis of morning urine glucose measurements. Instead, he prefers to continue with a fixed insulin dosage unless the patient remains unstable for more than several days.

Measurement of glycated proteins such as fructosamine and glycosylated Hgb are used increasingly in the dog and cat to monitor the response to treatment. The irreversible, nonenzymatic glycation process occurs throughout the life span of the protein, mainly albumin in the case of fructosamine, and is proportional to the glucose concentration over that time. These measurements reflect the average blood glucose concentration over the preceding 1–2 weeks in the case of serum fructosamine and 2–3 months in the case of glycosylated Hgb. Fructosamine concentrations <400 mmol/L indicate good glycemic control, whereas concentrations >500 mmol/L are found in newly diagnosed or poorly controlled diabetics. Glycosylated Hgb is less routinely available as an assay. Well-controlled diabetic dogs have between 4% and 6% glycosylated Hgb, whereas poorly controlled diabetics have concentrations >7%.

Diabetic records (Figure 12.87) should be kept by the owner for each patient, as alterations to stability can be assessed more easily over a period of time. Insulin requirements will be increased by infection, estrus (particularly the metestrus phase of the cycle), pregnancy, and ketoacidosis. It is, therefore, recommended that entire bitches should undergo ovariohysterectomy in order to avoid insulin resistance at subsequent seasons.

Investigation of Instability

If a patient appears to be poorly stabilized at home despite repeated attempts to provide adequate glycemic

Date	Urine exam	Insulin dose & time of injection	Food	Drink	Body weight	Blood results	Note
15 March	am glucose-ve ketones-ve	18 units lente insulin s.c. 8.00 am	3/4 tin Dogga 8.30 am 2.30 pm	0.9 L	24 kg	2.00 pm blood glucose 4.6 mmol/l	Bright and alert

FIGURE 12.87 Diabetic record.

control, the diabetic record should be checked, and the patient examined for signs of disease that could cause insulin resistance (e.g., infection, estrus, pregnancy, ketoacidosis, hyperadrenocorticism, or acromegaly). The daily routine should be discussed with the owner to make sure that the diet is constant and measured and that there is no access to titbits or scavenging. The insulin preparation should be checked for type, expiry date, and storage, as should the ability of the owner to administer the insulin (adequate mixing, correct dosage, and injection technique).

If an obvious cause cannot be determined, the patient should be hospitalized on its daily routine, and serial blood glucose determinations made every 1–2 hours throughout the day. Determinations made with glucose reagent strips and a glucose meter are simple, fast, and sufficiently accurate for this purpose. Some owners are prepared to record these measurements at home environment, which is useful as it provides a more realistic assessment of the patient in its own home environment. The use of a continuous glucose monitoring system or a flash glucose monitoring system has proved useful but is more expensive. The results should then be plotted on a graph against time, although it is important to realize that precise glucose curves may vary from day to day in any diabetic patient.

Three major causes of instability can be deduced from the graph of serial blood glucose determinations:

- The first is insulin-induced hyperglycemia, also called the Somogyi overswing, where excessive insulin dosage leads to paradoxical hyperglycemia (Figure 12.88). The blood glucose concentration is high in the morning before insulin is given but falls sharply to hypoglycemic concentrations (<3.5 mmol/L [<63.1 mg/dL]) after insulin administration. The hypoglycemic period is short in duration and is not associated with signs of hypoglycemia. In fact, the nadir can easily be missed if frequent sampling is not performed. The low blood glucose concentration stimulates the release of hormones antagonistic to insulin (e.g., glucagon, cortisol, and catecholamines), and these cause the glucose concentration to rebound quickly to high levels. If blood glucose and/or urine glucose concentrations were measured only before insulin and before the second feed, the concentrations would be high, and this could easily be misinterpreted as a reason for increasing the daily

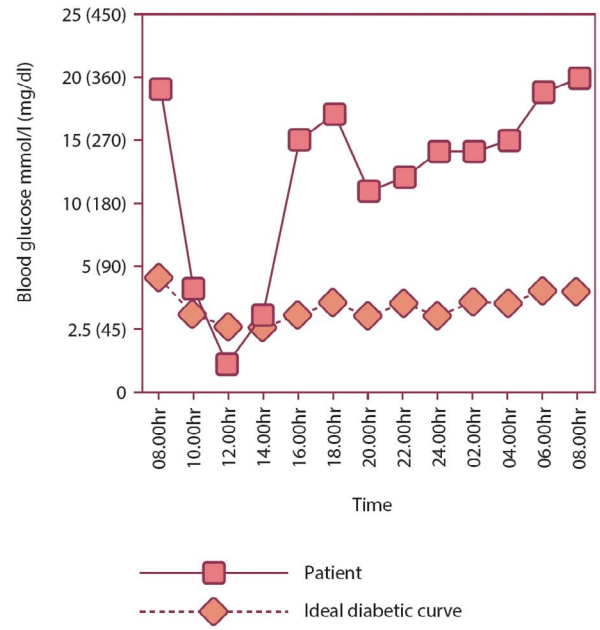


FIGURE 12.88 Insulin-induced hyperglycemia (Somogyi overswing).

insulin dose when, in fact, the patient is already being overdosed. The treatment for insulin-induced hyperglycemia is to reduce the daily dose of insulin in order to prevent the hypoglycemia that causes the dramatic swing in blood glucose concentrations.

- The second cause of instability is due to rapid metabolism of insulin, which means that an intermediate-acting insulin preparation does not last for a full 24 hours (Figure 12.89). In such cases, the blood glucose concentration is high in the morning before insulin is given but falls to normal levels for much of the day. However, after the second feed, the blood glucose concentration rises and remains high for the remainder of the day. This leads to a considerable period of hyperglycemia and results in glycosuria in the morning and often nocturnal polydipsia and polyuria. The treatment for rapid insulin metabolism is either to try a longer-acting insulin preparation (e.g., protamine zinc insulin or insulin glargine [Ultralente is no longer available in the United States]) or to administer two doses of lente insulin 12 hours apart, with two meals at the time of injection or four small meals given at approximately 6-hour intervals.

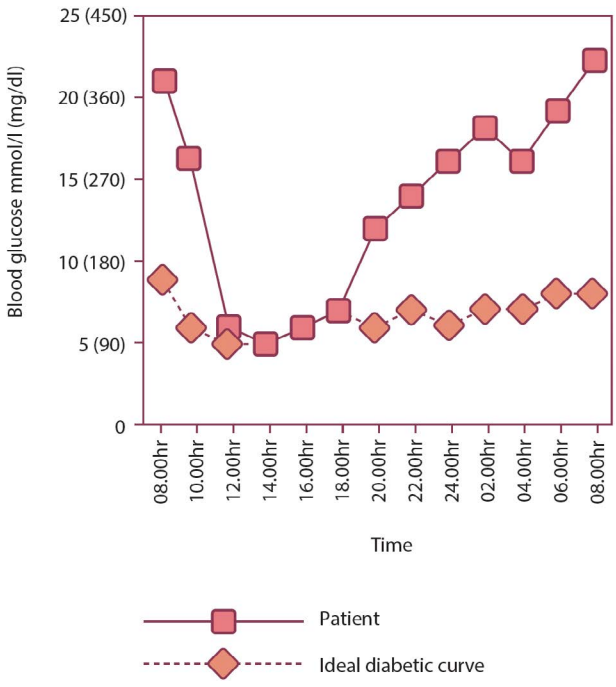


FIGURE 12.89 Rapid metabolism of insulin.

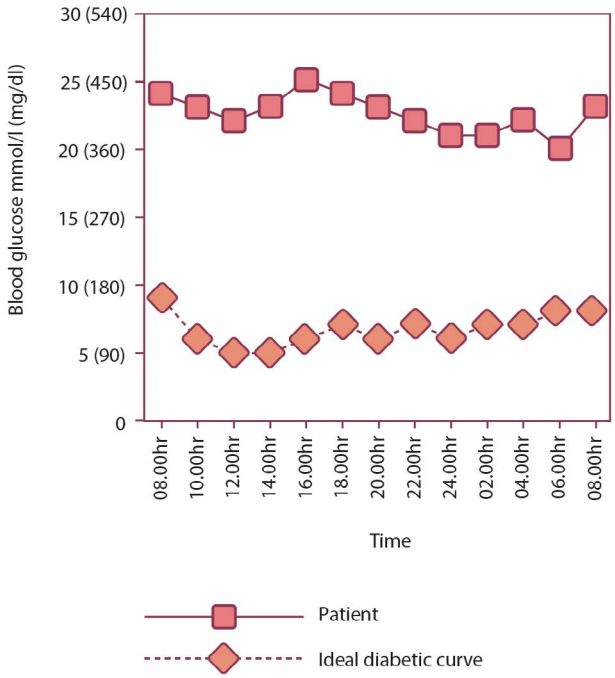


FIGURE 12.90 Insulin resistance.

- The third cause of instability is associated with insulin resistance. In these cases, the animal remains persistently hyperglycemic despite an insulin dosage of more than 2.2 U/kg per day (Figure 12.90). Although some patients can be stabilized satisfactorily at doses higher than this, peripheral antagonism to insulin activity is likely to be present. In cases where adequate stabilization is not possible, a thorough investigation of the patient is required to try and identify the precise cause of the insulin resistance. Some of the causes of insulin resistance are listed in Table 12.28. Correction or treatment of the underlying cause will usually enable the patient to be stabilized at a lower dose of insulin with improved glycemic control.

INSULINOMA

Definition/Overview

Functional islet cell tumors (insulinomas) are the most frequently occurring tumors of the endocrine pancreas

TABLE 12.28 Causes of insulin resistance

- Obesity
- Hyperadrenocorticism
- Exogenous glucocorticoid administration
- Metestrus phase of the estrous cycle
- Exogenous progestogen administration
- Acromegaly
- Hypothyroidism
- Hyperthyroidism
- Impaired absorption of insulin
- Excessive insulin antibody formation
- Pheochromocytoma
- Glucagonoma

in dogs. Most insulin-secreting tumors are malignant islet cell carcinomas that metastasize to regional lymph nodes and/or the liver. Early diagnosis is important, as dogs with metastases have significantly reduced survival times. Insulinomas are rare in cats.

Etiology

Causes of episodic weakness (Table 12.24), causes of hypoglycemia in adults (Table 12.29).

Pathophysiology

Insulinomas release insulin despite the presence of hypoglycemia. Hypoglycemia is normally the major inhibitory stimulus for insulin secretion. As a result of hyperinsulinism, tissue utilization of glucose continues, the hypoglycemia worsens, and ultimately clinical signs develop. The onset and severity of clinical signs are determined by the degree of hypoglycemia and the rate at which the plasma concentration of glucose falls. A rapid decline in plasma glucose concentration may occur with fasting, exercise, or excitement in dogs with insulinomas. The brain is an obligate consumer of glucose. Cerebral cells have limited stores of glycogen and a limited ability to utilize protein and amino acids for energy. These cells will be the first affected by hypoglycemia. Prolonged and profound hypoglycemia causes ischemic neuronal cell damage.

TABLE 12.29 Differential diagnosis of hypoglycemia in adult dogs and cats

- Incorrect anticoagulant/delayed separation of serum from red blood cells
- Functional islet cell tumor (insulinoma)
- Excessive insulin administration
- Extrapancreatic tumors, particularly hepatic tumors
- Liver disease (cirrhosis, hepatic necrosis)
- Septicemic or endotoxic shock
- Hypoadrenocorticism
- Idiopathic hypoglycemia in working dogs
- Xylitol toxicity in dogs
- Iatrogenic insulin overdosage
- Severe polycythemia

Hypoglycemia is a potent stimulus for the release of hormones that have an antagonistic action to insulin. These include glucagon, GH, glucocorticoids, catecholamines, and possibly thyroid hormones. These hormones act in concert to raise the plasma glucose concentration. Some of the clinical manifestations of hypoglycemia, such as muscle tremors, nervousness, restlessness, and hunger, may, in fact, result from stimulation of the sympathetic nervous system and increased levels of circulating catecholamines.

Clinical Presentation

Insulinomas usually occur in middle-aged to older dogs (mean age of 9 years) of any breed, although medium to large breeds appear to be predisposed. No sex predisposition has been reported. Insulinomas appear to be very rare in cats. A tentative diagnosis of hyperinsulinism is generally based on fulfilment of the criteria from Whipple's triad:

1. The presence of neurologic signs typical of hypoglycemia, which may be precipitated by exercise or excitement.
2. Hypoglycemia (plasma glucose <3 mmol/L [<54 mg/dL]) at the time of the clinical signs.
3. Resolution of clinical signs following feeding or administration of intravenous glucose.

Clinical signs associated with hypoglycemia include fatigue, generalized weakness, collapse, muscle tremors, altered behavior, confusion/disorientation, apparent blindness, ataxia, incoordination, stupor, and seizures. These signs are usually episodic in nature and may occur with fasting, exercise, or excitement in dogs with insulinomas. Provocative stimuli, such as IV administration of glucagon or glucose, result in excessive secretion of insulin from neoplastic beta cells. This response may be even greater if glucose is administered orally, as numerous intestinal hormones (glucagon, secretin, cholecystokinin, gastrin, and gastric inhibitory peptide) are secreted in response to oral glucose, and these in turn increase insulin secretion. It is by this mechanism that feeding has been reported to initiate clinical signs in dogs with insulinomas.

Seizure activity is one of the most common clinical manifestations of hypoglycemia. The seizures may be grand mal or focal in nature and are normally self-limiting, lasting between 30 seconds and 5 minutes. Peripheral neuropathy with nerve degeneration and demyelination has also been associated with canine insulinoma in a few cases. Insulinomas are generally small tumors and do not lead to malignant cachexia. Thus, weight loss is not a feature of this disease.

Diagnosis

Laboratory Findings

A presumptive diagnosis of insulinoma is based on the presence of typical clinical signs in association with

persistent hypoglycemia and an inappropriately high plasma insulin concentration. A fasting plasma glucose concentration of 3 mmol/L (54 mg/dL) or less is found in most cases. Some dogs with insulinoma show no clinical signs despite having extremely low blood glucose concentrations (<2 mmol/L [<36 mg/dL]) because they are able to adapt to these low concentrations over a prolonged period of time. Serum fructosamine concentrations are also reduced (<250 µmol/L), supporting substantial periods of hypoglycemia even in those patients with normal or low-normal fasting blood glucose concentrations.

Plasma insulin concentrations >20 mU/L in association with hypoglycemia are inappropriate, and an insulin-to-glucose ratio >4.2 is considered diagnostic.

In borderline cases, an IV glucose tolerance test using 0.5 g glucose/kg body weight has proved useful. Insulin-secreting tumors retain a degree of responsiveness to the glucose challenge; a glucose half-life of <20 minutes and/or a fractional clearance rate of more than 3%/minute is highly suggestive of insulinoma in the dog.

Although hypoalbuminemia, hypokalemia, and increases in serum ALP concentrations have occasionally been reported, these findings are not specific or helpful in achieving a definitive diagnosis.

Diagnostic Imaging

Abdominal ultrasonography using a high-quality diagnostic ultrasound machine has been used to examine the pancreas of dogs with suspected insulinomas. Most insulinomas are quite small (<2.5 cm) and are isoechoic to hypoechoic when compared with the surrounding pancreatic tissue. In one study, a pancreatic mass was identified as a spherical or lobular hypoechoic nodule in 75% of dogs with insulinomas (Figure 12.91). Tumors as small as 7 mm have been identified in the pancreas.

Cross-sectional imaging using CT or MRI has proved useful in identifying insulinomas in cases in which ultrasonography has failed to detect a lesion. The use of dual-phase (arterial and venous phases) or triple-phase (arterial, venous, and equilibrium phases) CT angiography for evaluation of insulinomas increases the chance that attenuation differences will improve visualization of a small mass. CT has also been shown to be more sensitive for the detection of lymph node and hepatic metastases.

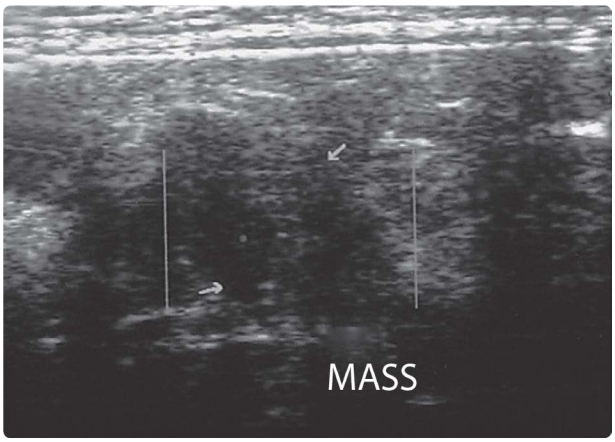


FIGURE 12.91 Ultrasonogram of the pancreas of a crossbred dog showing a hypoechoic mass, which proved to be an insulinoma on histology.

Management

Management of insulinomas should be directed at specific treatment of the tumor, reduction of insulin secretion, and correction of hypoglycemia. Sometimes, IV glucagon is needed to increase the blood glucose to desirably safe levels. The initial glucagon dose is 50.0 ng/kg as an IV bolus followed with a maintenance dose of 5–10 ng/kg per minute.

Surgical Management

Surgical resection of the pancreatic tumor and metastatic tumor masses should be the first approach to therapy (Figures 12.92–12.95). Most insulinomas are located in the left lobe of the pancreas, with masses in the right lobe or body occurring less frequently. Tumors are usually solitary, but multiple masses may occur. Rarely, there is a diffuse islet cell tumor with no discrete

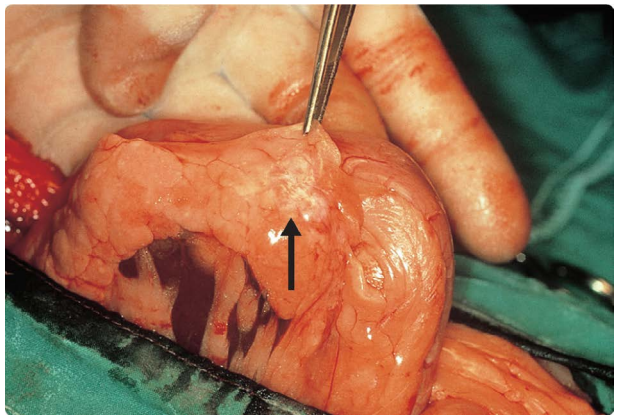


FIGURE 12.92 An insulinoma being pointed out at surgery (arrow).

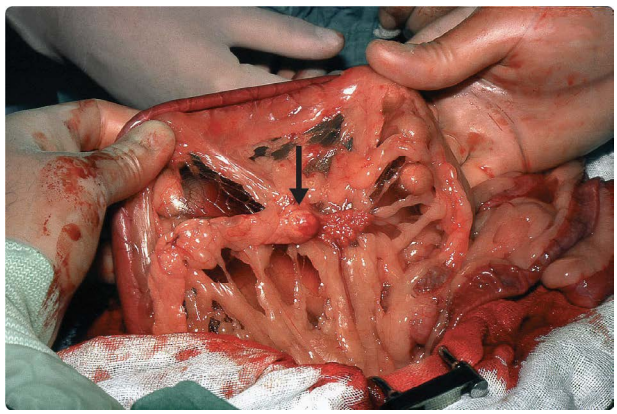


FIGURE 12.93 Surgical view of an insulinoma before (black arrow) ligation for removal. (*Courtesy of M. Schaer.*)

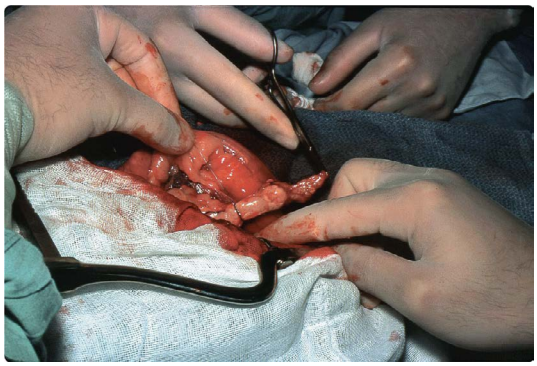


FIGURE 12.94 Surgical view of ligation of an insulinoma prior to removal. (*Courtesy of M. Schaer.*)

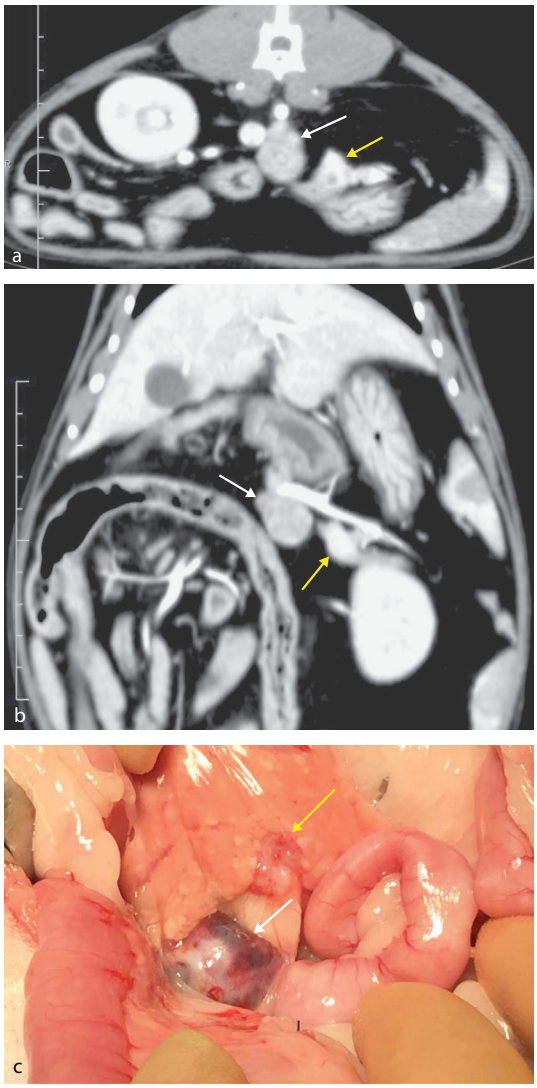


FIGURE 12.95 A 10-year-old Domestic Shorthair cat with hypoglycemia. The contrast CT shows an intensely contrast-enhancing mass in the left limb of the pancreas (yellow arrow) and a separate moderately contrast-enhancing lymph node (white arrow) on the **(a)** transverse and **(b)** dorsal reconstructed images. These lesions were confirmed at surgery **(c)** and histology confirmed an insulinoma with spread to the local lymph node.

nodule. There does not appear to be a difference in survival in relation to tumor location within the pancreas, but there is a suggestion that tumors with a high mitotic count carry a worse prognosis.

Postoperative recovery is routine in many cases, but complications, including pancreatitis, hyperglycemia, overt diabetes mellitus, and hypoglycemia, occur. In nearly all cases, hypoglycemia will recur eventually due to metastasis.

Medical Management

Medical management should be used if widespread metastasis is present or if hypoglycemia recurs after surgery. This should consist of dietary control (frequent small meals of a diet high in proteins, fats, and complex carbohydrates) and the use of prednisolone, which inhibits insulin and stimulates glycogenolysis, and diazoxide, a nondiuretic, benzothiadiazine antihypertensive drug that inhibits insulin secretion (Table 12.30). Octreotide, a somatostatin analog that inhibits insulin synthesis and secretion, has also been used and has been shown to be effective in some cases. Recently, the multireceptor tyrosine kinase inhibitor toceranib (Palladia), when used with prednisolone, has been shown to achieve long-term, improved survival in dogs with metastatic insulinoma.

The prognosis is guarded due to the malignant nature of the disease. However, many dogs do best with a combination of medical and surgical management. The median time to recurrence of clinical signs after surgery is 12 months (range 4–16 months), and the median postoperative survival time is 26 months (range 6–46 months).

TABLE 12.30 Management of hypoglycemia

- In acute hypoglycemic crisis, give 1 mL/kg of a 40%–50% glucose solution by slow IV injection, or, if the animal is still conscious, provide a meal containing glucose. Glucose administration is an emergency treatment and cannot be used for long-term control. If this proves ineffective in preventing severe hypoglycemia, glucagon should be used. The initial dose of glucagon is 50.0 ng/kg given as an IV bolus followed with a maintenance CRI dose of 5–10 ng/kg per minute.
- Management of chronic hypoglycemia requires a combination of therapies
  - *Diet:* Feed small meals high in protein and low in simple sugars 5–6 times daily
  - Exercise should be restricted
  - Diabetogenic drugs
- *Glucocorticoids:* Prednisolone (0.5–1 mg/kg daily in divided doses)
- Diazoxide, a nondiuretic benzothiadiazine antihypertensive drug that acts by suppressing insulin secretion (10 mg/kg in divided doses increasing up to 60 mg/kg daily if necessary)
- Octreotide, a long-acting somatostatin analog that inhibits insulin synthesis and secretion (10–20 µg SC q.12 h. or q.8 h.); only effective in some dogs, close monitoring required
- Streptozotocin and alloxan are nephrotoxic and not recommended

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CHAPTER

13

Nephrology/Urology

Mark J. Acierno

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INTRODUCTION

The kidneys are responsible for maintaining the body's fluid and electrolyte balance, filtering metabolic waste, and performing hormonal functions. Reduced renal function manifests itself in several ways including increased blood levels nitrogenous compounds This is referred to as azotemia. Uremia is the constellation of clinical signs that results from azotemia and includes vomiting, lethargy, anorexia, diarrhea, oral ulcerations, and uremic breath.

Azotemia is categorized by its underlying cause. This is clinically important because not all azotemia is the result of kidney disease. Prerenal and postrenal factors can result in increased levels of nitrogenous compounds despite otherwise healthy kidneys.

Prerenal azotemia is the result of decreased kidney perfusion in the absence of actual kidney disease or injury. Decreased renal blood flow leads to a reduction in glomerular filtration and a compensatory activation of the renin–angiotensin–aldosterone system. The ensuing increase in tubular sodium reabsorption and antidiuretic hormone-induced water reabsorption leads to production of concentrated urine. This is important, as the hallmark of prerenal azotemia is mild-to-moderate azotemia with an increased urine specific gravity. Treatment of the underlying condition (Table 13.1) will often lead to resolution of clinical signs.

Postrenal azotemia can result from either an obstruction in urine outflow or leakage of urine into the abdomen. With a urinary obstruction, the blockage causes increased hydrostatic pressure in Bowman's capsule and decreased glomerular filtration. This is most commonly observed in urethral obstructions, since unilateral ureteral obstructions leave one kidney functioning normally; however, azotemia can occur with unilateral ureteral obstructions if a patient has pre-existing kidney disease.

TABLE 13.1 Causes of prerenal azotemia

Hypotension	– Anesthesia – Dehydration – Hypoadrenocorticism (Addison's disease)
Hypoperfusion	– Cardiac disease – Hemorrhage – Shock
Thrombosis	– Renal artery or vein occlusion

A rupture of the urinary tract results in the accumulation of fluid in the abdomen. Because urea is highly diffusible, it is quickly resorbed back into circulation along with some of the fluid. Creatinine, which is not diffusible, becomes trapped. Patients who experience a urinary tract rupture develop an accumulation of fluid that has a blood urea nitrogen (BUN) comparable to serum plasma but a creatinine that is elevated.

Renal azotemia is a direct result of renal parenchymal disease. Because of differing etiology, prognosis and treatment, primary renal disease is classified clinically into acute kidney injury (AKI) or chronic kidney disease (CKD) and histologically as glomerular or tubular disease.

Differentiation between AKI and CKD is important in determining etiology, prognosis, and treatment options (Table 13.2). Immediate intervention and aggressive therapy are more likely to produce clinical recovery in AKI,

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TABLE 13.2 Differentiation of acute and chronic renal failure

	ARF	CRF
History	Exposure to toxins or drugs Acute illness Ischemic episode	PU/PD for some time Anorexia Weight loss over extended period
Body condition	Normal	Thin/emaciated
Renal size radiograph / US	Normal/increased	Small and irregular
PCV	Normal/increased	Anemia
Acidosis	Moderate/severe	Moderate
Serum potassium	Normal/increased	Normal to decreased
Osteodystrophy	None	Rare (e.g., rubber jaw)

since underlying causes may be identified and treated. In addition, surviving nephrons can undergo hypertrophy and compensate for ones that are lost to the renal insult. Lastly, some damaged nephrons may be capable of recovering if given sufficient time.

It is unlikely that a treatable cause of kidney disease will be identified in the CKD patient. Also, it is doubtful that remaining nephrons have additional compensatory capacity and there is little hope for nephron repair. Treatment in the CKD patient is directed toward supportive care. Although, differentiation between the two conditions is essential, there is no single test to discriminate between them. Diagnosis is made based on a combination of history, clinical signs, physical examination findings and diagnostic tests.

ACUTE KIDNEY INJURY

Definition/Overview

Acute kidney injury (AKI) is a condition characterized by a rapidly progressive impairment in the kidney's ability to filter metabolic waste, as well as maintain the body's fluid and electrolyte balance.

Etiology

Acute kidney injury is the result of damage that can be caused by ischemia, nephrotoxins, infectious agents, or systemic disease (Table 13.3). In companion animal medicine, AKI is most commonly the result of nephrotoxins and infectious agents.

Pathophysiology

There are many specific mechanisms by which the kidney can be injured. Some of the most common causes include infectious, nephrotoxins, ischemic, hypertension, and immune mediated. Many of the more common causes can be found in Table 13.4.

TABLE 13.3 Common causes of acute kidney injury

Nephrotoxins	– Aminoglycosides – Amphotericin B – Cisplatin and carboplatin – Cyclosporin – Ethylene glycol – Jerky treats – Melamine – NSAIDs – Toxic plants (e.g., cats: lilies, dogs: grapes) – Other
Infectious agents	– Babesiosis – Ehrlichiosis – Leishmania – Leptospirosis – Pyelonephritis – Rickettsiosis (e.g., *Rickettsia rickettsii*, Rocky Mountain spotted fever)
Systemic disease	– Heat stroke
Ischemia	– Severe hypotension (e.g., anesthetic induced)

Clinical Presentation

General

Clinical signs of AKI are somewhat dependent on the underlying cause, severity of the azotemia, and electrolyte imbalances. Signs that are often noted include depression, weakness, dehydration, anorexia, vomiting, diarrhea, uremic breath, oral ulcers, and hypothermia.

Ethylene Glycol

Specific

Ethylene glycol is an alcohol that does not become toxic until metabolized by the liver. Early clinical signs are due to the alcohol's effect on the central nervous system and include ataxia, proprioceptive deficits, muscle tremors, nausea, vomiting, and seizures. Polyuria and polydipsia are common because ethylene glycol and its metabolites exert a diuretic effect. Since it is potentially treatable in the early stages, ethylene glycol exposure should be considered in every dog with unexplained neurologic signs.

Differential Diagnosis

Prerenal azotemia, postrenal azotemia, Addison's disease, and CKD.

Diagnosis

Determining the likely underlying cause of the kidney injury is critical in assessing prognosis as well as developing an appropriate treatment plan. The importance of the client interview cannot be over emphasized. Questions should focus on possible exposure to environmental nephrotoxins (e.g., ethylene glycol, cholecalciferol-based

TABLE 13.4 Mechanism for common causes of acute kidney injury

Ethylene glycol	– Used as an antifreeze in cars (prohibited in some countries)
	– Toxic dose: 1.4 mL/kg in cats, 4.4 mL/kg in dogs
	– Ethylene glycol is broken down in the liver by a series of oxidative steps
	  – Several of the ethylene glycol metabolites are directly toxic to renal epithelial cells
	  – One of the metabolites, oxalate, leads to the formation of calcium oxalate crystals within the tubules

Leptospirosis	– Zoonotic disease
	  – Caused by a number of antigenically distinct serovars of the bacteria *Leptospira interrogans sensu lato*
	– Maintained in the wild by asymptomatic wild animals (hosts), which shed the bacteria in urine
	  – Infection occurs when leptospires penetrate mucous membranes or broken skin
	  – Renal tubular epithelial cells become colonized, resulting in interstitial lymphoplasmacytic inflammation

NSAIDs	– NSAIDs block the cyclooxygenase pathway preventing the formation of locally protective prostaglandins in the kidney – Activation of the renin–angiotensin system leads to vasoconstriction in the glomerular capillary bed – As the arterioles constrict, blood flowing out of the glomerulus and into peritubular capillaries decreases – If left unchecked, the resulting decreased blood flow to the medulla of the kidney leads to ischemic injury – Suppression of the renin–angiotensin system by IV fluid therapy can help prevent this vasoconstriction
Cholecalciferol-based rodenticides	– Cholecalciferol is metabolized to calcitriol, the active form of vitamin D – Calcitriol increases intestinal absorption, stimulates bone resorption, and encourages renal tubular reabsorption of calcium – This can lead to soft tissue (e.g., kidney) mineralization
***Lilium* and *Hemerocallis* (true lilies)**	– Lilies of the genera *Lilium* and *Hemerocallis* (i.e., Easter lilies, tiger lilies, etc.) are extraordinarily nephrotoxic; however, the mechanism of toxicity is not known – It is important to note that not all lilies are members of this group – Peruvian and peace lilies are examples of plants that are not toxic
Grapes/raisins	– The mechanism of toxicity is not known; however, it does not appear to be related to heavy metals, pesticides, or mycotoxins – Ingestion has been shown to causes acute tubular necrosis of the proximal tubule

rodenticides), household toxins (lilies, grape products), current medications (both human and pet), any medications or drugs that could have been consumed, and recent travel history. Often, travel will expose a patient to diseases not commonly encountered in the local environment.

Once the presence of azotemia (increased BUN, creatinine, and phosphorus) is confirmed, possible differential diagnoses (prerenal azotemia, postrenal azotemia, chronic kidney disease, Addison's disease) must be eliminated from consideration. A sodium-to-potassium ratio that is less than 29 should raise suspicion that the patient has hypoadrenocorticism, not kidney disease.

Urinalysis can be used to quickly differentiate between prerenal and renal azotemia. Isosthenuria is typical of acute kidney injury, while a urine specific gravity of greater than 1.025 in the dog and greater than 1.035 in the cat is typically associated with prerenal azotemia. The presence of glucosuria in the absence of hyperglycemia is suggestive of acute proximal tubule dysfunction but is also seen with Fanconi syndrome. The discovery of protein, in the absence of bacteria, white blood cells, or casts, may be suggestive of glomerular disease (see PLN). Only a urine protein-to-creatinine ratio can provide a quantitative assessment of urine protein concentration and should be performed on every proteinuric patient. Microscopic examination of the urine sediment allows detection of calcium oxalate monohydrate crystals, which are associated with ethylene glycol toxicity (Figure 13.1).

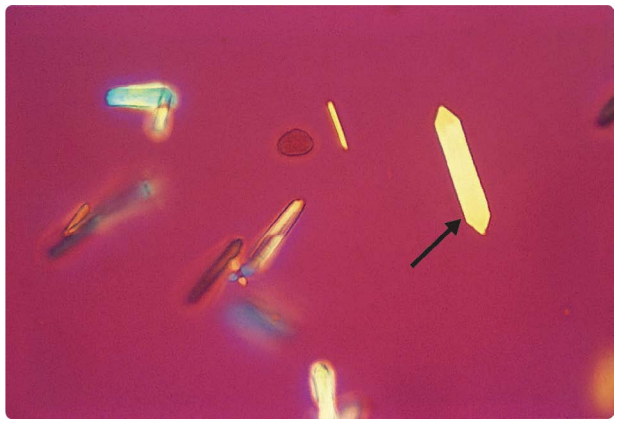


FIGURE 13.1 Calcium oxalate monohydrate crystals (arrow) typical of those observed in the urine sediment of animals with ethylene glycol intoxication. (*Courtesy of C.A. Osborne.*)

Bacteria may be seen in cases of pyelonephritis; however, the absence of bacteria and/or inflammatory cells does not eliminate pyelonephritis as a cause of AKI. Casts, often observed in AKI, can help determine the underlying cause (Figure 13.2 and Table 13.5).

Urine Culture

In cases in which pyelonephritis is suspected either due to pyelectasia or urinalysis findings, a urine culture and sensitivity should be performed.

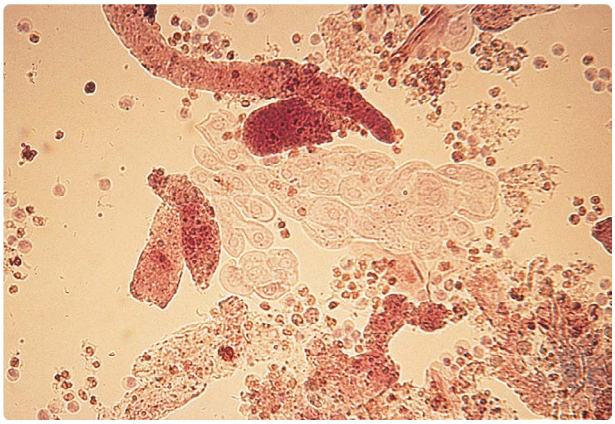


FIGURE 13.2 Granular casts in the urine sediment of a dog with acute kidney injury. (*Courtesy of D.F. Senior.*)

TABLE 13.5 Types of casts and associated conditions

Hyaline casts	Proteinuria—glomerulonephritis and amyloidosis
Granular casts	Degeneration of cells or precipitation of proteins – Associated with ischemic or toxic tubular injury
Fatty casts	Granular casts containing lipid – Associated with nephritic syndrome and diabetes
White cell casts	Pyelonephritis
Waxy casts	Final degeneration of granular cases – Associated with intrarenal stasis

Complete Blood Count

Changes in the complete blood count are often nonspecific; however, elevations in the white blood cell count can be associated with pyelonephritis and systemic infectious diseases. The absence of a stress leukogram (neutrophilia, lymphopenia, and eosinopenia) should raise the suspicion that the patient has hypoadrenocorticism.

Serum Chemistry

Acute kidney injury is accompanied by an elevation in BUN and creatinine. Elevations in phosphate usually parallel or exceed that of creatinine. Calcium is often mild to moderately elevated. Hypocalcemia is also associated with ethylene glycol toxicity. Serum bicarbonate decreases while potassium increases with the degree of renal dysfunction. Anion gap should always be calculated ($[Na^+ + K^+] - [Cl^- + HCO_3^-]$). Normal canine anion gaps range from 12 to 24 mEq/L, while normal feline values are 13–27 mEq/L. Increases are associated with metabolic acidosis caused by ketones, lactate, or uremia; however, significant increases in an AKI patient are suggestive of toxin ingestion. In veterinary medicine, the most common toxin is ethylene glycol, although methanol, ethanol, and salicylic acid should be considered as other potential toxins.



FIGURE 13.3 Ultrasound of a kidney of a CKD cat. The kidney is small, hyperechoic, and has poor corticomedullary definition. There is mild-to-moderate irregularity of the cortical borders.

Radiographs and Ultrasound

When available, ultrasound is the preferred imaging modality (Figure 13.3). Ultrasound can provide information about the renal architecture, outflow tract, and allows interrogation of the renal blood flow. Patients with AKI usually present with kidneys of normal to increased size while small, irregular-shaped kidneys are suggestive of chronic disease.

Infectious Disease Serology

In areas where leptospirosis is endemic, infection should be considered in any patients demonstrating signs of AKI. There are two commonly performed tests: Microscopic agglutination titer (MAT) and polymerase chain reaction (PCR). MAT measures antibodies to leptospirosis serovars, while the PCR probes for *Leptospira* DNA in urine or blood. Generally, a MAT >1:800 in the absence of recent vaccination suggests exposure, while a fourfold increase in paired titers 14 days apart indicates an active infection. The test can be negative in the early phase of the infection even when the animal is quite sick. The benefit of the PCR is that it can be positive before elevations in the MAT. Although laboratories can test urine or blood, the recommendation is to test both. Previous treatment with antibiotics can produce false negative results, and the test is not 100% specific. Enzyme-linked immunosorbent assays (ELISA) testing for *Leptospira*-specific antibodies are available; however, they are associated with significant problems with sensitivity and specificity. Studies have identified one cage side test, in particular WITNESS (Zoetis), as having reliable results. Other serologic testing (leishmaniasis, rickettsia, babesiosis, etc.) should be considered based on patient location and the relevant travel history.

Ethylene Glycol Test

Any patient with a severe metabolic acidosis, increased anion gap, calcium oxalate crystalluria, hypocalcemia,

or any combination of these signs should be tested for ethylene glycol ingestion. This should be done regardless of the patient's history, as most owners will underestimate exposure risk. It is important to note that some commercially available test kits may not be sensitive enough to detect ethylene glycol exposure in cats as the lethal serum concentration is below the threshold of the test; therefore, it is important to know the limitations of the test.

Management

Successful treatment of AKI is dependent on determining an underlying cause, correcting dehydration, establishing a brisk diuresis, and correcting life-threatening electrolyte imbalances. Often, treatment must begin before the cause can be established; however, the importance of accurate fluid therapy cannot be overemphasized. Studies in people and animal models clearly demonstrate that even imperceivable overhydration can be fatal in AKI patients.

Due to inappetence, vomiting, and an impaired ability to concentrate urine, dehydration is common in AKI patients. Initial fluid therapy must account for three factors: (1) Patient dehydration, (2) maintenance fluids, and (3) insensible losses. Although balanced electrolyte solutions contain small amounts of potassium, studies in people suggest these fluids are associated with a better outcome than 0.9% sodium chloride.

First, the patient's level of dehydration must be estimated (Table 13.6), and then the volume of fluids needed to correct dehydration can be calculated using the equation: Deficit in L = % dehydration × kg body weight. This deficit must be divided and administered over 12–24 hours in order to give time for fluids to equilibrate between the vascular, interstitial, and cellular compartments. Commonly available formulas for calculating "maintenance" fluids assume normally functioning kidneys and are of little use in formulating AKI fluid therapy plans; rather, an indwelling urinary catheter should be aseptically placed to measure urine output. Hourly urine production is then used as a surrogate for "maintenance" fluid rate. Finally, insensible losses can be estimated as 20 mL/kg per day plus any fluids lost to vomiting or diarrhea (See Example A).

Once dehydration has been corrected, fluid therapy should account only for maintenance fluids and insensible losses. Hourly urine production rate continues to be used as a surrogate for maintenance. Insensible losses are estimated as earlier (See Example B).

Our goal should be a brisk diuresis of at least 1 mL/kg/h. Well-hydrated animals producing less than 0.25 mL/kg/h of urine are considered to be oliguric, while anuric patients produce no urine. These conditions necessitate aggressive treatment. Occasionally, AKI patients will produce large volumes of urine once dehydration is corrected. Polyuric patients are probably either less severely affected or represent a later course of the disease process. These patients are generally easier to manage, as they are less likely to develop life-threatening electrolyte abnormalities and fluid overload; however, they still require careful monitoring. Significant azotemia and uremia can persist during this polyuric phase and is not considered a negative prognostic indicator.

TABLE 13.6 Signs used to determine degree of dehydration

Percent dehydration	Clinical signs
<5%	Not detectable
5%–6%	Subtle loss of skin elasticity
6%–8%	Delay in return of skin to normal position Slight increase in capillary refill time (CRT) Dry mucous membranes
10%–12%	Skin stands in place when tented Increase in CRT Eyes sunken Dry mucous membranes Shock—tachycardia, cold extremities, weak pulses
12%–15%	Death imminent

EXAMPLE A

10 kg male neutered Shih Tzu presents for signs consistent with AKI and on the basis of increased CRT, sunken eyes, and dry mucous membranes is determined to be 10% dehydrated. He is producing 5 mL/h urine. Total dehydration is determined to be 1 L (L = 10 kg × 0.10), which will be given over 12–24 hours. Thus:

Dehydration component of the fluid therapy = 83 mL/h (1,000 mL/12 h)

Maintenance fluids = patient's hourly urine production: 5 mL/h

There has been no vomiting or diarrhea, so the **insensible losses** = 8 mL/h [(20 mL/kg x10)/24]

Initial hourly fluid rate = 96 mL/h (83 mL/h + 5 mL/h + 8 mL/h)

Urine output per hour is monitored regularly and the maintenance fluid component of the formula adjusted.

EXAMPLE B

Our patient is now well hydrated and is producing 9 mL/h.

Maintenance fluids = patient's hourly urine production 9 mL/h

There has been no vomiting or diarrhea so **insensible losses** = 8 mL/h [(20 mL/kg x10 kg)/24h]

Hourly fluid rate = 17 mL/h (9 mL/h + 8 mL/h)

Urine output is monitored regularly and the maintenance component of the formula adjusted.

Mannitol is considered to be the initial treatment of choice for oliguric and anuric animals that are well hydrated and not fluid overloaded. Although clinical studies are lacking, experimental models suggest mannitol can increase renal blood flow, shrink swollen tubular cells, dislodge tubular obstructions, and scavenge free radicals. It is given as a 0.25–1.0 g/kg IV bolus over 30 minutes. If urine production improves, a CRI 1–2 mg/kg per minute can be started. Mannitol is contraindicated in patients with ethylene glycol intoxication because it can further exacerbate hyperosmolality. If there is no response to or the patient is overhydrated, furosemide therapy should be attempted.

Furosemide is a loop diuretic which has been associated with the induction of diuresis and resolution of tubular obstructions under experimental conditions. Furosemide is typically given as a bolus (2 mg/kg IV), and if urine production increases, it is continued as a CRI (0.25–1.0mg/kg/h). Aminoglycoside toxicity should not be treated with furosemide as it can potentiate further kidney injury. Studies in people have failed to demonstrate improved survival in AKI patients who received furosemide or mannitol; however, widespread access to advanced therapies such as dialysis makes it unclear if these studies are directly applicable to animals.

Small retrospective studies had suggested that fenoldopam, a peripheral dopamine D1 receptor agonist, and diltiazem, a calcium channel blocker, might be helpful in the treatment of AKI. More recent prospective studies have failed to demonstrate a benefit of either drug. Evidence suggests that use of diltiazem may actually be contraindicated depending on the AKI cause; therefore, use of these drugs is not recommended.

Patients that produce significant amounts of urine in response to rehydration or mannitol/furosemide therapy are less likely to require specific treatment for electrolyte and acid–base imbalances. Oliguric and anuric patients that do not respond to medical management can quickly develop fatal hyperkalemia and metabolic acidosis.

Hyperkalemia

The most common life-threatening electrolyte imbalance encountered in AKI is hyperkalemia. Restoring urine production is critical. Elevation in serum potassium causes a reduction of the transmembrane electrochemical gradient and changes nerve and muscle cell excitability. Clinically, signs of hyperkalemia include muscle weakness, reduced cardiac contractility, arrhythmias, and neurologic abnormalities. Classic ECG findings include bradycardia, disappearance of the P wave, spiking of the T wave, and widened QRS complexes (Figure 13.4). These changes begin to appear when potassium approaches 6.5 mEq/L. Cardiac arrest can occur at any time.

In the absence of adequate urine production, only dialysis can provide a long-term solution to hyperkalemia; however, there are several strategies for short-term management of this condition (Table 13.7).

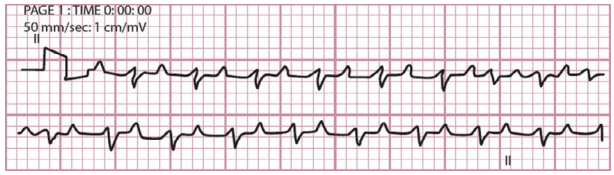


FIGURE 13.4 Example of an ECG of a patient with hyperkalemia (lead II).

TABLE 13.7 Strategies for the treatment of hyperkalemia

– Calcium gluconate (10% solution) 0.5–1.0 mL/kg can be given IV over 10–15 minutes – Protects against cardiac toxicity for approximately 30 minutes – Note: Calcium gluconate comes in several concentrations, this dose is only for 10%
– Albuterol sulfate (90 µg/actuation) 1–5 actuations delivered via "AeroDawg" chamber – Effect and duration may be dose dependent, with serum potassium decreases taking 30–60 minutes to reach maximal effect
– Regular insulin 0.1–0.25 u/kg and glucose 1–2 g per unit of insulin given – Potassium transported into cells with glucose, provides short-term correction – Note: It is important to periodically check blood glucose after administration and treat possible hypoglycemia
– Sodium bicarbonate 1–2 mEq/kg over 20 minutes – Corrects for acidosis allowing K+ back into cells, effect can last up to 1–2 hours – Note: Reserved for cases where serum bicarbonate <12 mEq/L and pH <7.2

Metabolic Acidosis

Metabolic acidosis is also common in AKI as the renal tubules are responsible for recapturing filtered bicarbonate as well as manufacturing new buffer. Generally, metabolic acidosis is not treated unless serum bicarbonate is less than 12 mEq/L and pH <7.2. A dose for bicarbonate can be calculated as (body weight in kg × 0.3) × (16 – measured bicarbonate mEq/L). Typically, only two-thirds of the dose is given with one-third given IV over 30 minutes, while another one-third can be given with IV over 4 hours. Acid–base status should be re-evaluated before additional bicarbonate is administered as needed.

Emesis

AKI patients commonly experience significant vomiting that can complicate treatment, worsen electrolyte abnormalities, and contribute to dehydration. The vomiting is likely due to both stimulation of the chemoreceptor trigger zone by uremic toxins and gastric irritation. Emesis should be addressed with a combination of antiemetic and gastric protectant medications (Table 13.8). Since there are antiemetics in at least three different class of drugs, multiple drugs can be used to control emesis. For example, it is not uncommon to combine a metoclopramide CRI with maropitant. Until emesis is controlled, these medications should be given IV.

TABLE 13.8 Protocols used in control emesis in acute kidney injury patients

Antiemetics	Medication	Class	Dose
	Metoclopramide (Reglan)	Dopamine inhibitor	0.01–0.02 mg/kg/h IV constant rate infusion or 0.2–0.5 mg/kg IV, p.o. q.8 h.
	Maropitant citrate (Cerenia)	NK1 inhibitor	1 mg/kg SC q.24 h. (dogs) 1 mg/kg SC or IV (cats)
	Ondansetron (Zofran)	5-HT3 inhibitor	0.1–1.0 mg/kg IV q.6–12 h.
	Dolasetron (Anzemet) 0.6–1.0 mg/kg IV q.24 h.	5-HT3 inhibitor	
Control of gastric irritation			
	Pantoprazole (Protonix)	Proton pump inhibitor	0.5–1 mg/kg IV q.24 h. given over 15 minutes
	Omeprazole (Prilosec)	Proton pump inhibitor	0.7 mg/kg p.o. q.24 h.
	Sucralfate (Carafate)	Gastric coating	0.5–1.0 mg/kg p.o. (dog) 0.25 mg/kg (cat)
	Famotidine (Pepcid)	H_2 receptor antagonist	0.5 mg/kg p.o., SQ, IV q.24 h.

Drug Dosage

Many drugs are excreted by the kidneys. In AKI, dosages of these drugs must be adjusted to reflect the reduced clearance. Although measuring serum drug levels and adjust dosages accordingly is ideal, it is rarely performed. A more common methodology is to give one standard dose and reduce subsequent dosages by multiplying them by 1/serum creatinine. This is based on the principle that increases in serum creatinine are inversely proportionate to the decrease in glomerular filtration rate (GFR). However, this approximation is only valid until serum creatinine approaches 4 mg/dL. Many will reduce the dosages based on serum creatinine until it rises above 4.0 and then use the calculation as a guide while empirically adjusting the dosage. Nephrotoxic drugs and renally excreted drugs with a narrow therapeutic index should be avoided in AKI patients.

Leptospirosis

Patients should be treated as outlined previously with special attention paid to fluid therapy. Patients who are oliguric or anuric benefit from advanced renal therapies such as dialysis/continuous renal replacement therapy (CRRT), and referral should be considered. Whenever possible, doxycycline should be used as the initial antimicrobial therapy as it treats both the leptospiremia and clears the carrier state; however, doxycycline is metabolized by the liver and excreted in the bile. In patients with evidence of liver impairment, antibiotics in the beta-lactam category (penicillin, ampicillin) should be used for 2 weeks to clear the leptospiremia. This is then followed with doxycycline to clear the carrier state.

Specific Toxin Ingestion

Ethylene Glycol

Exposure is always a medical emergency. Several cageside tests are available for ethylene glycol detection. These tests differ in their sensitivity as well as the complexity of the testing procedure. In the absence of an in-hospital diagnostic test, the treatment of ethylene glycol should begin whenever a combination of compatible laboratory findings (severe metabolic acidosis, increased anion gap, hypocalcemia, calcium oxalate monohydrate crystalluria) is seen in an animal demonstrating appropriate clinical signs. Because it is rapidly absorbed and likely to lead to emesis, vomiting should be not induced. Also, due to the risk of aspiration and the lack of efficacy, activated charcoal should not be administered. Initial serum chemistry should be obtained and repeated at 24 and 48 hours.

4-methylpyrazole (4-MP), an antidote, should be administered at once (Table 13.9). The first step in ethylene glycol's metabolism into toxic intermediaries takes place in the liver by alcohol dehydrogenase. Methylpyrazole binds to and inactivates alcohol dehydrogenase so that the ethylene glycol can leave the body unchanged through the kidneys. Ethanol can also be administered IV as alcohol dehydrogenase will preferentially metabolize the ethanol; however, 4-MP is safer and more efficacious. Aggressive IV fluid therapy should be started, and urine output monitored for at least 48 hours. If urine output decreases, follow AKI fluid therapy recommendations outlined previously.

In dogs, the greatest benefit of treatment is seen in the first 5–8 hours and cats within 3 hours of ingestion. In one study, those cats treated 3 hours or less after exposure with 4-MP had 100% survival while those that received ethanol had a 25% survival; however, 4 hours after ethylene glycol ingestion, there was 100% mortality regardless of treatment.

In 2015, the U.S. FDA withdrew approval for Antizol-Vet, making 4-MP unavailable to the American veterinary market. Compounded 4-MP is available but is not legal in some states. Check local laws before administering compounded 4-MP. In instances where 4-MP is unavailable, an ethanol solution can

TABLE 13.9 Treatment of ethylene glycol toxicity

Canine 4-MP treatment	4-MP (methylpyrazole 50 mg/mL) – 20 mg/kg IV first dose – 15 mg/kg at 12 hours – 15 mg/kg at 24 hours – 5 mg/kg at 36 hours
Feline 4-MP treatment	4-MP (methylpyrazole 50 mg/mL) – 126 mg/kg 4-MP (methylpyrazole 50 mg/mL) slow IV initial dose – 31.25 mg/kg IV at 12 hours – 31.25 mg/kg IV at 24 hours – 31.25 mg/kg IV at 36 hours
Ethanol treatment	Create 7% ethanol solution – Remove 175 mL from a 1 L bag of saline – Add 175 mL of 80-proof vodka Alternative – Remove 78 mL from a 1 L bag of saline – Add 78 mL of 190-proof grain alcohol (e.g., Everclear) Administer IV loading dose of – 8.6 mL/kg continued as a CRI of 1.43 mL/kg/h

be administered IV (Table 13.9). Ethanol can lead to significant central nervous system (CNS) depression, vomiting, and compound the clinical signs of ethylene glycol ingestion.

NSAID Toxicity

Nonsteroidal anti-inflammatory drugs (NSAIDs) are potent inhibitors of prostaglandin synthesis. Prostaglandins are important for maintaining normal renal blood flow, and their absence can lead to hypoxic kidney injury. Each NSAID has a different toxic dose, and whenever possible, poison control should be consulted. Rate of absorption from the GI can be affected by the formulation with gel caps being absorbed faster than tablets. Generally, if ingestion is discovered in the first 2–4 hours, vomiting should be induced. Due to extensive enterohepatic circulation, activated charcoal should be administered and repeated. Initial serum chemistry should be obtained and repeated at 24 and 48 hours. Aggressive IV fluid therapy should be started, and urine output monitored for at least 48 hours. Misoprostol, a synthetic prostaglandin E1 analog, can be given to dogs at a dose of 2.0–5.0 mcg/kg every 8 hours. Due to its long half-life, naproxen toxicities should be treated for at least 72 hours. Recently, significant NSAID toxicities have been successfully treated with therapeutic plasma exchange. These patients demonstrated little or no residual kidney injury. Owners who are interested should be referred as soon as possible, as treatment is time sensitive. Some NSAID toxicities may also be amenable to lipid therapy.

Cholecalciferol-based Rodenticides

Because of restrictions placed on traditional anticoagulant rodenticides, use of cholecalciferol-based products is becoming more common. If ingestion is discovered in the first 2 hours, vomiting should be induced and activated charcoal administered and repeated. Initial serum chemistry should be obtained and then repeated every 24 hours for 4 days. Aggressive IV fluid therapy should be started, and urine output monitored. Sodium chloride is the preferred fluid as it promotes calcium excretion. A combination of furosemide (2 mg/kg every 6 hours) and prednisone (2–3 mg/kg every 12 hours) should be administered to further increase calcium excretion. Phosphate binders (e.g., aluminum hydroxide) can be used as needed. If urine output decreases, follow AKI fluid therapy recommendations outlined previously. As treatment for cholecalciferol toxicity can last weeks, pamidronate 1.3–2.0 mg/kg given IV over 2 hours has become the preferred treatment of choice. Often only one dose is needed. Serum renal, calcium and phosphorus levels should be monitored for 6 weeks.

Grapes and Raisins

Ingestion of grapes and raisins as well as products containing them has been associated with development of AKI in dogs. The mechanism of toxicity is unknown. Interestingly, not all dogs are susceptible to the toxic effects. As it is an idiosyncratic reaction, there is no minimum dose that should be considered safe. Ingestion of anything more than palm-full should be considered toxic. Grapes delay gastric emptying; therefore, if ingestion is discovered in the first 6 hours, vomiting should be induced, and a single dose of activated charcoal administered. Initial serum chemistry should be obtained and then repeated at 24 hours. Aggressive IV fluid therapy should be started, and urine output monitored for at least 48 hours. If urine output decreases, follow AKI fluid therapy recommendations outlined previously. Dogs showing signs of AKI have a guarded prognosis. In one study, although about half of affected patients survived; 35% of survivors had had signs of CKD.

Lily Ingestion

True lily plants of the family *Liliaceae* (i.e. Easter lilies, tiger lilies, etc.) are extraordinarily nephrotoxic to cats, and even the smallest exposure should be considered potentially fatal. Simply drinking the water from a vase containing lilies can cause irreversible kidney damage. While the mechanism of the toxicity is not known, it causes severe acute proximal tubular necrosis. If ingestion is discovered in the first 2 hours, vomiting should be induced, and activated charcoal administered. Initial serum chemistry should be obtained and then repeated at 24 hours. Aggressive IV fluid therapy should be started, and urine output monitored for at least 48 hours. If urine output decreases, follow AKI fluid therapy recommendations outlined previously. Prognosis for cats presenting for lily ingestions is guarded. In one small study, cats that became oliguric or anuric died despite aggressive interventions.

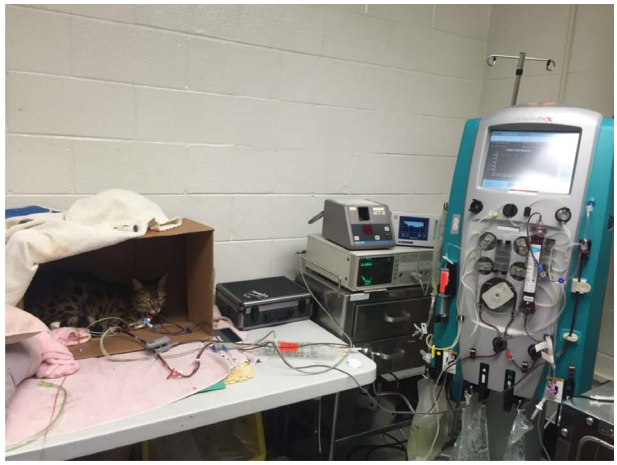


FIGURE 13.5 Patient receiving continuous renal replacement therapy. A box with towel over the front was set up to make the patient feel safe and more comfortable.

Advanced Renal Therapies

In recent years, the increasing availability of intermittent hemodialysis and continuous renal replacement therapy has made these modalities a viable option for patients with AKI (Figure 13.5). They should be considered whenever an AKI patient is experiencing azotemia, electrolyte imbalances, or fluid overload that does not respond to conventional therapy. In addition, many centers offer therapeutic plasma exchange which can help with protein bound toxins such as NSAIDS.

If an owner is interested in advanced therapies, a center should be consulted as soon as possible Chance of a successful treatment increases with earlier intervention. In addition, if there is any chance that a client may be interested in dialysis, the jugular veins should not be disturbed. In many patients, these are the only veins in which a dialysis catheter can be placed, and even a single blood draw can render a vein unusable. An up-to-date list of dialysis centers can be found at http://WWW.ASVNU.ORG.

Prognosis

Prognosis is completely dependent on the underlying cause. While leptospirosis patients may require advanced medical care including dialysis, most will do well. Those patients that are unfortunate enough to be exposed to ethylene glycol are much less fortunate. When an underlying case cannot be determined, it is generally accepted that the likelihood of recovery is 50%, although access to dialysis may improve outcome.

CHRONIC KIDNEY DISEASE

Definition/Overview

Chronic kidney disease (CKD) is characterized by a progressive decrease in the kidney's ability to concentrate urine, excrete nitrogenous waste, produce hormones, and maintain electrolyte balance. This deterioration in renal function is due to a gradual, irreversible loss of nephrons and is the most common type of kidney disease in companion animals. CKD is often divided into two categories based on the underlying etiology: Congenital and acquired.

TABLE 13.10 Congenital causes of chronic kidney disease in the dog and cat

Condition	Breed
Amyloidosis	Dog: Shar Pei, Beagle, English Foxhound Cat: Abyssinian, Siamese
Renal dysplasia	Dog: Shi Tzu, Lhasa Apso, Golden Retriever, Soft-coated Wheaten Terrier, others
Fanconi syndrome	Dog: Basenji
Polycystic kidney disease	Dog: Cairn Terrier, Bull Terrier Cat: Persian
Glomerulopathy	Dog: Bernese Mountain Dog, Brittany Spaniel, Rottweiler, Soft-coated Wheaten Terrier, English Cocker Spaniel, Samoyed, Dalmatian, Bull Terrier

In congenital kidney disease, the animal is either born with renal lesions (e.g., aplasia, dysplasia) or born with a condition that will lead to kidney disease in the future (e.g., Shar Pei fever). While many congenital renal diseases are thought to be inherited, the mode of transmission and pathogenesis is often unclear. The patient's condition usually becomes apparent early in life, often in the first year, and is progressive (Table 13.10).

Acquired CKD is the result of an insult to the renal parenchyma that causes nephron loss and precipitates a gradual decline in renal function. While in some cases it is possible to determine and treat the underlying cause of the renal disease (i.e., pyelonephritis), most cases are idiopathic. Regardless of the etiology, most cases of CKD have a similar clinical presentation, course, and treatment.

Pathophysiology

Although the exact pathophysiology of most CKD cases is not known, one possible explanation for the progressive nature of the condition is glomerular hyperfiltration. In glomerular hyperfiltration, an initial insult reduces the number of functioning nephrons (Figure 13.6). This could be a sequela of acute kidney injury, a congenital defect, or the result of a chronic disease process (e.g., hypertension). Remaining nephrons compensate by dilating glomerular arterioles, increased renal plasma flow, and increased single-nephron GFR. This process increased intraglomerular hydrostatic pressure, which eventually leads to mechanical disruption of the capillaries and protein loss through the glomerulus. Excess filtered protein is reabsorbed by the epithelial cells of the proximal convoluted tubule (PCT), broken down by cellular lysosomal mechanisms and re-enters the body as amino acids. This

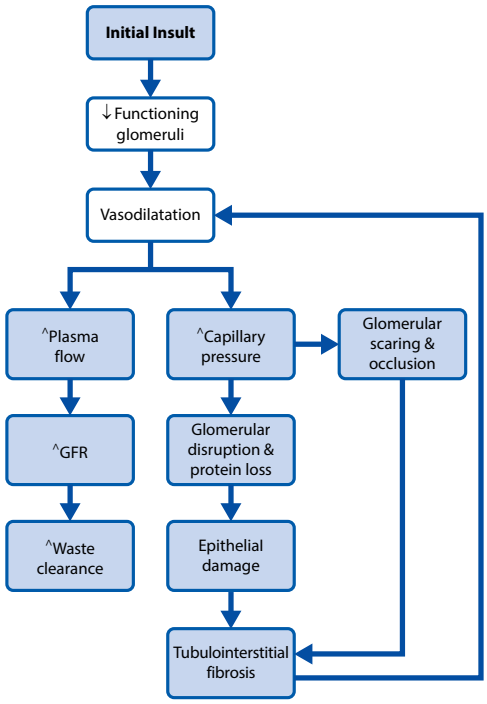


FIGURE 13.6 Pathway by which glomerular hyperfiltration leads to kidney damage.

process releases oxygen free radicals, which stimulate the release of inflammatory cytokines. The resulting inflammation damages epithelial cells. Increased glomerular pressure also results in scarring and eventual occlusion of the glomerular capillaries. Continued damage to tubular epithelial cells, combined with glomerular capillary injury, leads to tubulointerstitial fibrosis, which is the hallmark of CKD (Figures 13.7 and 13.8). Thus, what starts as a compensatory mechanism eventually perpetuates additional renal damage.

Differential Diagnosis

Prerenal, primary renal, or postrenal azotemia; acute renal injury

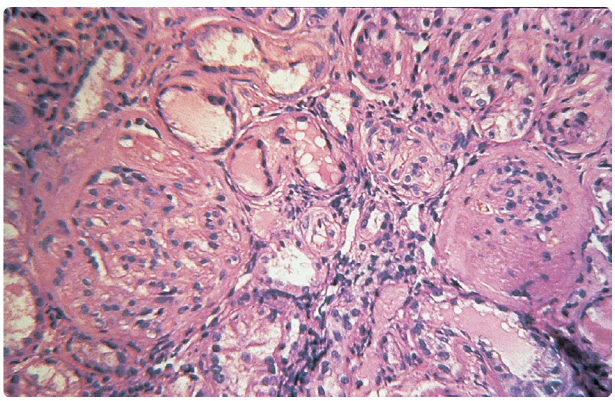


FIGURE 13.7 Histopathology of the kidney from a dog with chronic kidney disease. Glomerulosclerosis and a mononuclear interstitial infiltrate. (*Courtesy of D.F. Senior.*)

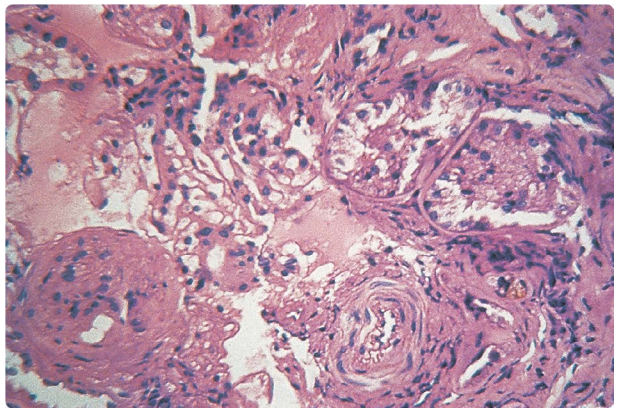


FIGURE 13.8 Histopathology of the kidney from a dog with chronic kidney disease. Tubular atrophy and interstitial fibrosis. (*Courtesy of D.F. Senior.*)

Clinical Presentation

Common clinical features of CKD include polyuria/polydipsia, weight loss, lethargy, anorexia, vomiting, dehydration, oral ulcers, and uremic breath. In cats, blindness secondary to hypertension is not uncommon and is often the primary reason that owners seek veterinary care.

Diagnosis

The diagnosis of CKD is made on the basis history, physical examination, and laboratory blood work. Once the presence of azotemia is confirmed, possible differential diagnosis (prerenal azotemia, postrenal azotemia, and AKI) must be eliminated from consideration. A complete blood count, serum chemistry, urinalysis with urine protein-to-creatinine ratio, and ultrasound should be performed on all CKD patients.

Serum Chemistry

Traditionally, the diagnosis of chronic kidney disease focused on elevations in BUN and creatinine. However, CKD patients are often muscle wasted, which can artificially decrease creatinine. In addition, BUN can be affected by many nonrenal factors (e.g., diet, hydration, GI bleeding), making it a somewhat unreliable indicator. Symmetric dimethylarginine (SDMA) is a newer and more consistent marker of kidney function. SDMA is product of protein modification and is produced in the cytoplasm of all nucleated cells. Because it is cleared exclusively by the kidneys, it is an excellent marker of kidney function. Elevations in SDMA have the ability to detect decreased kidney function up to 17 months before creatinine in cats and as much as 9 months in dogs. SDMA should be part of screening blood work in older pets and those with suspected renal impairment. It important to note that SDMA is essentially a measure of glomerular filtration and can be increased in dehydrated patients; therefore, accessing patient hydration status is essential.

Elevation of serum phosphate is common. Calcium is often mildly to moderately elevated as a result of secondary hyperparathyroidism. Serum bicarbonate

decreases with the degree of renal dysfunction and significant decreases may be associated with a worse long-term prognosis. Potassium levels are usually maintained in the normal range in dogs, but hypokalemia can be observed in cats.

Complete Blood Count

A normochromic, normocytic, nonregenerative anemia is the most common hematologic finding in patients with CKD. Elevations in the white blood cell count can be associated with chronic pyelonephritis or a systemic infectious disease; however, the white blood cell counts are usually unremarkable.

Urinalysis

The most common urinalysis finding in CKD is isosthenuria (specific gravity 1.007–1.015); however, some cats may be able to concentrate urine in the early phases of CKD. The finding of large amount of glucose in a normoglycemic patient is suggestive of proximal tubular dysfunction and can be seen in dogs with Fanconi syndrome (Figure 13.9). The detection of protein, in the absence of gross hematuria, bacteria, white blood cells, or casts in the urine sediment, may be the result of glomerular disease. A quantitative assessment of urine protein concentration requires that a urine protein-to-creatinine ratio (UPC) be performed (see section on Glomerular Disease). In cats, UPC may be prognostic even in the absence of overt proteinuria. Studies suggest that cats with CKD and a UPC <0.43 can be expected to live approximately 2 years from the time of diagnosis. Those with a UPC >0.43 live only about 9 months. Even in the absence of microscopically detected bacteria, a urine culture should be considered if pyelonephritis is suspected.

Blood Pressure Measurement

Hypertension is a common complication of CKD that eventually affects the majority of cats and dogs. Not only can hypertension have negative consequences for the eyes, heart, and nervous system, it can also potentiate further kidney damage; therefore, identifying and treating these patients is essential. Specific guidelines for measuring and treating hypertension can be found in the hypertension section.

Fanconi facts	Failure of proximal tubule transport Sodium, bicarbonate, potassium, glucose, amino acids not resorbed 10–16% of Basenjis affected, documented in other breeds
Diagnosis	Signs of CKD and glucosuria with normal blood glucose are suggestive Aminoaciduria is diagnostic
Treatment	Oral supplementation: Bicarbonate goal (serum >12 mmol/l [12 mEq/l]); potassium goal (serum 4–6 mmol/l [4–6 mEq/l]); calcium goal (serum 2.25–2.5 mmol/l [9–10 mg/dl]) Renal failure diet
Prognosis	Good with proper treatment

FIGURE 13.9 Fanconi syndrome characteristics.

Radiographs and Ultrasound

When available, ultrasound is the preferred imaging modality. It can provide an unparalleled view of the renal architecture and outflow tract; nevertheless, radiographs can be helpful is accessing kidney size and for looking for ureteral stones. Typically, CKD is characterized as bilateral loss of renal mass; however, certain disease processes, such as polycystic kidney disease, have a characteristic ultrasound appearance. Enlarged kidneys are suggestive of an underlying disease process (e.g., lymphoma, feline infectious peritonitis [FIP], hydronephrosis), primary renal neoplasia, or AKI. Mild dilatation of the renal pelvis (pyelectasia) can be seen with chronic kidney infections. Congenital renal dysplasia and aplasia are characterized by an abnormal renal architecture with loss of the delineation between the cortex and medulla.

Management

Staging

Patients with CKD should be staged according to the guidelines developed by the International Renal Interest Society (IRIS). These guidelines classify patients on the basis of renal function, proteinuria, and blood pressure (Table 13.11). For example, a 15-year-old cat with an SDMA of 37, creatinine of 3.0, UPC of 2.0, and blood pressure of 170 mmHg would be classified as a Stage 3, proteinuric, hypertensive patient. The IRIS scoring system not only allows for a common nomenclature for describing, discussing, and monitoring patients, it allows for best practice to be developed and promulgated for disease stage.

Fluid Therapy

Many patients with CKD present with some degree of dehydration. This can complicate management of CKD as dehydration leads to hypoperfusion and prerenal azotemia. Thus, proper rehydration can result in significant reductions in azotemia. Therefore, the degree of dehydration should be estimated, and, if significant, a regimen of replacement fluids should be calculated and administered intravenously over 12–24 hours (Table 13.6). In mildly dehydrated patients, subcutaneous fluids can be administered during the office visit. In either case, when patients have difficulty maintaining proper hydration, the daily administration of subcutaneous fluids at home can help prevent dehydration, reduce azotemia, and improve the patient's quality of life (Figure 13.10a, b) An alternative possibility is the placement of an esophagostomy tube (Figure 13.11a–h). These are easily inserted (with practice), can remain in position for extended periods of time, and can be used to provide the pet's fluid and nutritional needs. They also provide a route for medication administration.

TABLE 13.11 IRIS stages of CKD

		Stage 1	Stage 2	Stage 3	Stage 4
Creatinine* in mg/dL	Canine	<1.4 (125 µmol/L)	1.4–2.8 (125–250 µmol/L)	2.9–5.0 (251–440 µmol/L)	>5.0 (440 µmol/L)
	Feline	<1.6 (140 µmol/L)	1.6–2.8 (140–250 µmol/L)	2.9–5.0 (251–440 µmol/L)	>5.0 (440 µmol/L)
SDMA* in µg/dL	Canine	<18	– 18–35	– 36–54	– >54
	Feline	<18	18–25	26–38	>38

UPC ratio Canine	Nonproteinuric <0.2	Borderline proteinuric 0.2–0.5	Proteinuric >0.5
Feline	Nonproteinuric <0.2	Borderline proteinuric 0.2–0.4	Proteinuric >0.4

Systolic blood pressure in mmHg	Normotensive <140	Prehypertensive 140–159	Hypertensive 160–179	Severely hypertensive >180

* If the SDMA and creatinine are discordant, you should use the one that produces the higher stage.

Control of Acidosis

One of the primary functions of the kidney is to maintain acid–base balance. The renal tubules reabsorb filtered bicarbonate, generate new bicarbonate, and excrete acids. As CKD progresses, the ability of the kidneys to perform this function fails. Even when mild, chronic acidosis enhances protein catabolism, promotes bone demineralization, and contributes to the array of clinical signs. Because most feline maintenance diets are acidified, changing the patient to an appropriately buffered kidney disease diet helps prevent and correct metabolic acidosis. When the patient is being fed an appropriate diet, additional oral alkalization therapy is only indicated when total CO_2 is <18 mEq/L or serum bicarbonate is <17 mEq/L. Initially, sodium bicarbonate at a dose of 5–10 mg/kg q.8–12 h. or potassium citrate at 40–60 mg/kg q.8–12 h. can be given. The exact dose needs to be tailored to the individual patient.

Potassium

Hypokalemia is a common finding in cats with CKD and is associated with muscle weakness, muscle mass loss, ileus, and potentially cardiac arrhythmias; however, the most commonly observed manifestation is anorexia. This condition is not recognized in dogs. The mechanism by which cats develop hypokalemia is unknown; however, it is generally believed to be a combination of malnutrition and excessive renal losses. In one study, one-third of healthy cats fed a potassium restricted diet developed interstitial nephritis and fibrosis. This suggests that low potassium is not only an effect of kidney disease but can contribute to its progression. For this reason, feline kidney disease diets are potassium supplemented and, in most cases, will prevent hypokalemia. In patients that do not respond to diet therapy alone, oral supplementation with potassium citrate 20–30 mg/kg p.o. q.24 h. can be given (a convenient powder form is commercially available for the smaller-sized animal).

Hyperphosphatemia

Because of its role in muscle and nerve conduction, calcium is highly regulated within the body. Parathyroid hormone (PTH) is released by the parathyroid gland in response to decreases in circulating

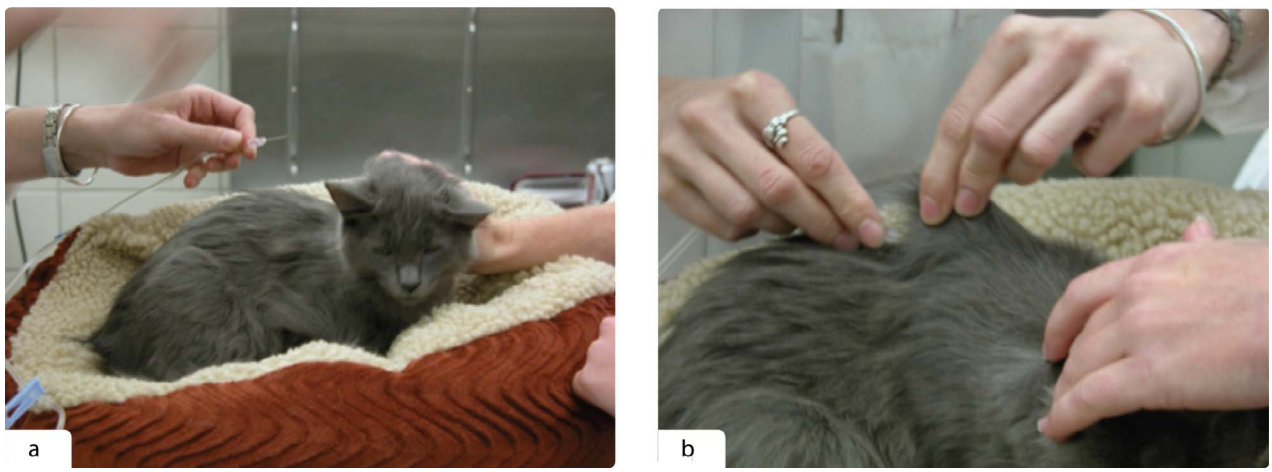


FIGURE 13.10 (a, b) Cat with chronic kidney disease receiving subcutaneous fluids.

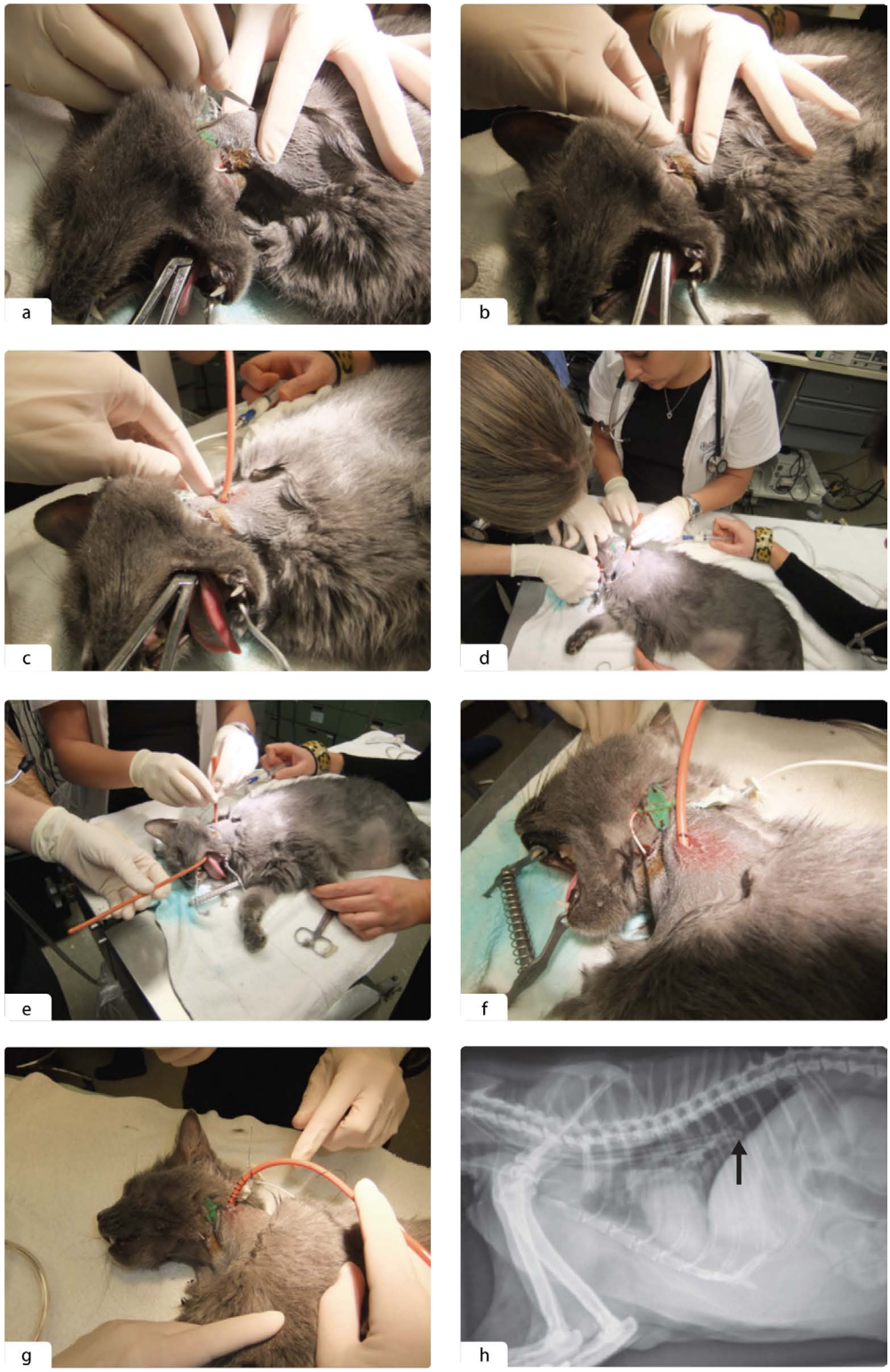


FIGURE 13.11 Esophagostomy tube placement. The patient is anesthetized and monitored. Although most tubes are placed on the left lateral cervical area, the right can be used as well. A red rubber or silicone tube is selected and marked so that the end of the tube will be located in the esophagus between the 6th and 9th intercostal spaces. The left lateral cervical area is clipped and scrubbed. The jugular vein is identified and isolated. **(a)** A pair of Mixter hemostats (tip forms a right angle) is inserted into the mouth and a small stab incision is made through the skin just over the tip of the hemostat. **(b)** The hemostat is seen poking through the skin. **(c)** A feeding tube is inserted into the open jaws of the hemostat. **(d)** The feeding tube is pulled into the esophagus and out of the mouth. **(e, f)** The tube is fed back into the mouth and down the esophagus. **(g)** A purse-string suture and a finger trap are placed to hold the tube in place. **(h)** Radiography confirms correct placement. Note the end of the tube is caudal to the heart and cranial to the lower esophageal sphincter (arrow).

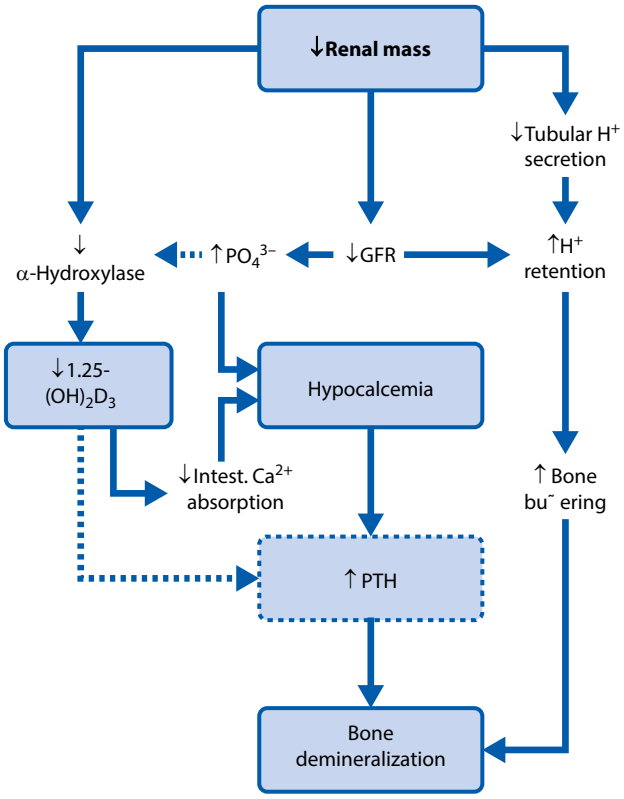


FIGURE 13.12 Pathogenesis of renal secondary hyperparathyroidism in chronic kidney disease. Renal production of calcitriol normally inhibits parathyroid hormone production and release by the parathyroid gland. Broken arrows indicate an inhibitory action.

calcium (Figure 13.12). PTH causes the release of stored calcium and simulates an enzyme in the renal tissue, alpha-1 hydroxylase, to convert calcidiol to calcitriol. Calcitriol, the active form of vitamin D3, stimulates absorption of calcium from the intestinal tract, enhances the activity of PTH, and provides the negative feedback for PTH release. Phosphate is normally absorbed from the diet, used for metabolic processes, and subsequently undergoes renal excretion. As renal mass decreases and GFR falls, excessive levels of phosphate accumulate in the blood. Phosphate acts to inhibit alpha-1 hydroxylase, thus preventing the formation of calcitriol and removing the negative feedback on PTH. Thus, hyperphosphatemia leads to loss of calcitriol, increased release of PTH, and further harvesting of calcium and phosphorus from bone. Soft tissue mineralization becomes a concern when serum calcium and phosphorus are elevated. In addition, PTH is believed to be a uremic toxin which is responsible for some the signs seen in CKD patients.

Lastly, calcitriol may also play a role in slowing the progression of renal disease. Therefore, controlling hyperphosphatemia is essential.

There is no medical treatment that will rapidly decrease serum phosphorus levels; however, fluid therapy can help in dehydrated patients. Since the primary source of serum phosphorus is dietary, the first step is to change the patient's diet to a low-phosphorus kidney disease diet. In some cases, this will adequately control serum phosphorous levels. If after 1–2 weeks hyperphosphatemia has not resolved, a phosphate-binding agent should be added. Aluminum hydroxide and aluminum carbonate are commonly used and effective in binding phosphorus in the intestine. These are dosed at 30–80 mg/kg q.24 h. divided and given with meals. Cats often find liquid phosphate binders to be unpalatable and may do better with powered forms. Lanthanum carbonate (Fosrenol) 30 mg/kg divided and given with meals is an alternative. It should be crushed and mixed well with food. Calcium acetate given at 60–90 mg/kg q.24 h. divided with meals may also be effective in binding phosphate but may contribute to hypercalcemia; therefore, monitoring of serum calcium is essential. Regardless of the binder selected, the medication should be started at the lowest dose and then adjusted as needed based on serum phosphorus levels. Two weeks should be given between rechecks. Several new phosphate binders have been introduced for use by human kidney disease patients. These new drugs are expensive and have not been shown to be more effective or safer in cats and dogs.

Since elevated PTH levels result from inhibition of calcitriol synthesis, supplementation with exogenous calcitriol has been proposed as a treatment for secondary hyperparathyroidism. Studies suggest that calcitriol therapy slows progression of CKD and improves survival in CKD dogs. Since studies have shown no such benefit in cats, calcitriol should not be used in this species. Prior to calcitriol use, calcium and phosphate serum levels should be within normal range. Calcitriol given at 2.0–2.5 ng/kg per day has been effective in normalizing serum PTH levels; however, dosages must be tailored to each patient. Ionized calcium and PTH must be monitored. The goal is to minimize PTH without inducing hypercalcemia. Since calcitriol can significantly increase intestinal calcium and phosphorus absorption, it must not be given with food. It is recommended that calcium and phosphate levels be monitored 1 week after starting therapy and monthly thereafter.

Proteinuria

Proteinuria can accelerate the progression of CKD, and steps to mitigate protein loss should be taken when the UPC exceeds 0.4 in the cat and 0.5 in the dog. Therapy usually involves feeding of a protein-restricted diet and administration of a renin–angiotensin–aldosterone system (RAAS) inhibitor. The goal of the therapy is to reduce the protein-to-creatinine ratio by at least 50% and preferably into the normal range. More treatment information is available in the PLN section.

Treatment of Anemia

The cause of anemia in CKD is multifactorial and includes decreased red blood cell (RBC) life span due to uremic toxins, nutritional deficiencies impairing RBC production, and intestinal bleeding; however, the most important cause of anemia is the loss of erythropoietin production by renal interstitial cells (Figure 13.13). Erythropoietin

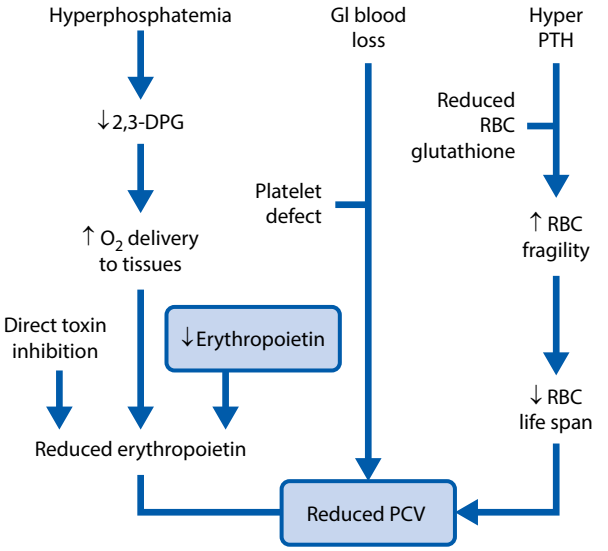


FIGURE 13.13 Pathogenesis of anemia in chronic kidney disease. The major cause of anemia is reduced renal production of erythropoietin.

is a glycoprotein that increases the number of committed stem cells in the bone marrow that will develop into erythrocytes. In the absence of erythropoietin, erythroid stem cells undergo apoptosis. Release of erythropoietin depends on oxygen sensors located on renal interstitial cell membranes. These sensors upregulate production of erythropoietin during hypoxia and downregulate production when blood oxygen levels are normal.

Patients who are symptomatic for their anemia or have a critically low packed cell volume (PCV) should immediately receive a compatible transfusion. Those patients with low PCVs that are not symptomatic should be started on a recombinant erythropoietin replacement therapy. Two options exist: Epoetin alfa (Epogen), and darbepoetin alfa (Aranesp®). Epoetin alfa is significantly less costly. Because it is a human recombinant protein, epoetin alfa simulates an immune response in 25%–30% of patients. This can inactivate the exogenous hormone as well as the endogenous erythropoietin. The resulting red cell aplasia can be difficult to treat and can leave the patient transfusion dependent. For this reason, epoetin alfa should be reserved only for patients with significant anemia and cost concerns. The induction dose is 50–150 units/kg SQ 3 times a week. Response time is variable, but increases in PCV are usually seen in 1–2 weeks, and target PCV should be obtained within a month. Once PCV has returned to 24%–28%, the dose is tapered down to the minimum needed to maintain efficacy. Often 50–100 units/kg SQ 1–2 times a week is sufficient. The PCV should be rechecked every 2 weeks during induction and then monthly. Failure of the PCV to rise despite increasing dosages of epoetin alfa is strongly suggestive of an immune response. The drug should be discontinued at once, and its use can be re-attempted in 3–4 weeks. As the immune response is likely to persist, these patients may never again respond appropriately to therapy. In addition, once an immune response develops to epoetin alfa, darbepoetin alfa is unlikely to be effective. Use of epoetin alfa has also been associated with hypertension, and, therefore, blood pressure should be checked regularly.

Although darbepoetin alfa is costlier, experience suggests that it is much less likely to stimulate an immune response. The induction dose is 0.45–1.5 mcg/kg subcutaneously (SC) every 7 days. This continues until the patient's PCV reaches the low end of the normal range. At this point, the patient is changed to every-other-week dosing. Initially, PCV should be checked weekly and then monthly once stable. Due to the high demand for iron needed for erythropoiesis, it is recommended that patients receiving either epoetin alfa or darbepoetin alfa receive iron supplementation (10 mg/kg intramuscularly (IM) every 3–4 weeks). Like Epogen, use of darbepoetin alfa has been associated with hypertension, requiring regular blood pressure evaluations.

Diet

The mainstay of CKD management is the correction of dehydration and nutritional support. Dietary formulations for patient with CKD have traditionally focused on protein restriction in hopes of slowing the progression of kidney disease. While protein restriction does help reduce uremia and can significantly improve the patient's quality of life, it is not clear that controlling protein alone can significantly change the disease course. Nevertheless, it is clear that patients with CKD who are fed a kidney disease diet live longer than those fed a maintenance formulation. Control of acidosis, hyperphosphatemia, and hypokalemia are helpful in treating these patients. Studies demonstrate that proper regulation of serum phosphorus alone can improve survival of CKD patients. The ratio of omega-3 to omega-6 fatty acids may also play an important role in slowing the progression of renal disease. Commercially available kidney disease diets are generously supplemented with omega-3 fatty acids.

Anorexia

Patients with CKD often suffer from anorexia. While the exact cause of inappetence is unknown, it is probably related to uremic toxins combined with irritation of the gastrointestinal tract. Due to their low protein, restricted phosphorus, and reduced sodium, kidney disease diets can be unpalatable. Owners should try several different brands and formulations in order to find one that their pet will eat. Some owners report good success with rotating several different diets. Many CKD pets will eat frequent small meals rather than one or two large ones; therefore, feeding schedules and amounts may need to be adjusted. Warming of wet food can also make a renal diet more palatable, especially to cats; however, when utilizing a microwave oven, care must be taken as nonuniform heating can lead to oral burns. Transdermal mirtazapine (Mirataz®) has been approved for use in the United States and the EU as an appetite simulant in cats. Recently, capromorelin (Elura®) was

approved in the United States as an appetite simulant for cats with CKD. Because hypergastrinemia can occur with CKD, many patients respond to H2-histamine receptor blockers such as famotidine 0.5 mg/kg IV, p.o. q.24 h. When present, nausea can usually be relieved with maropitant citrate (Cerenia®) or dolasetron mesylate (Anzemet®) (see Table 13.8).

Advanced Renal Therapies

Renal transplantation for cats with CKD is now being performed at select referral centers. In order to be a candidate, a patient must be documented to be free of infectious diseases such as feline leukemia virus, feline immunodeficiency virus, and toxoplasmosis. Recent thoracic radiographs and an abdominal ultrasound are required to show the absence of a malignancy. In addition, an echocardiogram may be required to demonstrate that the patient does not have on underlying cardiac condition. A good candidate would be a middle-aged cat that is suffering from increasing azotemia despite appropriate therapy and in good body condition. Six-month survival approaches 60% while 3-year survival is greater than 40%. While renal transplantation has been performed in dogs, the success rates have not been encouraging due to problems with tissue rejection. Centers performing renal transplantation can be found online at WWW.ASVNU.ORG.

Hemodialysis for the CKD patient is available at some centers. While technically feasible, cost, complications, and the need for frequent treatments has made this option impractical for most.

Prognosis

CKD is an insidious disease, and progression is inevitable; however, when properly managed, patients can do well for relatively long periods of time. In general, cats will do well for longer periods of time than dogs.

PROTEIN-LOSING NEPHROPATHY

Definition/Overview

Normally, the glomerulus provides an effective barrier against the loss of albumin and other large proteins. In protein-losing nephropathy, the barrier is disrupted, and excessive amounts of protein cross the glomerular filtration barrier into the tubules. As a result, tubules become damaged by inflammation and fibrosis. Thus, what starts as a localized disruption of the glomerulus leads to a generalized disease of the nephron and kidney.

Pathophysiology

The glomerular capillary bed is unique in that it can filter molecules based on the size and charge of a molecule. The wall of the glomerular capillary is composed of three distinct layers: Endothelial cells, glomerular basement membrane, and epithelial cells (Figure 13.14). The endothelial cells form the inner lining of the capillary

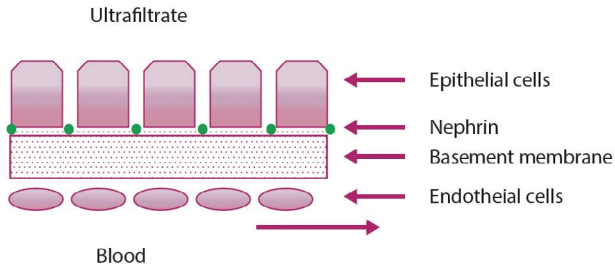


FIGURE 13.14 The components of the glomerular membrane.

tube. While the endothelial cells do not provide a significant filtration barrier, they do serve other important functions such as the inhibition of clot formation. The basement membrane, which provides the structural scaffold of the glomerulus, possesses a negative charge that helps establish glomerular charge selectivity. It is composed of type IV collagen, laminin, and heparan sulfate. Collagen is primarily responsible for the structural support, laminin is involved with cell adhesion, and heparan sulfate provides the basement membrane its negative charge. Epithelial cells, called podocytes, freely float in Bowman space. These cells give rise to an array of parallel projections called foot processes, which are attached to the basement membrane. The projections interdigitate to form slit pores. Proteins, such as nephrin, bridge slit pores and limit the size of molecules that can pass.

The degree to which a protein can pass across the glomerular capillary wall is a function of molecular size and charge (Figure 13.15). Selectivity is based primarily on podocyte slit pores and to a lesser extent the negative charge. Typically, small negatively charged proteins, such as inulin (5,200 MW) are freely filtered. Larger ones such as myoglobin (17,000 MW) are partially filtered, while albumin (69,000 MW) is minimally filtered. Under normal circumstances, most filtered proteins are

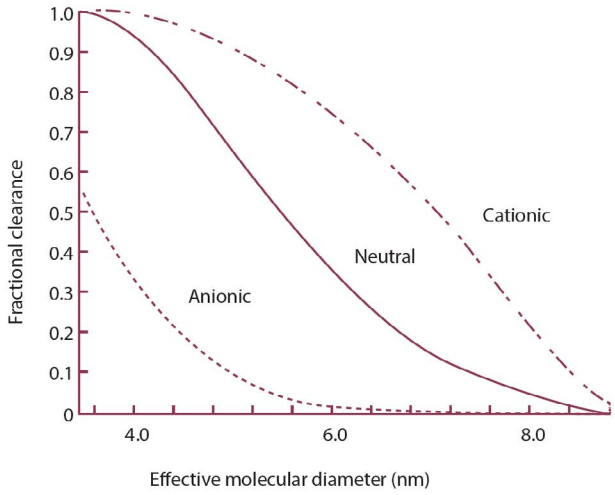


FIGURE 13.15 Charge selectivity of glomerulus demonstrated by fractional clearance of anionic and neutral molecules. The neutral molecule is more freely filtered because it is not repelled by the membrane's charge.

reabsorbed in the proximal convoluted tubule. Large proteins are taken into the tubular epithelial cells by carrier-mediated endocytosis and then catabolized in the lysosomes where they are broken down into amino acids. The process of breaking down large amounts of proteins into amino acids is thought to release oxygen free radicals and leads to the release of inflammatory cytokines. The resulting inflammation causes fibrosis and scarring of the tubules.

There are two broad disease categories associated with disruption of the normal filtration barrier of the glomerulus and the development of protein-losing nephropathy (PLN): Glomerulonephritis (GN) and amyloidosis. These cannot be distinguished from each other on the basis of clinical signs or laboratory data. Only a renal biopsy can differentiate the two conditions.

Amyloidosis

Amyloidosis is caused by an inappropriate deposition of fibrils into glomerulus. These fibrils are formed by the polymerization of protein subunits, which have a specific tertiary structure called a beta-pleated sheet. These subunits, such as serum amyloid A (SAA), are produced in the liver and are one of a number of acute-phase reactants manufactured in response to inflammation. The exact function of these proteins is unknown, but production appears to be simulated by interleukin-2 (IL-2), IL-6, and tumor necrosis factor (TNF), which are released by macrophages. Once polymerized, the amyloid fibrils cannot be degraded because the beta-pleated sheet conformation prevents enzymatic degradation. When deposited in the glomerulus, the fibrils act to disrupt normal function (Figure 13.16).

Glomerulonephritis

Glomerulonephritis (GN) results from the deposition of preformed circulating immune complexes or complexing of circulating antibodies with exogenous or endogenous antigens on the glomerular basement membrane. The presence of immune complexes leads to activation of complement, neutrophil chemotaxis, platelet aggregation, and activation of the coagulation system. This results in protein spilling across the glomerulus and into the proximal tubules. Eventually, the glomerulus responds to the immune response with cellular proliferation, thickening of the basement membrane, and eventually sclerosis.

GN can be divided into three categories based on histologic appearance: (1) Membranoproliferative glomerulonephritis, (2) membranous nephropathy, and (3) proliferative glomerulonephritis.

Membranoproliferative glomerulonephritis (MPGN) is the most common type of GN seen in the dog and accounts for up to 60% of all cases. While a familial form of the disease is seen with Bernese Mountain dogs, and a rapidly progressive form has been associated with *Borrelia burgdorferi* infection, the underlying cause of most cases is unknown. The classic histopathologic appearance is that of thickened capillary loops and mesangial hypercellularity (Figures 13.17–13.20).

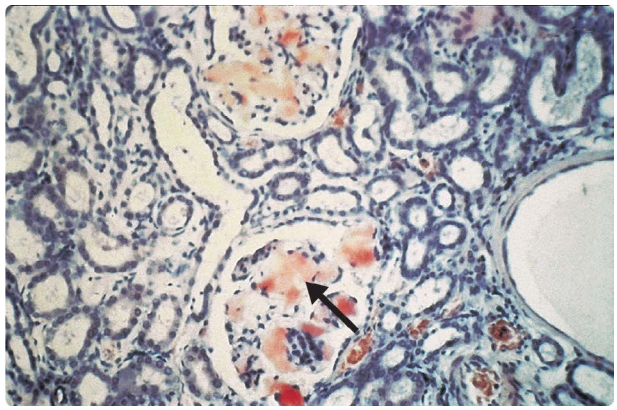


FIGURE 13.16 Histopathology of the kidney of a dog with amyloidosis. Red-staining amorphous amyloid is evident in the glomeruli (arrow). (*Courtesy of D.F. Senior.*)

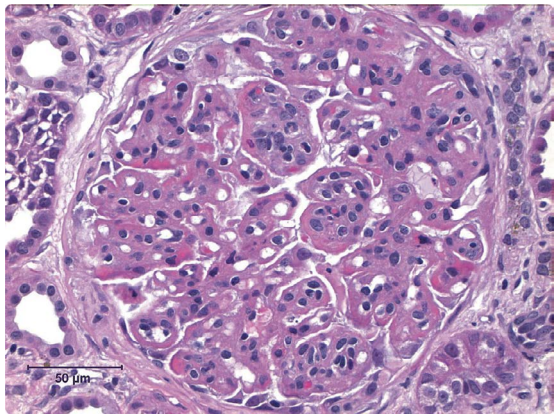


FIGURE 13.17 Illustrations of the histologic and ultrastructural features of membranoproliferative gomerulonephritis in a dog. The light microscopic appearance of a single glomerulus is shown stained with H&E. (*Courtesy of R.P. Groman, G.E. Lees, B.R. Berridge, and F.J. Clubb Jr.*)

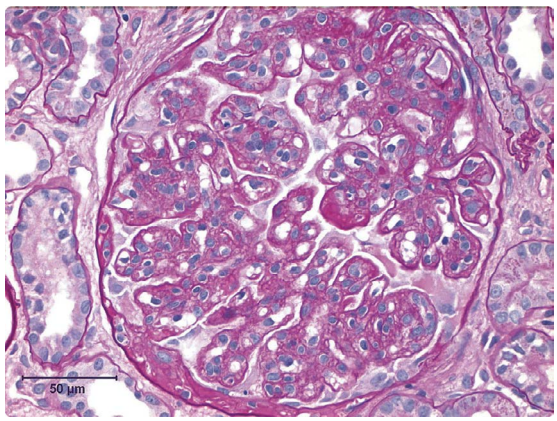


FIGURE 13.18 Illustrations of the histologic and ultrastructural features of membranoproliferative gomerulonephritis in a dog. The light microscopic appearance of a single glomerulus is shown stained with PAS. (*Courtesy of R.P. Groman, G.E. Lees, B.R. Berridge, and F.J. Clubb Jr.*)

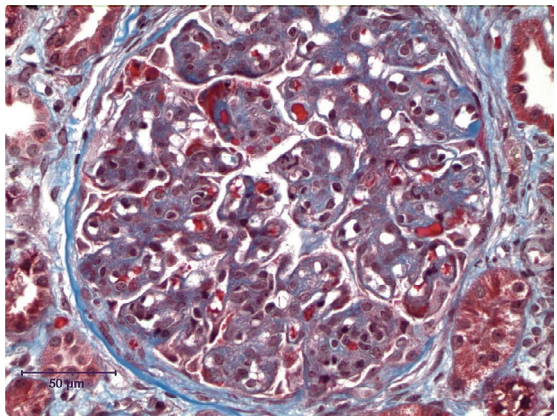


FIGURE 13.19 Illustrations of the histologic and ultrastructural features of membranoproliferative gomerulonephritis in a dog. The light microscopic appearance of a single glomerulus is shown stained with Masson's trichrome. (*Courtesy of R.P. Groman, G.E. Lees, B.R. Berridge, and F.J. Clubb Jr.*)

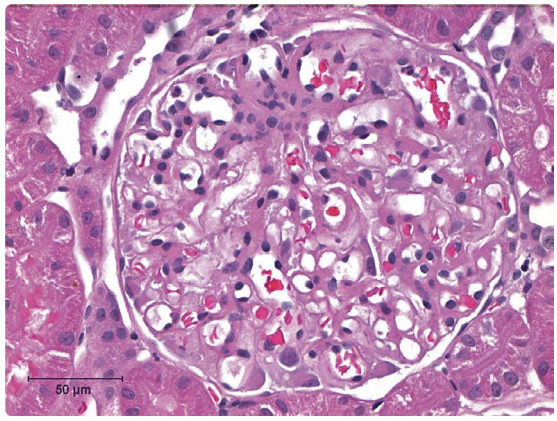


FIGURE 13.21 Illustrations of the histologic and ultrastructural features of membranous glomerulonephritis in a dog. The light microscopic appearance of representative glomeruli is shown stained with H&E. (*Courtesy of R.P. Groman, G.E. Lees, B.R. Berridge, and F.J. Clubb Jr.*)

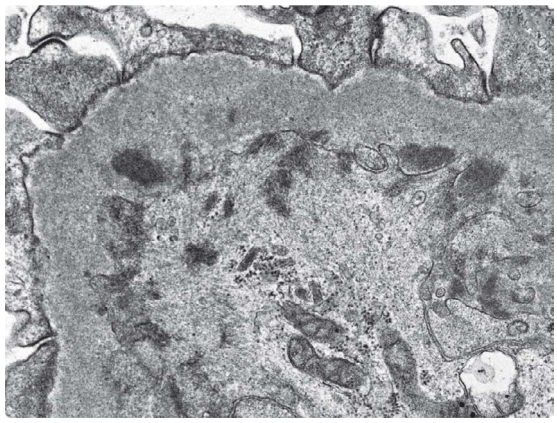


FIGURE 13.20 Illustrations of the histologic and ultrastructural features of membranoproliferative gomerulonephritis in a dog. The transmission electron micrograph shows subendothelial electron-dense immune deposits in the capillary wall. (*Courtesy of R.P. Groman, G.E. Lees, B.R. Berridge, and F.J. Clubb Jr.*)

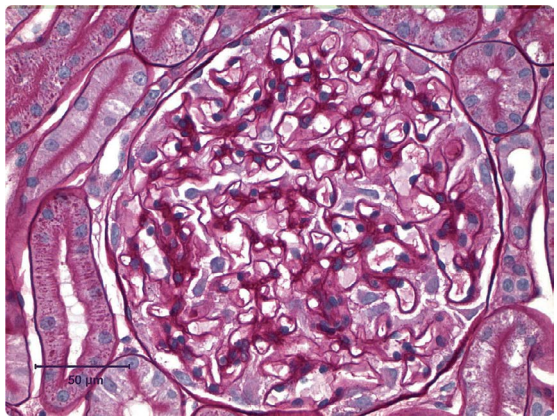


FIGURE 13.22 Illustrations of the histologic and ultrastructural features of membranous glomerulonephritis in a dog. The light microscopic appearance of representative glomeruli is shown stained with PAS. (*Courtesy of R.P. Groman, G.E. Lees, B.R. Berridge, and F.J. Clubb Jr.*)

Membranous nephropathy (MN) is the second most common type of GN lesions seen in the dog and is the most common in the cat (Figures 13.21–13.24). In this condition, the glomerular basement membrane becomes thickened due to the deposition of immune complexes in the subepithelial spaces and the resulting proliferation of the basement membrane. Proliferative glomerulonephritis accounts for as little as 2% of GN cases and is characterized by endocapillary or mesangial proliferation.

Clinical Presentation

Generally, PLN is a disease of middle-aged to older dogs. Clinical features of PLN are somewhat dependent on the stage at which the disease is diagnosed. While some dogs are azotemic and sick, many cases are detected on routine urinalysis in otherwise healthy patients.

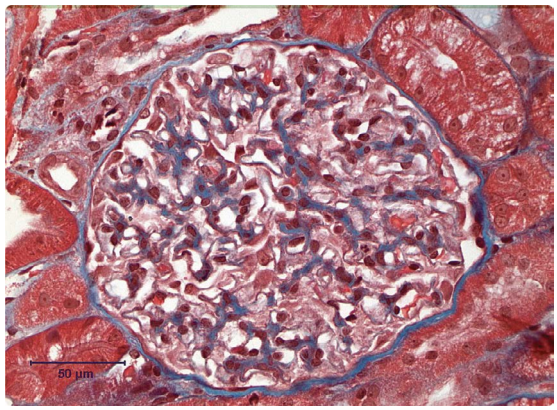


FIGURE 13.23 Illustrations of the histologic and ultrastructural features of membranous glomerulonephritis in a dog. The light microscopic appearance of representative glomeruli is shown stained with Masson's trichrome. (*Courtesy of R.P. Groman, G.E. Lees, B.R. Berridge, and F.J. Clubb Jr.*)



FIGURE 13.24 Illustrations of the histologic and ultrastructural features of membranous glomerulonephritis in a dog. The transmission electron micrograph shows intramembranous electron-dense immune deposits in the capillary wall. (*Courtesy of R.P. Groman, G.E. Lees, B.R. Berridge, and F.J. Clubb Jr.*)

Diagnosis

Urinalysis

The hallmark of PLN is the finding of inappropriate amounts of urine protein in the absence of bacteria, casts, or white blood cells. It is impossible to determine the significance of proteinuria detected on urinalysis or dipstick; therefore, the finding of proteinuria always warrants further investigation.

Normal renal protein excretion in dogs and cats is less than 20 mg/kg per day. A 24-hour urine collection is the gold standard for quantifying the magnitude of protein excretion; however, this is neither convenient nor practical in the clinical setting. Because the urine protein-to-creatinine ratio (UPC) has been shown to closely correlate with 24-hour protein excretion, this value is most commonly used. Healthy dogs and cats have been shown to have a UPC of less than 0.5 and 0.4, respectively. It is important to note that the presence of white blood cells, bacteria, epithelial cells, and casts can significantly increase the UPC; therefore, UPC should only be performed in tandem with a urine sediment examination. Interestingly, RBCs have a minimal effect on the UPC.

Studies have shown that there are day-to-day variations in the amount of protein that is lost through the glomerulus of PLN patients. For example, a patient with a UPC of 4.0 can expect as much as a 50% day-to-day variation in the UPC. This makes monitoring and treating these patients challenging, as 1.0–2.0 changes in the UPC could either be either be a response to treatment or just day-to-day variability. One way to avoid this is to have the owner collect and refrigerate free catch samples over 3–4 days and then submit a pooled sample of the urine. This minimizes the day-to-day variation and provides a more accurate assessment of protein loss. Providing the urine is properly refrigerated, the UPC is stable.

Serum Chemistry

Findings are dependent on the stage of the disease. In many otherwise healthy patients, the chemistry may be normal. In slightly more advanced cases, the patient may have hypoalbuminemia. Finally, patients presenting with signs of kidney disease usually have elevations in BUN, creatinine, phosphorus, and a decrease in bicarbonate.

Complete Blood Count

In all but the most advanced cases, the CBC will be normal. In patients with clinical signs of kidney disease, a normocytic, normochromic, nonregenerative anemia may present. Changes in the white blood can occur with specific infectious diseases.

Underlying Cause

As glomerulonephritis can be secondary to an identifiable underlying disease (Table 2.13.1), and amyloidosis is associated with inflammation, a thorough search for an inciting cause is essential. Infectious, neoplastic, endocrine, inflammatory, and drug-related causes must be considered (Figure 2.13.1).

Infectious Disease Serology

Serologic tests should be selected on the basis of the patient's geographic location and the relevant travel history.

Blood Pressure

Hypertension can be both a cause and a result of proteinuria hypertension; thus, evaluation of blood pressure is essential

Radiographs and Ultrasound

Imaging plays an important part in the diagnostic plan for PLN. Protein-losing nephropathy can be secondary to neoplastic processes, and ultrasound and radiographic studies in combination with a thorough physical examination are essential in elimination this as a possible underlying cause. Ultrasound can also provide information about the renal architecture. In addition, this modality can be used to obtain renal biopsies in a minimally invasive fashion.

If an underlying disease process is found, then therapy aimed at treating the primary condition should be initiated; otherwise, the condition is labeled as idiopathic. Prognosis may be better if the cause can be identified and treated.

Management

Amyloidosis versus Glomerulonephritis

The only way to differentiate amyloidosis from glomerulonephritis is by renal biopsy. There is no meaningful difference between the clinical pathology and physical exam findings in these two conditions. At a minimum, tissue samples should be stained with Congo red to determine if the patient has GN or amyloidosis (see Figure 13.16). In addition, several forms of GN are recognized and can only be differentiated on the bases on a renal biopsy sample examined by light, electron, and

immunofluorescence microscopy. As this requires special equipment and staining, there are a limited number of centers that perform this type of histopathological study. One such laboratory is International Veterinary Renal Pathology Service in the United States. Another is the European Veterinary Renal Pathology Service (EVRPS). Since different forms of protein-losing nephropathy have different treatment options and prognosis, these pathology services should be utilized whenever possible.

Amyloid-Specific Treatment

Colchicine, an inhibitor of microtubule assembly, has been shown to inhibit release of serum amyloid A from hepatocytes and may be of benefit before overt signs of kidney disease develop. It has been used in humans with familial Mediterranean fever to prevent onset of renal amyloidosis. The efficacy of this drug in treatment of renal amyloidosis in animals in not established. Colchicine has significant side effects, including vomiting, diarrhea, and nausea. In addition, there is no known benefit to starting treatment after azotemia develops. The currently recommended canine dose is 0.025–0.03 mg/kg p.o. q.24 h.

Although controversial, dimethyl sulfoxide (DMSO) has been advocated for the treatment of amyloidosis. Theoretical benefits include solubilization of amyloid fibrils, reduced serum concentration of SAA, as well as reduced renal inflammation. There are no studies to determine if DMSO is beneficial in the treatment of amyloidosis, but case reports suggest a benefit. The canine dose is 90 mg/kg diluted 1:4 with sterile saline given subcutaneously 3 times a week. Methylsulfonylmethane (MSM) is a derivative of DMSO that can be given orally. Theoretical benefits are the same as for DMSO, but it is considered more convenient since it can be given at home. It should be noted that there is no data or published case reports to support the use of MSM. Recommended canine dose is 88 mg/kg q.8 h.

GN Specific

Angiotensin-converting enzyme (ACE) inhibitors have been shown to decrease UPC and improve clinical outcome in patients with GN. The effect may be due to decreased glomerular hydrostatic pressure secondary to dilation of the efferent arteriole. There is also evidence that ACE inhibitors may inhibit cytokine production, thereby decreasing interstitial fibrosis. Although enalapril can be used, it is cleared exclusively through the kidney, while benazepril (0.25–0.5 mg/kg p.o. q.12–24 h.), which has renal and hepatic clearance, is preferred. There is some evidence that angiotensin receptor blockers (ARBs) may be as if not more effective than ACE inhibitors. Telmisartan 1.0–2.0 mg/kg p.o. q.24 h. has been shown to effectively decrease proteinuria in cats. This likely true in dogs as well.

Immunosuppression

When histopathologic evidence of an active immunologic basis for the PLN exists, immunosuppressive therapy is strongly recommended. Such evidence would include electron-dense deposits detected on electron microscopy and immunoglobulin or complement-associated immune complexes detected by immunofluorescent microscopy. In cases where the PLN is progressive and histopathology is unavailable, the use of immunosuppressive drugs could be considered providing the owner is aware of potential risks. In cases of progressive canine GN, mycophenolate 10 mg/kg p.o. q.12 h. has been recommended with or without cyclophosphamide 200–250 mg/m^2 every 3 weeks. Response to treatment can be measured by changes in the UPC. A complete response is defined as a UPC of <0.5, while a partial response is defined as a reduction of the UPC by 50% of the pretreatment value. In dogs that demonstrate no response to immunosuppressive therapy after 8 weeks, immunosuppression should be discontinued. In patients that do have a response to therapy, immunosuppressive therapy should continue for 12–16 weeks, after which the dose may be tapered while monitoring UPC and degree of azotemia.

COMMON AMYLOID AND GN THERAPIES

Diet Therapy

Patients with PLN should be fed a properly formulated kidney disease diet which is low in protein, high in omega-3 polyunsaturated fatty acids, and low in sodium. Studies in people with PLN have shown that feeding a high-protein diet is associated with increased glomerular protein loss, additional renal pathology, and higher mortality. Conversely, patients fed a low-protein diet lose less protein in their urine, experience less renal pathology, and live longer. The reason for this paradox is unclear but may involve damage caused by the increased protein being presented to the proximal tubule when a high-protein diet is consumed.

Thromboembolism

Thromboembolism is a known cause of death in patients with glomerular disease. Much of the blame has been placed on antithrombin III, which, because of its size, is lost through the damaged glomerulus at a rate comparable to albumin. However, not all animals with low albumin experience thromboembolic events, and, therefore, other factors are likely involved. Risk of thromboembolism appears to be greatest when antithrombin III is less than 75% of normal. This correlates with a serum albumin of approximately 2.0 g/dL. There are few studies upon which to base anticoagulation recommendations. Low-dose aspirin had been recommended to inhibit platelet aggregation and clot formation; however, recent research suggests that previously recommended doses may not be efficacious. A more effective option is clopidogrel 1.0–2.0 mg/kg q.24 h. in dogs and 18.75 mg/cat p.o. q.24 h. Clopidogrel is a platelet aggregation inhibitor which appears to be effective in decreasing the risk of thromboembolism.

Blood Pressure

The majority of patients with glomerular disease develop significant hypertension during the course of their disease. Hypertension can lead to ocular, cardiac, and cerebral damage and potentiate further kidney injury. Therefore, blood pressure should be checked periodically, and antihypertensive therapy administered as needed. See the Hypertension section of this chapter for more information.

Fluid Therapy

While fluid therapy is a cornerstone in the treatment of AKI and CKD, it should be used with great caution in PLN patients. These patients are extremely vulnerable to fluid overload and edema. In addition, colloids should not be routinely given to prevent or treat edema as the colloids themselves may further potentiate kidney injury. When necessary, only enough fluids to correct dehydration should be administered. This should be done over relatively long periods of time (i.e., 24 hours) and under close supervision. In patients where edema has already occurred, fluid therapy should be avoided.

Prognosis

Prognosis is variable and dependent on degree of proteinuria and response to treatment. In general, patients who are azotemic at the time of diagnosis will not respond as well as those that are asymptomatic.

HYPERTENSION

Definition/Overview

The definition of "normal" blood pressure and hypertension has recently undergone significant revision. Blood pressure is now categorized on the basis of how likely a range of pressures is to cause target organ damage (TOD). In addition, studies have shown that cats whose blood pressure falls in the range of 140–159 mmHg are likely to develop organ-damaging hypertension in the near future. It is thought that this may be true for dogs as well. This has given rise to a new category: Prehypertensive. On the basis of this criteria, canine and feline blood pressures are divided into the following four categories:

Normotensive—minimal TOD risk SBP <140 mm Hg
Prehypertensive—low TOD risk SBP 140–159 mm Hg
Hypertensive—moderate TOD risk SBP 160–179 mm Hg
Severely hypertensive—high TOD risk SBP ≥180 mm Hg

Etiology

Clinically, hypertension is divided into three categories: (1) Situational, (2) idiopathic, and (3) secondary. Situational hypertension is an elevation in blood pressure that is the consequence of stress in an otherwise normotensive animal (e.g., in-clinic experience). It is problematic as it can be mistaken for actual hypertension, resulting in unnecessary treatment. Idiopathic hypertension is the result of an imbalance between cardiac output, systemic vascular resistance, and the autonomic nervous system. Idiopathic (essential) hypertension accounts for more than 90% of all cases of elevated blood pressure in human patients; however, it is thought to be uncommon in dogs and accounts for only 13%–20% of hypertensive cats. Secondary hypertension occurs as a consequence of another disease or medication and accounts for the majority of small animal cases (Table 13.12). Clinically, this is important because it allows clinicians to focus their blood pressure screening efforts on specific "at-risk" populations.

Pathophysiology

Normal blood pressure is the result of a complex interaction between the heart, the kidneys, the autonomic nervous system, and the endothelial signaling mechanisms (Figure 13.25). These factors determine cardiac output and systemic vascular resistance, which are the ultimate blood pressure determinants (BP = CO × SVR). Although the relationship between renal disease and

TABLE 13.12 List of conditions and medications commonly associated with secondary hypertension in the dog and cat

Dogs	Chronic kidney disease	Cats	Chronic kidney disease
	Acute kidney disease		Acute kidney disease
	Hyperadrenocorticism		Hyperthyroidism
	Diabetes mellitus		Primary hyperaldosteronism
	Obesity (small effect)		Hyperadrenocorticism
	Pheochromocytoma		Epogen/darbepoetin alfa
	Glucocorticoids		
	Epogen/darbepoetin alfa		
	Phenylpropanolamine		

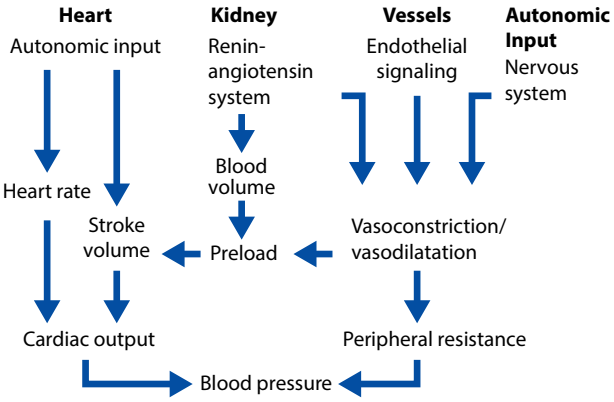


FIGURE 13.25 Complex interactions between heart, kidneys, vessels, nervous system, and endothelial signaling system, which determine blood pressure.

hypertension has been studied extensively, the connection between the two remains elusive. Recent data suggests that the cause is multifactorial.

Clinical Presentation

When increases in blood pressure are mild, the patient usually has no obvious clinical signs directly attributable to hypertension. As the elevations in systolic pressure increase, damage to the target organs, (eyes, heart, brain, and kidneys) starts to become apparent. Ocular damage is so common in CKD cats that loss of vision and not the underlying renal disease often initiates the initial office visit. Retinal edema, tortuous vessels, and hemorrhage characterize hypertensive retinopathy (Figure 13.26a, b), while choroidopathy results in ischemic necrosis of the choriocapillaris and the retinal pigmented epithelium. This presents clinically as blindness from retinal detachment.

The heart is a muscle, and as the pressure against which the heart must pump increases, cardiac changes occur. The most common change in dogs and cats is cardiomegaly associated with left ventricular concentric hypertrophy. This results in reduced diastolic ventricular internal diameter with decreased cardiac output as well as dilation of the proximal aorta. Clinically, these changes can present as a murmur, an arrhythmia, and, in cats, a gallop sound.

As systolic blood pressure exceeds the capacity of the autoregulatory mechanisms of the cerebral vasculature, hypertensive encephalopathy becomes apparent. Initially, this may present as vocalization and progress to ataxia, depression, disorientation, and seizures. This condition constitutes an emergency.

Differential Diagnosis

Situational hypertension, error in measurement

Diagnosis

Actual blood pressure is measured by placing a catheter in a suitable artery and connecting it to a transducer, which reports the pressure on a multifunction

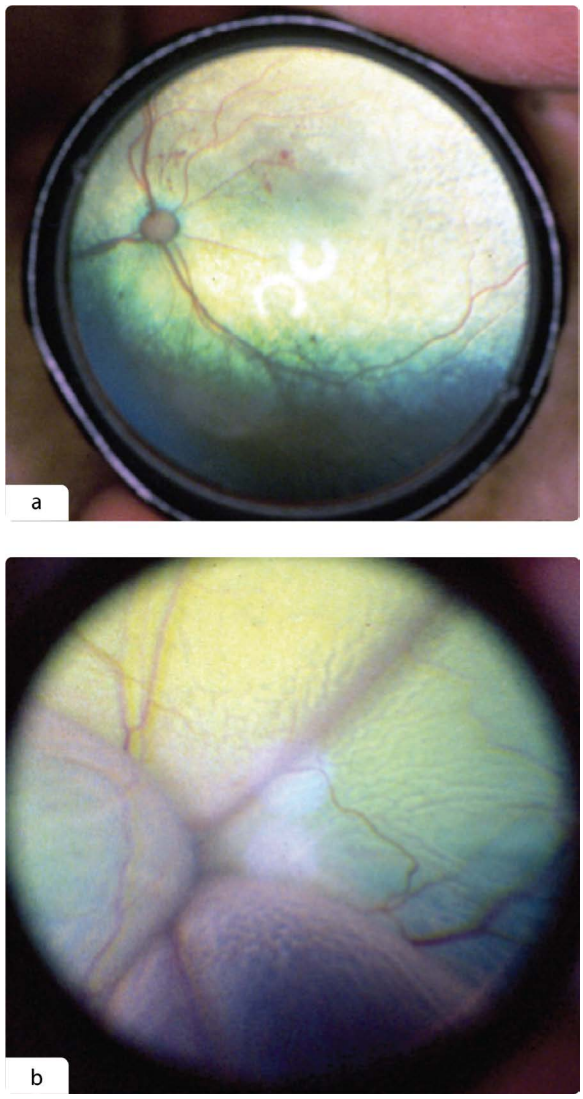


FIGURE 13.26 (a) Ocular changes consistent with hypertension. Note the tortuous vessels, hemorrhage, and edema. **(b)** Retinal detachment secondary to hypertension. (*Courtesy of P. Miller.*)

monitor (Figure 13.27a, b). While this is the most accurate way to measure blood pressure, it is invasive, painful, and neither convenient nor practical in the clinical setting. Indirect measurements of blood pressure using Doppler and oscillometric techniques are clinically most useful.

Oscillometric devices work by inflating a cuff around a distal extremity until arterial blood flow is occluded (Figure 13.28). The unit then slowly deflates the cuff while monitoring for pulsations created by arterial blood flow. These pulsations crescendo until they reach a point of maximal intensity, at which point they decrescendo. When plotted, this increase and decrease in pulse intensity forms an "oscillometric envelope" (Figures 13.29 and 13.30) The point of maximal intensity in the graph is the mean arterial pressure. These units then use proprietary algorithms to estimate systolic and diastolic pressures. Oscillometric units are



FIGURE 13.27 Direct blood pressure measurements are made by placing a catheter in an artery, connecting the catheter to a transducer, and displaying blood pressure on a monitor. **(a)** Patient with arterial catheter in a hind limb and the transducer at the level of the heart. **(b)** Multifunction monitor displaying blood pressure.

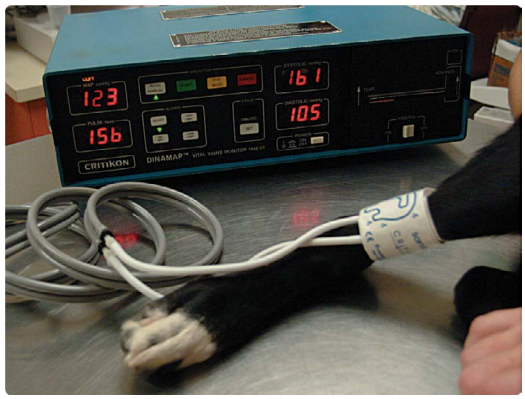


FIGURE 13.28 Oscillometric blood pressure measuring device.

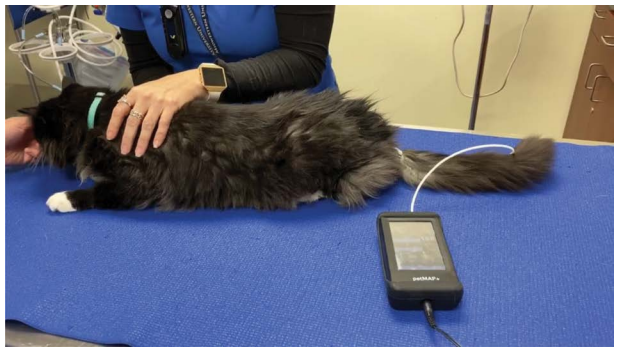


FIGURE 13.30 Feline patient having its blood pressure measured using an oscillometric device. Notice the minimal restraint and cuff on the tail.



FIGURE 13.29 Oscillometric envelope plotted against cuff pressure (red arrow). Notice that the arterial pulse intensity initially crescendos as cuff pressure decreases then begins to decrescendo. The point of maximal pulse intensity represents MAP.

popular in clinical practice because they are automated and provide systolic, diastolic, and mean arterial pressure. Nevertheless, these units can produce spurious results, especially if the oscillometric envelope is not correctly captured. For this reason, units that display the envelope for the user to evaluate may be preferred.

The Doppler flow detector is a commonly used blood pressure measuring device. The only equipment needed is the Doppler flow detector, a sphygmomanometer, and a selection of different sized cuffs (Figure 13.31). These



FIGURE 13.31 Feline patient having blood pressure measured with a Doppler device.

devices work by emitting an ultrasound wave and then comparing the frequency of the initial signal to the one that is reflected back to the probe. If the wave is reflected off the surface of a moving object, such as blood cells coursing through an artery, the frequency is shifted. The Doppler unit makes this change in frequency audible, and the operator hears this as a characteristic "swoosh" sound.

The first step in Doppler blood pressure measurement is to palpate an artery in the distal portion of an extremity (Figures 13.32–13.36). The hair over the artery is clipped, and a cuff with a width 30%–40% of the circumference of the limb is placed proximal to the clipped area. To ensure conduction, ultrasound gel is placed on the Doppler probe, which is then placed over the clipped area. The probe is then adjusted until the sound of arterial blood pulsations can be clearly heard. The cuff is inflated approximately 10–20 mmHg past the point at which blood flow can no longer be detected. Then, the cuff is gradually deflated while the operator observes the sphygmomanometer's display. The pressure at which the sound of blood flow first returns is the systolic pressure. Although the systolic blood pressure is easily obtained, determining diastolic pressure is often not possible.



FIGURE 13.32 Measuring blood pressure using the Doppler method. The artery is palpated.



FIGURE 13.33 Measuring blood pressure using the Doppler method. An area over the artery is clipped.



FIGURE 13.34 Measuring blood pressure using the Doppler method. A cuff, whose width is 30–40% the circumference of the limb, is selected.



FIGURE 13.35 Measuring blood pressure using the Doppler method. Ultrasound gel is placed on the probe to improve conduction.

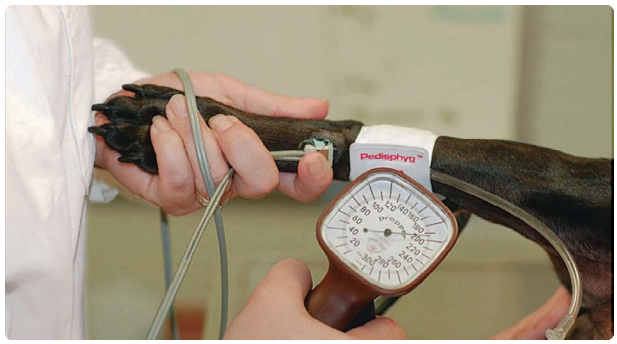


FIGURE 13.36 Measuring blood pressure using the Doppler method. The probe is placed over the artery and the sound of blood flowing is heard. The cuff is inflated to 20 mmHg greater than needed to occlude the blood flow and then the cuff is slowly deflated until the sound of blood flowing is heard again. This sound represents systolic blood pressure.

Principals of Accurate Measurement

Regardless which blood pressure measuring technology is used, four principles help to ensure accurate measurements: Acclimation to the patient, proper cuff size selection, consistency of personnel, and repeatability of results.

Perhaps the most important factor in attaining accurate and repeatable blood pressure measurements is proper acclimation of the patient. "Situational hypertension"

refers to elevations in blood pressure that are the result of stress or anxiety. An example might be the stress created by a visit to the veterinarian. While cats may display in a more obvious and dramatic response to an office visit, nervousness or excitement can profoundly affect canines as well. In order to minimize situational hypertension, blood pressure should always be measured in a quiet area away from other animals and before other procedures. The patient should be allowed to acclimate to its surroundings, and the owner should be present. Restraint should be kept to an absolute minimum. Some animals will demonstrate an effect whereby the blood pressure readings continue to decrease as the measurement process continues. This is the part of the acclimation process, and pressure measurements should continue until readings stabilize.

Proper cuff size selection is essential to accurate blood pressure measurement. Although some veterinary oscillometric devices come with an integrated cuff selection system, most devices require that the operator select an appropriately sized cuff. The width of the cuff should be 30%–40% of the circumference of the extremity where the cuff is being placed. A cuff that is too wide can underestimate blood pressure, while a cuff that is too small may artificially increase values.

Consistency of personnel and technique are an essential part of obtaining accurate blood pressure measurements. Whenever possible, the same team should be involved in the process, and they should utilize the same technique each time pressure is measured. The phenomenon by which this produces more accurate measurements is probably related to operator experience.

Individual blood pressure measurements can be inaccurate for a variety of reasons. Blood pressure measurements should be repeated 5–7 times and the individual measurements compared. If there is a significant variation (>10%) between the measurements, the readings should be discarded, and the process repeated. It is important to record the limb used, body position, cuff size, all measurements, and the staff involved so that all parameters are consistent between visits. Even something as innocuous as changing limbs can have an effect on measured pressures.

Management

It is important that cases of situation hypertension not be confused with and treated for actual blood pressure elevations. Therefore, elevations in blood pressure that are accompanied with obvious signs of TOD should be treated immediately, while other cases should be verified on three separate visits (Figure 13.37). In cases of moderate hypertension (systolic pressure <180 mmHg) these repeat measurements can be within 8 weeks; however, in severe hypertension, these visits should be sooner. When a patient's disposition makes accurate clinic blood pressures impossible, it may be possible to schedule a visit from a mobile veterinarian or teach the owner to use an oscillometric device at home.

As most small animals with elevated blood pressure suffer from secondary hypertension, the first step should be to identify and, when possible, treat the underlying condition. While this may decrease blood pressure and make hypertension more amenable to therapy, finding an underlying cause is not justification to withhold or delay treatment.

Dog-Specific Therapy

Angiotensin-converting enzyme (ACE) inhibitors are the initial drug of choice in treating canine hypertension (Table 13.13). ACE inhibitors exert their effect by

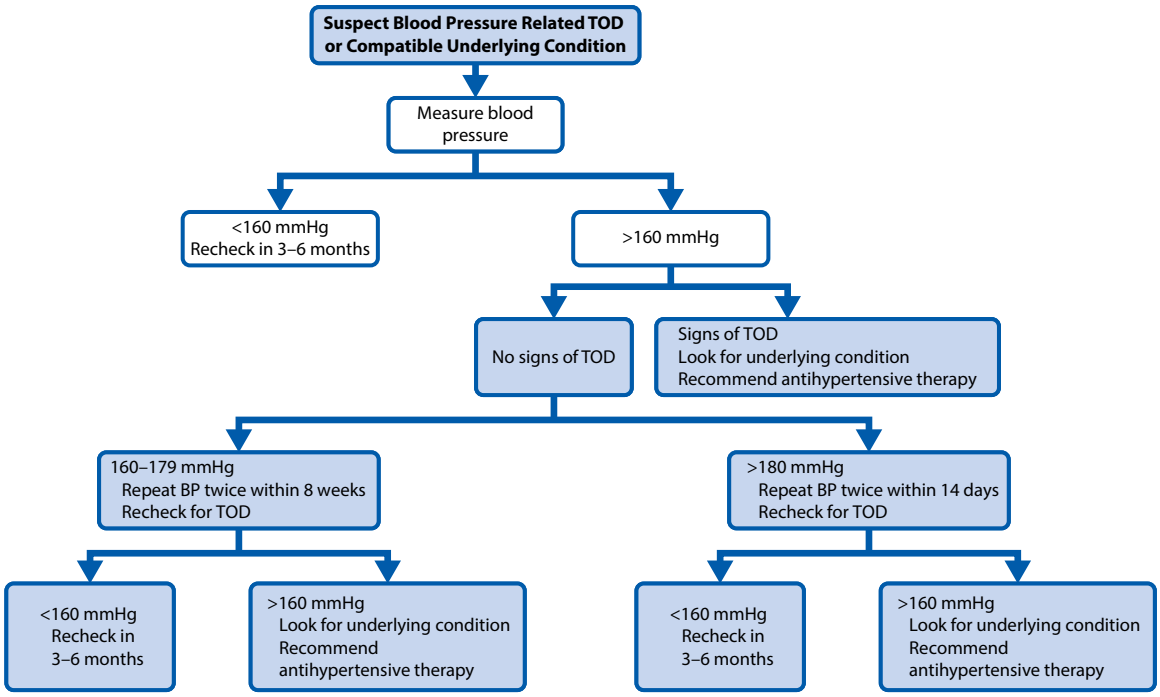


FIGURE 13.37 Recommended approach to the evaluation of a possibly hypertensive patient involves reliable measurements of blood pressure as well as the identification of possible target organ damage (TOD).

TABLE 13.13 Commonly used antihypertensive drugs in the dog and cat

Drug	Class	Canine dose	Feline dose
Enalapril	ACE inhibitor	0.5–1.0 mg/kg p.o. q.12–24 h.	0.25–0.5 mg/kg p.o. q.12–24 h.
Benazepril	ACE inhibitor	0.5–2.0 mg/kg p.o. q.12–24 h.	0.5 mg/kg p.o. q.12–24 h.
Telmisartan	ARBs	1 mg/kg p.o. q.24 h.	1.5 mg/kg p.o. q.12 h. x14 days, then 1.5 mg/kg p.o. q.24 h.
Amlodipine	Ca++ channel blocker	0.1–0.5 mg/kg p.o. q.24 h.	0.625–1.25 mg per cat p.o. q.24 h.
Atenolol	β Blocker	0.25–1.0 mg/kg p.o. q.12–24 h.	6.25–12.5 mg per cat p.o. q.12–24 h.
Propranolol	β Blocker	0.2–1 mg/kg p.o. q.8–12 h.	2.5–5 mg per cat p.o. q.8–12 h.
Spironolactone	Aldosterone inhibitors	1.0–2.0 mg/kg p.o. q.12 h.	1.0–2.0 mg/kg p.o. q.12 h.

blocking the conversion of angiotensin I to angiotensin II and help lower blood pressure in three ways. First, angiotensin II is a powerful vasoconstrictor, and inhibiting its synthesis leads to systemic vasodilatation. Secondly, angiotensin II directly promotes sodium absorption in the proximal tubule; this leads to intravascular volume expansion. Lastly, aldosterone release is stimulated by angiotensin II, and this further promotes sodium and water reabsorption in the kidney. The two most commonly used ACE inhibitors are enalapril and benazepril. Because enalapril is cleared exclusively by the kidneys, and its half-life can be significantly increased by renal disease, its use should be avoided in CKD patients. Instead, benazepril, which is cleared by the kidneys and liver, is preferred. In some CKD patients, ACE inhibitors have been associated with a worsening of azotemia; therefore, renal values should be checked 7–14 days after starting therapy in these patients. Although not as well studied in the dog as in cats, angiotensin receptor blockers (ARBs) are a reasonable alternative to ACE inhibitors in dogs.

ACE inhibitors and ARBs sometimes fail to produce the desired blood pressure decrease. In these patients, a calcium channel blocker can be added to the ACE inhibitor therapy. These agents exert their effects by blocking the influx of calcium needed to cause smooth muscle contraction and act to decrease systemic vascular resistance. Amlodipine besylate (Table 13.13) is the most widely used calcium channel blocker. Theoretically, calcium channel blockers have the potential to worsen renal disease despite lowering blood pressure. This effect is thought to be mediated by calcium channel blocker's preferential dilation of the glomerular afferent arteriole, paradoxically resulting in glomerular hypertension. Therefore, calcium channel blockers should not be used as a monotherapy agent in dogs. As ACE inhibitors and ARBs preferentially dilate the afferent arteriole, coadministration of these drugs with a calcium channel blocker results in a neutral effect on glomerular capillary hydrostatic pressures.

Cat-Specific Therapy

ACE inhibitors are less effective in treating feline hypertension. Studies have shown that as many as 50% of hypertensive cats fail to respond to enalapril. While benazepril has been shown to produce a statistically significant decrease in feline blood pressure, the actual reduction is relatively modest. For this reason, amlodipine besylate, a calcium channel blocker, has been the drug of choice in controlling feline hypertension. It is long acting, gradual in effect, and is often successful in controlling feline hypertension as a monotherapy agent. Decreases in blood pressure are somewhat dose dependent but can range from 30 to 70 mmHg. Although use of amlodipine as a monotherapy agent is discouraged in the dog, it does not appear to be problematic in cats.

ARBs are a newer class of drug that exerts their effect by directly blocking the angiotensin II type I receptors (Figure 13.38). Like ACE inhibitors, they are vasodilators. Several studies have demonstrated that telmisartan produces a predictable 23–25 mmHg decrease in feline blood pressure. In addition, because it affects only angiotensin II type I receptors, it has theoretical benefits over calcium channel blockers, including anti-inflammatory and antiproliferative effects. Telmisartan (Semintra®, Boehringer Ingelheim Vetmedica GmbH) is currently the only veterinary antihypertensive approved for use in cats by both the United States and Europe.

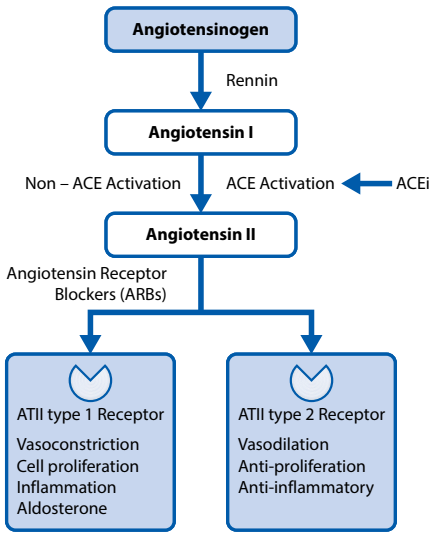


FIGURE 13.38 ACE inhibitors work by preventing the conversion of angiotensin I to angiotensin II; however, over time, this blockage becomes less effective. ARBs block the angiotensin II type 1 receptor, leaving the type 2 receptor unaffected. This has theoretical benefits, including anti-inflammatory and anti-proliferative effects.

Adjunctive Therapy

Beta-blockers are useful adjunctive therapy in dogs or cats where the initial antihypertensive agent has failed to produce the desired effect. Beta-adrenergic receptors are found in both the heart (beta-1) and lungs (beta-2). Blockade of the beta-1 receptors slow the heart and lower blood pressure, while blockade of the beta-2 receptors can trigger bronchial constriction. Therefore, only selective beta-1 antagonists (see Table 13.13) should be utilized.

It has long been known that aldosterone contributes to hypertension by stimulating sodium and water reabsorption in the kidney and thereby increasing intravascular volume. More recently, it has become apparent that aldosterone plays a role in the inflammation, fibrosis, and necrosis seen in TOD. Inhibiting aldosterone may have protective effects on target organs. Although more research is needed, hypertensive patients may benefit from the use of aldosterone antagonists such as spironolactone (see Table 13.13).

Goals and Monitoring

The goal of treating hypertensive patients is to gradually lower systolic pressure to less than 140 mmHg (Figure 13.39). It is important in the initial stages of treatment to monitor the patient regularly and avoid making rapid adjustments in medication. Changes in antihypertensive therapy should only be made every 1–2 weeks. Proteinuria is common in hypertensive patients and has been shown to be a negative prognostic indicator. Therefore, reducing proteinuria should be a secondary goal of therapy. Reductions in proteinuria can be achieved using a combination of ACE inhibitors and ARBs. Once the patient's blood pressure and proteinuria has been regulated, it should be rechecked every 3 months. Complete blood count and serum chemistry should be checked twice a year.

Prognosis

When diagnosed and treated before significant target organ damage, prognosis is generally good; however, hypertension is often secondary to an underlying condition, which may be life limiting.

INCONTINENCE

Definition/Overview

Incontinence refers to involuntary escape of urine during the storage phase of the urinary cycle. This can present in different ways; however, the most common presentation is an intermittent or continuous dribbling of urine combined with episodes of normal voiding.

Etiology

Causes of incontinence include urethral sphincter incompetence, anatomic abnormality in the termination of the ureters (ectopic ureters), an inability of the bladder to dilate, spasms of the bladder, or damage to the nerves controlling micturition (Table 13.14). Nevertheless, urethral sphincter mechanism incompetence and ectopic ureters are the most common causes and account for 85% of all incontinence cases.

Pathophysiology

The urinary cycle is divided into two phases: The filling phase, and the emptying phase (Figure 13.40). During the filling phase, the hypogastric nerve provides sympathetic stimulation of β-receptors in the body of the bladder, resulting in relaxation and stretching, while stimulation of α-receptors in the bladder's trigone region and proximal urethra causes constriction (Figure 13.41). Thus, the sympathetic branch of the autonomic nervous system dominates the filling phase of micturition by constricting the outflow of the bladder while allowing the body of the bladder to distend. Sympathetic stimulation also blocks parasympathetic transmission, thereby inhibiting urination.

As the bladder fills, sensory receptors embedded in the wall of the bladder become active, and signals travel

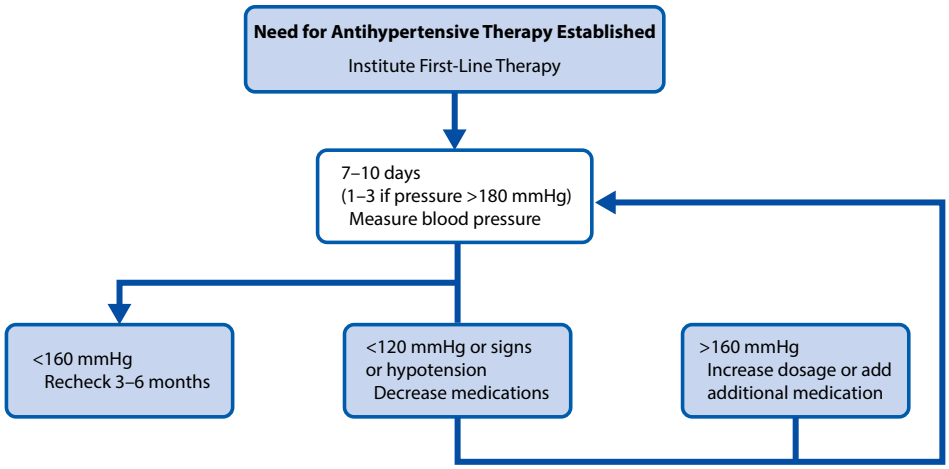


FIGURE 13.39 Stepwise approach for management of hypertension involves repeat blood pressure measurement and making medication adjustments.

TABLE 13.14 Causes of incontinence

Cause	Typical signalment	Clinical signs	Relative frequency
USMI	Post-spay female	Dribbling of urine when resting Previously normal urination	Frequent
Ectopic ureters	Young female	Continual urine dribbling Noted from early age	Common
Detrusor instability – Urge incontinence – Idiopathic instability	Middle-aged female	Pollakiuria, urgency	Less common
Neurologic disease	None	*Upper motor:* Erratic reflexive bladder emptying with a difficult-to-express bladder *Lower motor:* No attempts to urinate, easily expressed bladder	Less common
Pelvic entrapment of bladder	Adult large-breed female	Continual urine dribbling	Less common

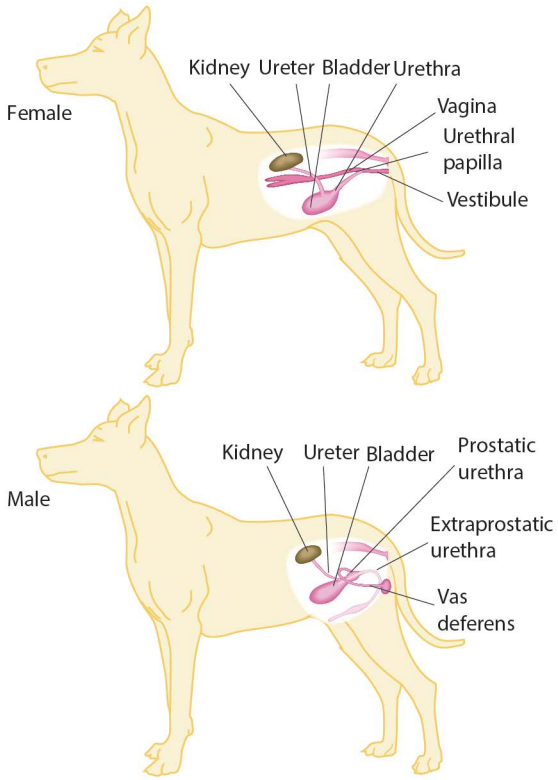


FIGURE 13.40 Functional components of the urinary tract. Urine is produced in the kidney, travels to the bladder via the ureter, and is stored in the bladder. The urethra acts as a valve and prevents the dribbling of urine and, when appropriate, directs urine out of the body.

via the pelvic nerve to the spinal cord. This information is relayed to the brainstem where these impulses are integrated with information from the forebrain. Once it is an appropriate time and place to void, the impulse to empty the bladder is carried down the spinal cord. Parasympathetic neurons located in the pelvic nerve transmit impulses to the parasympathetic ganglia in the bladder wall. Nerve fibers leave this nucleus and innervate smooth muscle fibers of the detrusor muscle, causing contraction of the bladder body and relaxation of the bladder neck. At the same time, reflex contraction of the striated muscle of the urethra mediated by the pudendal nerve is inhibited. The parasympathetic nervous system dominates the emptying phase of the urinary cycle by coordinating the contraction of the bladder as well as relaxation of the bladder neck, proximal urethra, and external sphincter.

Urethral sphincter mechanism incompetence (USMI) is the most common cause of canine urinary incontinence, affecting as many as 20% of all spayed dogs. The onset of incontinence is usually seen 2–3 years after an uneventful ovariohysterectomy but can occur any time after the procedure. Owners typically describe a dribbling of urine that is most noticeable when the animal is asleep. The exact mechanism by which removal of the ovaries leads to incontinence is unknown. Historically it had been thought that since estrogen upregulates urethral sphincter α-receptors, loss of estrogen decreased responsiveness of the urethra to sympathetic stimulation. More recently, elevations of gonadotropin-releasing hormone and luteinizing hormone resulting from loss of gonadal feedback have been implicated in decreased urethral contractility. In addition, spayed female dogs seem to have an increase concentration of collagen in their urine outflow tract, resulting in a less elastic urethra. Lastly, some cases of USMI seem to respond to surgical intervention. Taken together, the evidence suggests the cause of USMI is either multifactorial or that USMI is actually a collection of conditions with a common presentation.

Ectopic ureters (EU) are a congenital abnormality characterized by termination of one or both ureters at a point distal to the neck of the bladder. Affected animals typically leak urine from birth. Ectopic ureters are categorized as extramural or intramural based on their point of attachment and behavior. Intramural ectopic ureters attach to the bladder and tunnel below the submucosa and empty into urethra or vagina. Over 95% of EUs are reported to be intramural. Extramural ectopic ureters attach and empty directly into the urethra, the vagina, or the uterus. In cases of unilateral EU, normal urine voiding is reported as one ureter is properly emptying into the bladder. Normal urination may or may

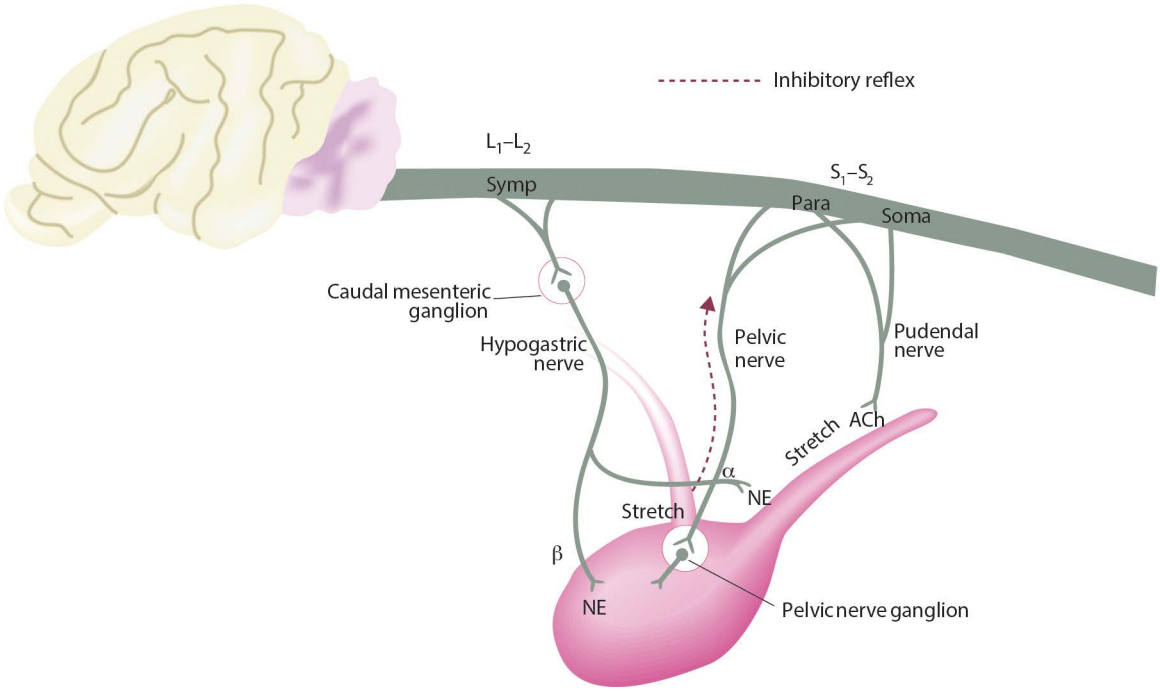


FIGURE 13.41 Schematic diagram representing the autonomic and somatic innervation of the bladder and urethra. Sympathetic (Symp) nerve fibers responsible for the storage phase of urination travel in the hypogastric nerve and stimulate receptors in the body and neck of the bladder. Beta receptors in the body of the bladder allow the detrusor muscle to relax and fill. Alpha receptors in the neck of the bladder and proximal urethra result in contraction and continence. Parasympathetic (Para) nerve fibers responsible for the voiding phase of the urinary cycle travel in the pelvic nerve. Sensory information travels from the bladder to the spinal cord via the pelvic nerve. Somatic (Soma) control of the external urethral sphincter travels in the pudendal nerve.

not occur in bilateral cases. Almost 90% of canine EU occurs in females, and depending on the study, 32%–91% of these are bilateral. Although ectopic ureters have been reported in cats, they are rarely diagnosed.

Detrusor instability is characterized by sudden urge to urinate and an involuntary bladder contraction (Figure 13.42). When this occurs secondary to infection, neoplasia, or urolithiasis, this condition is referred to urge incontinence. When an underlying condition is not diagnosed, the condition is called idiopathic detrusor instability.

Location of the bladder within the pelvis ("pelvic bladder") has also been associated with urinary incontinence. Although this condition is most often seen in large breed female dogs, it has also been reported in males. In most dogs, the bladder is positioned in the abdomen, while in affected animals, the bladder neck and some portion of the bladder body are located in the pelvic canal. The exact role that bladder position plays in dogs is not clear. In people, the bladder neck and proximal urethra are normally located within the abdomen. Increased abdominal pressure caused by normal activity is equally applied to the bladder body, neck, and proximal urethra. This uniform distribution of pressures helps maintains continence. In a patient with a pelvic bladder, the neck and proximal urethra are outside the abdomen, shielding it from these uniform pressures; however, at least 50% of dogs with a pelvic bladder are completely unaffected. This suggests that other factors are involved. It has been proposed that "pelvic bladder" in dogs is actually part of a syndrome characterized by shortened urethra, dysfunctional detrusor, and abnormal urethral musculature and not an issue of uniform distribution of pressures.



FIGURE 13.42 Dog with urge incontinence. The patient was later found to have a bladder mass.

Clinical Presentation

The most common presentation is an intermittent or continuous dribbling of urine combined with episode of normal voiding.

Differential Diagnosis

Nocturia, pollakiuria, and urgency.

Diagnosis

A detailed history that focuses on the timing, volume, possible trauma, and events surrounding the leakage of urine (e.g., sleeping, excitement) are essential. In addition, determining the quality and quantity of the purposeful urinations is important. Nocturia, pollakiuria, and urgency, which can all be confused with incontinence, can be eliminated on the basis of a thorough history.

A detailed inspection of the genitals should be performed. The area around the genitals should be checked for moisture, urine staining of the fur, and skin scalding. These are classic signs of incontinence, and if not seen, the clinician should consider alternative explanations. The external genitalia should be examined to be sure they are anatomically correct. In addition, observing the animal urinate is important in confirming normal micturition.

Laboratory data should include a complete blood count (CBC), serum chemistry panel, urinalysis, and diagnostic imaging. A urine culture should be considered. The CBC and chemistry panel help rule out systemic disease, while the urinalysis may implicate cystitis as a cause of the incontinence. Urine culture results can be difficult to interpret. Although urinary tract infections can lead to urge incontinence, infection can also be the result of anatomic abnormalities. Diagnostic imaging is essential to look for uroliths or other abnormalities (Figure 13.43).

A thorough neurological examination is a critical part of the incontinence workup. Disorders affecting the spinal cord above the fifth lumbar vertebra (upper motor neuron lesions) produce an involuntary, erratic, reflexive emptying of the bladder with increased resistance of the external urethral sphincter. Typically, these animals present with significant neurologic abnormalities that are easier to detect. Lesions of the sacral spinal cord (lower motor neuron lesions) prevent bladder sensation from traveling up the spinal cord, and as a result, the patient makes no attempts to urinate even as the bladder becomes overdistended. Sacral lesions also affect the pudendal nerve and result in the loss of external sphincter resistance. Typically, patients with sacral lesions have an easily expressed overdistended bladder and dribble urine.



FIGURE 13.43 Ultrasound of a bladder reveals a mass (between arrowheads). The mass was eventually determined to be a tissue reaction to suture material used in a previous cystotomy.

USMI

Due to its prevalence, typical presentation, and the relative safety of medical treatment, the diagnosis of USMI is often made empirically (Table 13.15). Definitive diagnosis requires that a urethral pressure profile (UPP) be performed. This test, which requires specialized equipment, is available only at select referral institutions; therefore, it reserved for atypical presentations (e.g., male dogs) or refractory cases. During a UPP, a pressure-measuring catheter is inserted into the bladder and withdrawn through the urethra. When finished, the computer generates a mapping of the pressures. This allows the clinician to determine if the pressure exerted by the urethral sphincter is adequate and if the functional length of the urethra is normal.

TABLE 13.15 Commonly utilized drugs for treating incontinence

Drug	Class	Dosages
Dicyclomine	Anticholinergic	Dogs: 5–10 mg per dog p.o. q.8 h.
Estriol	Hormone	Dogs: 2 mg p.o. q.24 h./14 days, then 1 mg q.24 h./14 days, then 0.5 mg q.24 h. or to lowest effective dose
Flavoxate	Anticholinergic	Dogs: 100–200 mg per dog p.o. q.12–24 h.
Oxybutynin	Anticholinergic	Dogs: 0.2 mg/kg p.o. q.8–12 h.
Phenylpropanolamine	Alpha agonist	Dogs: 1–1.5 mg/kg p.o. q.12–24 h. Cats: 1–1.5 mg/kg p.o. q.12–24 h.
Testosterone cypionate	Hormone	2.2 mg/kg IM every 4–6 weeks

Ectopic Ureters

Typically, ectopic ureters are suspected in young female dogs that have a history of dribbling urine since they were very young. Interestingly, because of the small volume of urine produced and the expectation that young puppies will have "accidents," this condition is often initially overlooked. The diagnosis of ectopic ureters has historically been made on the basis of excretory urography, retrograde vaginourethrography, or some combination of these radiographic procedures. Collectively, these tests have a sensitivity of only 70%–80%. The use of rigid cystoscopy has been shown to be 100% sensitive and specific. This combined with the ability to laser correct the EU in one minimally invasive procedure has made cystoscopy the diagnostic of choice.

Urge Incontinence/Idiopathic Detrusor Instability

The diagnosis of urge incontinence is made on the basis of finding an underlying cause for the bladder instability. As in all cases of incontinence, a thorough physical, neurologic examination, history, urinalysis with microscopic examination of the sediment, and culture are essential. Radiographs and ultrasound examination of the lower urinary are critical to look for neoplasia, urolithiasis, or structural abnormalities (Figure 13.43). Cystoscopic examination of the lower urinary tract should be considered in cases where an obvious cause is not found.

Diagnosis of idiopathic detrusor instability should only be considered once urge incontinence has been eliminated from consideration. Definitive diagnosis of idiopathic detrusor instability is diagnosed based on the results of a cystometrogram. During this test, a catheter is placed in the bladder, and it is slowly filled with saline. The normal canine bladder will allow uninterrupted filling until a threshold volume of 22 mL/kg is reached. At this point, involuntary bladder contractions begin. Dogs with idiopathic detrusor instability will experience involuntary bladder contractions at a greatly reduced volume. While simple in principle, the equipment to perform this test is complex and only available at a limited number of referral institutions.

Pelvic Bladder

Diagnosis of a pelvic bladder is made on the basis of contrast radiographs (Figures 13.44 and 13.45). Contrast radiographs show an abnormally shaped, caudally displaced bladder that fails to taper at the junction with the urethra. Since many dogs with pelvic bladder syndrome will often demonstrate a dysfunctional detrusor and an abnormal urethral musculature, a urethra pressure profile and cystometrogram may be indicated.

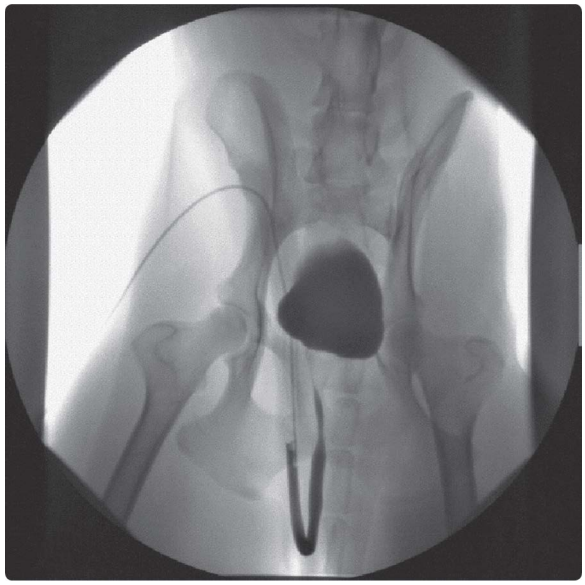


FIGURE 13.44 Pelvic bladders are usually seen in female dogs; however, this example is in a 2-year-old male Greyhound. Note the position of the bladder and its failure to taper at the junction with the urethra.

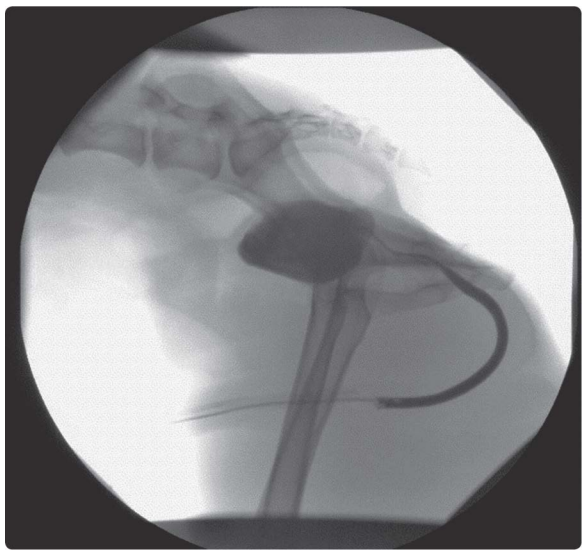


FIGURE 13.45 Pelvic bladders are usually seen in female dogs; however, this example is in a 2-year-old male Greyhound. A urethral pressure profile and cystometrogram revealed a nonresponsive detrusor muscle and incompetent urethra.

Management

Spay-Related Incontinence

Alpha-adrenergic agonists such as phenylpropanolamine have long been considered the mainstay for the treatment for USMI (see Table 13.15). Total resolution of urinary incontinence can be expected in 85% of cases while a significant improvement in clinical signs occurs in most dogs. Since the side effects of phenylpropanolamine include hypertension, tachycardia, increased intraocular pressure, and hepatic glycogenolysis, this drug should be avoided in patients with hypertension, glaucoma, or diabetes mellitus. Blood pressure should be measured prior to and shortly after starting phenylpropanolamine, as the drug can induce hypertension in otherwise normotensive dogs.

Estriol (Incurin®) is an estrogen-based treatment for USMI. Estrogens work by exerting a permissive effect on the α-receptors of the urethral sphincter, resulting in increasing responsiveness to the sympathetic nervous system and increased urethral tone. Common side effects include loss of appetite, vomiting, excessive water drinking, and a swollen vulva. For most patients, these seem to resolve quickly. Unlike previously available estrogen formulations, Estriol does not appear to be associated with bone marrow suppression.

For the small percentage of USMI patients that do not adequately respond to medical management, several procedural options exist. The first, urethral collagen injection, involves the endoscopic placement of collagen or extracellular matrix into the urethral submucosa. Approximately 68% of dogs treated with this method attained full urinary continence, and an additional 25% of owners reported a significant decrease in urine dribbling. These endoscopically placed injections result in bulging of the urethra into the lumen and significantly improved urethral closure. The primary limitation of this procedure is its temporary nature, as most dogs return to incontinence over time. While many of the dogs that relapse will respond to medical management, most will require additional injections within 2 years.

Another option is the surgical placement of a hydraulic urethral occluder. A hydraulic urethral occluder is an inflatable silicone cuff that is surgically placed around the proximal urethra (Figure 13.46a–d). The cuff is attached to an inflation port, which is secured subcutaneously to the abdominal wall. The occluder works by providing resistance to the proximal urethra. When the patient urinates, pressure in the bladder overcomes the resistance, and normal micturition occurs. The resistance provided by the occluder can be adjusted through the injection port.

Treatment of USMI in male dogs is similar but often less rewarding than their female counterparts. Only 44% of incontinent male dogs improve with administration of phenylpropanolamine. Testosterone alone or in combination with α-agonists may be attempted; however, only 38% of testosterone-treated dogs became completely continent, while 50% showed no response. In addition, use of testosterone may be associated with serious side effects. For male dogs that do not respond to medical management, injection of a bulking agent and hydraulic urethral occluders may be options.

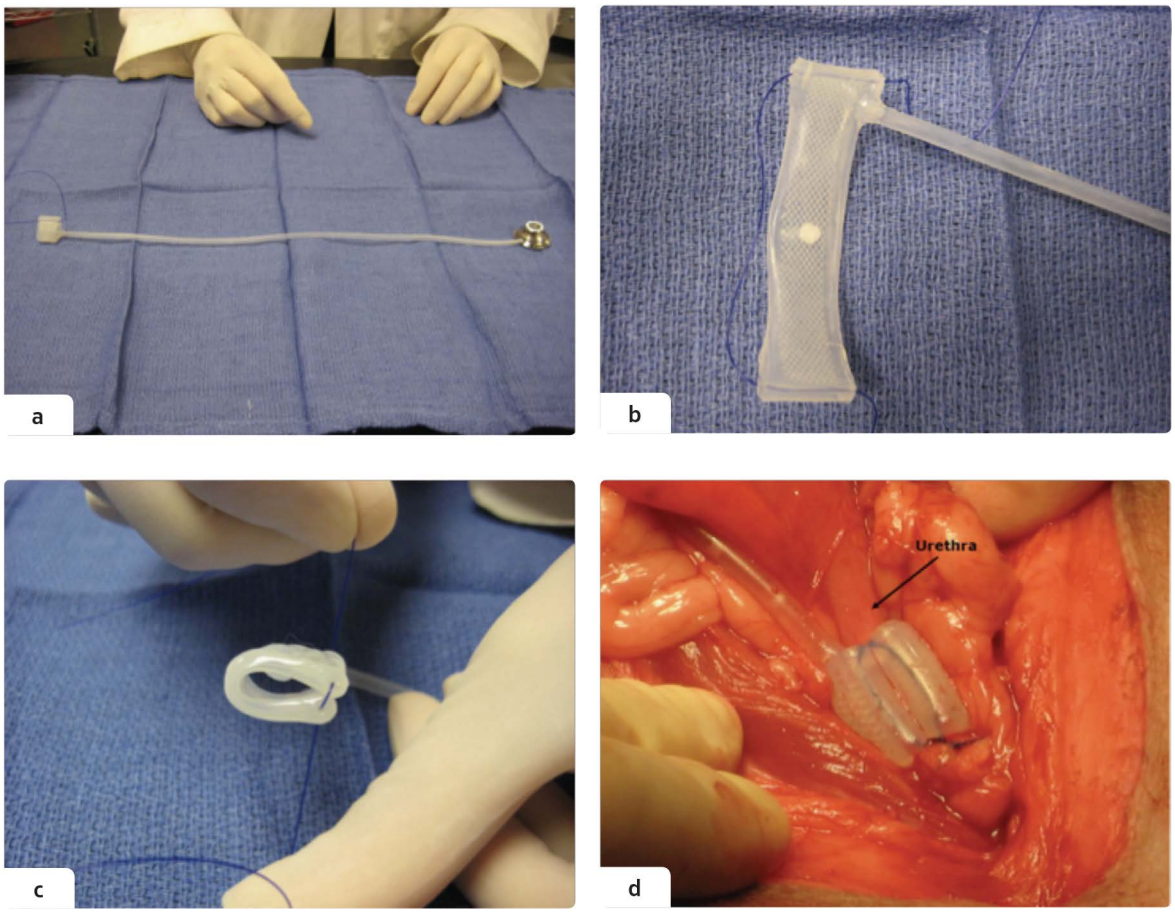


FIGURE 13.46 **(a)** Hydraulic urethral occlusion device. Note the cuff, which will be surgically placed around the urethra, and the inflation port, which will be secured subcutaneously to the abdominal wall. **(b, c)** Close-up of a cuff that will be placed around the neck of the bladder. **(d)** Cuff placed around the urethra. (*Courtesy of A. Berent.*)

Ectopic Ureters

Extramural ectopic ureters, which are rare, attach and directly empty into the urethra, the vagina, or the uterus. These must be surgically reimplanted. Intramural ectopic ureters attach to the bladder correctly and then tunnel below the submucosa and empty into urethra or vagina. These are amenable to correction by laser ablation, which is less invasive, more effective, and associated with fewer complications than surgical techniques (Figure 13.47a–f). In addition, the ectopic ureter is both diagnosed and corrected during the same anesthetic event. Nevertheless, some dogs will experience a degree of incontinence after correction. The reason for this is unclear; however, many will respond to medical therapy.

Some degree of hydronephrosis is common in dogs born with ectopic ureters (Figure 13.48a, b). An abdominal ultrasound should be performed to examine the architecture of the affected kidney. Although some kidneys may need to be removed, many will regain function once the abnormality is corrected. The decision to perform a nephrectomy should not be taken lightly.

Urge Incontinence/Idiopathic Detrusor Instability

Treatment of urge incontinence is based on the successful resolution of the underlying condition. Usually, no additional therapy is needed. Treatment for idiopathic detrusor instability relies on anticholinergic drugs that interfere with parasympathetic nervous system's stimulatory effect on the detrusor muscle. Commonly used drugs include flavoxate, oxybutynin, and dicyclomine (see Table 13.15).

Pelvic Bladder

Treatment of pelvic bladder syndrome is often unrewarding. Treatment with phenylpropanolamine may be helpful in some cases but likely to be ineffective (see Table 13.15). Some have recommended colposuspension; however, there is little evidence to support the use of this procedure.

Prognosis

Most common causes of incontinence are treatable, and, therefore, prognosis is good.

FELINE LOWER URINARY TRACT DISEASE

Definition/Overview

Feline lower urinary tract disease (FLUTD) is a term given to cats that exhibit clinical signs, including straining to urinate, hematuria, pollakiuria, and periuria. Feline lower urinary tract disease is quite common and accounts for nearly 5% of all cats presenting for veterinary care. The condition can be divided into two groups: (1) Cats that present with a urethra obstruction, and (2) cats that are displaying clinical signs but are not obstructed. While the former group is almost always male, the later can be either. A cat with an obstructed urethra is always a medical emergency.

Etiology

FLUTD can be the result of feline idiopathic cystitis (FIC), urethral plugs, uroliths, and other causes. Most cases fall into the category of idiopathic, although urethral plugs are common. Uroliths are less common, accounting for 10% or fewer of FLUTD cats. Despite common misconceptions, UTIs in young health cats are exceedingly rare and almost never the cause of FLUTD. Tumors are occasionally seen but are also very uncommon.

Pathophysiology

Idiopathic Cystitis

Most cases of FLUTD are idiopathic, making this a frustrating disease to diagnose and treat. It is thought that the clinical signs may be the result of urethral spasms which are secondary to stress or anxiety. When normal cats are subjected to stressful events, (e.g., introduction of a new housemate), there is an initial catecholamine release followed by period of acclimation and a return to baseline levels. Some cats with FIC have been shown to have an exaggerated and an extended catecholamine response, which is similar to some anxiety disorders. Besides generalized anxiety, this catecholamine release can also have an effect on specific organs.

Urethral Plugs

Urethral plugs are a mix of a proteinaceous matrix and struvite crystals that is likely related to idiopathic cystitis. In addition to having an abnormal response to stress, cats with FLUTD can have defects in the urinary tract glycosaminoglycan layer. This layer protects the bladder wall from noxious substances in urine. A defect in the glycosaminoglycans results in pain and inflammation of the bladder wall. Pain stimulates further release of catecholamines, which increases urothelium permeability, leading to leakage of serum constituents into the urine. This provides the proteins needed for matrix formation and increases urine pH, promoting the formation of massive numbers of struvite crystals. The protein matrix forms a web-like structure in the urethra that traps the struvite crystals, leading to the plug.

Urinary Tract Infections

Urine osmolality in young healthy cats is so high that it acts to inhibit bacterial growth. This combined with normal host defense mechanisms make urinary tract infections extremely rare in these patients. Any appearance of clinical improvement in a FLUTD cat after antibiotic administration is likely coincidental. In the absence of a urine culture obtained by cystocentesis, the use of antibiotics is not recommended.

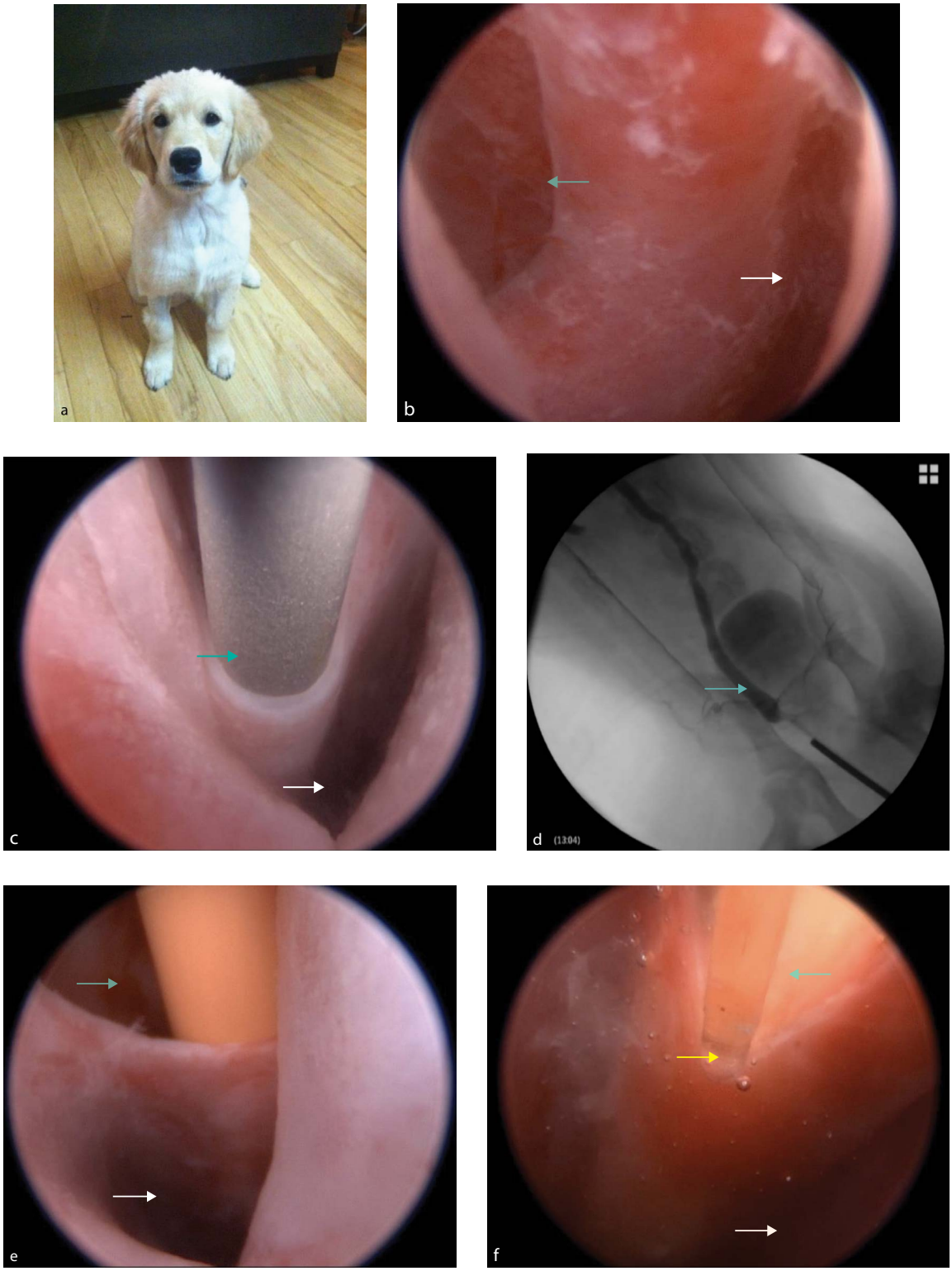


FIGURE 13.47 Urethrocystoscopy view of ectopic ureter correction surgery. **(a)** Female Golden Retriever puppy surrendered to rescue organization. The foster family reported urine dribbling at home. **(b)** Where the opening of the urethra should be, there are two openings. The white arrow points to the urethra, while the blue arrow points to the opening of the EU. **(c)** There is a guidewire in the EU (blue arrow), while the opening of the urethra is shown by the white arrow. **(d)** With a balloon catheter inserted into the EU, contrast is injected and observed under fluoroscopy. Notice the EU (blue arrow) is highlighted against the bladder and travels up toward the kidney. **(e)** A red rubber is inserted in the EU (blue arrow). Notice the thin piece of tissue separating the EU from the urethra (white arrow). **(f)** View from inside the urethra (white arrow). The red rubber is inserted in the EU (blue arrow), and the laser tip (yellow arrow) is ablating the tissue between the EU and the ureter creating a functional urethra. (*Photos property of Mark Acierno.*)

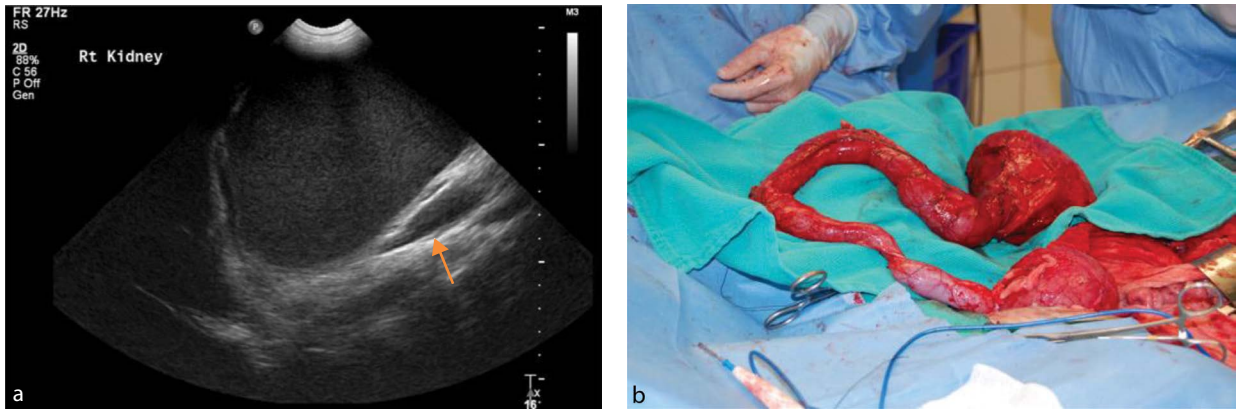


FIGURE 13.48 (a) Ultrasound of kidney of male dog with ectopic ureter. Notice the degree of hydronephrosis with total loss of normal parenchyma. The arrow points to the dilated ureter. **(b)** Surgical appearance of kidney and urethra. The point attachment of the ureter was the prostate.

Other

Uroliths and neoplasia can result in signs consistent with FLUTD; however, they are uncommon. These topics are covered elsewhere in this chapter.

Clinical Presentation

Obstructive

Urethral obstruction usually occurs in male cats between 1 and 8 years of age. Obstructed cats strain unproductively to urinate and may cry out. Owners may mistake these attempts for constipation. Licking of the genital region is also frequently observed. Patients often hide in a secluded area. Cats examined soon after obstruction may be fractious and resist examination. After more prolonged obstruction, patients become progressively more depressed. An enlarged firm bladder is felt on abdominal palpation.

Nonobstructive

Signs of nonobstructive FLUTD are variable but usually include stranguria, pollakiuria, hematuria, and dysuria. Affected cats may vocalize during urination and urinate in inappropriate places. The bladder of cats with nonobstructive FLUTD is usually small with a thickened wall. Attempts at collecting urine through cystocentesis are often unrewarding due to the frequent attempts at urination that occurs, especially when the patient is handled.

Differential Diagnosis

Inappropriate urination (behavioral), uroliths, urinary tract infection, neoplasia, anatomic defects.

Diagnosis

All cats presenting for FLUTD should have diagnostic imaging. This will allow for inspection of the urinary tract for uroliths, anatomic malformations, and neoplasia. As is true with many urinary tract conditions, ultrasound combined with radiographs is likely to yield more information than either alone. Nevertheless, treatment of an unstable obstructed patient should not be delayed. In these cases, radiographic studies should be performed once the obstruction is relieved.

Obstructive

Obstructive FLUTD is identified by palpation of an enlarged, firm bladder. Urinalysis can be performed on urine collected by cystocentesis, before urethral catheterization, or via the catheter after relief of the obstruction. Serum creatinine, BUN, and potassium allow assessment of the degree of prerenal azotemia; however, these are likely to resolve quickly once the obstruction is relieved. An electrocardiogram (ECG) tracing should always be performed to assess cardiotoxicity associated with hyperkalemia.

Nonobstructive

Along with diagnostic imaging, laboratory data should include a CBC, serum chemistry panel, and urinalysis. The CBC and chemistry panel help rule out systemic disease. Crystalluria is not an uncommon urinalysis finding and is unlikely to be the cause of the condition; rather, it is most likely a result of the inflammation. For this reason, the crystalluria is not usually considered a therapeutic target.

Management

The first step in assessing a cat that presents with FLUTD is to quickly recognize patients that are obstructed. These cats are almost always male and can be identified by the palpation of an enlarged, firm bladder. Affected cats may azotemic, hyperkalemic, acidotic, bradycardic, and have an ECG consistent with atrial standstill secondary to hyperkalemia (e.g., absence of P waves, prolonged QRS, spiked T waves) (Figure 13.49). Patients should have an IV catheter placed and be sedated. See Figure 13.50 for treatment algorithm.

Once the urinary catheter is placed, urine output should be monitored for at least 24–48 hours for



FIGURE 13.49 An ECG example of hyperkalemia causing atrial standstill. Note the characteristic absence of P waves, prolonged QRS, and spiked T waves.

Obstructive algorithm:

- Draw blood for possible serum chemistry and electrolytes.
- Place IV catheter and begin ˜uid s.
- Monitor ECG and treat hyperkalemia as needed (**Table 13.7**).
- Carefully attempt to catheterize with a sterile Slippery Sam™ or 3.5-French open-end tomcat catheter (**Figure 13.51a, b**).
- If obstruction cannot be relieved, attempt to dislodge by ˜ushing urethra with sterile saline or la ctated Ringer's solution.
- If bladder is extremely ÿrm, remove urine by cystocentesis. This decreases back-pressure and allows for aseptic collection of urine for analysis and culture.
- If obstruction will not dislodge, use retropulsion with the urethral oriÿce pinched o¸.
- A small amount of lidocaine gel may be infused into the catheter to decrease urethral spasm.

Once urethral patency is established:

- If a 'Slippery Sam' catheter was used to relieve obstruction, the catheter can be sutured in place.
- If a tomcat catheter was used:
  - Measure distance from prepuce to neck of bladder.
  - Note distance on a sterile 5-French polyvinyl catheter (soft red rubber) and insert into the urethra up to that point.
  - Place tape on external part of tube (as close to prepuce as possible) and suture tape to prepuce with two sutures.
  - Tape free end of tube to tail.
  - Attach extension set to urinary catheter and place sterile collection bag on the other end of the extension set.
- Place e-collar before the patient awakens.

FIGURE 13.50 Algorithm for treating obstructed cats.

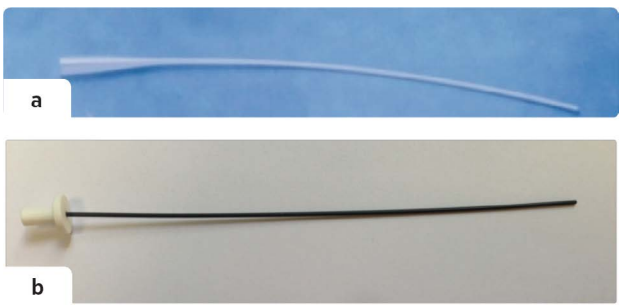


FIGURE 13.51 Examples of a tomcat catheter (a) and a Slippery Sam™ catheter (b).

evidence postobstructive diuresis. This is a high rate of urine output that occurs when an obstruction is relieved. The cause is unknown; however, significant amounts of dilute urine can be produced, leading to hypovolemia. Recommendations are to measure urine output every 2–4 hours and set the IV fluid rate so that it matches urine production. Fortunately, postobstructive diuresis is self-limiting and usually resolves in 24–48 hours. It is not clear if there is an optimal amount of time to leave the urinary catheter in place; however, it seems prudent to wait for postobstructive diuresis (if any) to resolve and the urine to be clear of gross blood contamination.

All Cats

A wide variety of empirical treatments have been claimed to be successful in the treatment of idiopathic cystitis and urethral plugs. The waxing-waning nature of the clinical signs makes evaluation of treatment modalities difficult. Compounding the problem is a lack of well-controlled clinical trials. Nevertheless, a multifaceted approach involving environmental enrichment, diet, pheromones, and pharmacology seems to alleviate signs and decrease recurrence in many cats.

Environment

Feline lower urinary tract disease may actually be a clinical manifestation of a physiologically inappropriate response to stress. This is similar to the colitis that some dogs experience when subjected to a stressful event such a boarding. As such, we must look for possible stressors in the cat's environment and ways to reduce them. Surveys that require the owner to answer detailed questions about the home environment have been developed. These surveys are helpful in extracting information from the owner in a systematic and concise way that may be difficult in a time limited clinic interaction (**Figure 13.52**).

In multicat households, the "cats +1" rule should be applied to all shared resources. If there are two cats in the household, then there should be three litter boxes, three food bowls, three water bowls, three scratching posts, etc. Litter boxes should be kept very clean and away from other pets. Having a dog interrupting private time in the box or rummaging through the litter looking for "treats" can be very stressful. Water bowls need to be kept clean and filled. Some cats seem reluctant to drink if their whiskers can touch the sides of the bowl; therefore, an extra-wide drinking bowl may be helpful. As with litter boxes, bowls should be out of the reach of curious children and hungry dogs. Cats also seem to prefer surveying the environment from elevated vantage points. This gives the cat a place where they can feel safe catnapping. Cat hammocks and window perches can provide them with the necessary comfort. Toys that encourage interaction between owners and their pets should be encouraged. When there is conflict between pets, steps must be taken to mitigate adverse interactions, even if it requires physical separation. Owners are encouraged to carefully observe the cat for signs of inter-pet conflict, as stressful interactions may be subtle to the casual observer.

Household Resource Checklist

The following questions ask about your cat's resources so we can learn more about the environment your cat(s) live in. Please ✓ **DK** if you don't know, **NA** if it does not apply, or **Yes** or **No** after each question. If you have more than one cat, please answer for **all** cats. Resources (food, water, litter, and resting areas) for each cat are assumed to be out of (cat) sight of each other, such as around a corner or in another room. If they are in sight of each other, please answer **No**.

Space		DK	NA	Yes	No
1	Each cat has its own resting area in a convenient location that provides some privacy.	☐	☐	☐	☐
2	Resting areas are located such that another animal cannot sneak up on the cat while it rests.	☐	☐	☐	☐
3	Resting areas are located away from appliances or air ducts that could come on unexpectedly (machinery) while the cat rests.	☐	☐	☐	☐
4	Perches are provided so each cat can look down on its surroundings.	☐	☐	☐	☐
5	Each cat can move about freely, explore, climb, stretch, and play if it chooses to.	☐	☐	☐	☐
6	Each cat has the opportunity to move to a warmer or cooler area if it chooses to.	☐	☐	☐	☐
7	A radio or TV is left playing when the cat is home alone.	☐	☐	☐	☐
Food and water					
8	Each cat has its own food bowl.	☐	☐	☐	☐
9	Each cat has its own water bowl	☐	☐	☐	☐
10	Bowls are located in a convenient location to provide privacy while the cat eats or drinks.	☐	☐	☐	☐
11	Bowls are located such that other animals cannot sneak up on the cat while it eats or drinks	☐	☐	☐	☐
12	Bowls are washed regularly (at least weekly) with a mild detergent.	☐	☐	☐	☐
13	Bowls are located away from machinery.	☐	☐	☐	☐
Litter boxes					
14	Each cat has its own box (one box per cat, plus 1).	☐	☐	☐	☐
15	Boxes are located in convenient, well-ventilated locations that still give each cat some privacy while using it.	☐	☐	☐	☐
16	Boxes are located on more than one level in multi-level houses.	☐	☐	☐	☐
17	Boxes are located so another animal cannot sneak up on the cat during use.	☐	☐	☐	☐
18	Boxes are located away from machinery that could come on unexpectedly during use.	☐	☐	☐	☐
19	The litter is scooped daily.	☐	☐	☐	☐
20	The litter is completely replaced weekly.	☐	☐	☐	☐
21	Boxes are washed regularly (at least monthly) with a mild detergent (like dishwashing liquid), rather than strongly scented cleaners.	☐	☐	☐	☐
22	Unscented clumping litter is used.	☐	☐	☐	☐
23	A different brand or type of litter is purchased infrequently (less than monthly).	☐	☐	☐	☐
24	If a different type of litter is provided, it is put in a separate box so the cat can choose to use it (or not) if it wants to	☐	☐	☐	☐
Social contact					
25	Each cat has the opportunity to play with other animals or the owner if it chooses to on a daily basis.	☐	☐	☐	☐
26	Each cat has the option to disengage from other animals or people in the household at all times.	☐	☐	☐	☐
27	Do any cats interact with outdoor cats through windows?	☐	☐	☐	☐

FIGURE 13.52 Example of a Household Resource questionnaire that can be used to collect information about the pet's environment. (*Courtesy of C.A. Buffington.*)

Body care and activity					
28	Horizontal scratching posts are provided.	☐	☐	☐	☐
29	Vertical scratching posts are provided.	☐	☐	☐	☐
31	Chew items (e.g. cat-safe grasses) are provided.	☐	☐	☐	☐
32	Toys to chase that mimic quickly moving prey are provided.	☐	☐	☐	☐
33	Toys that can be picked up, carried, and tossed in the air are provided.	☐	☐	☐	☐
34	Toys are rotated on a regular basis (at least weekly) to provide novelty.	☐	☐	☐	☐

If you have additional comments on any of the questions, please write them below, including the question #.

Please help us understand what your cat does around the house by placing a check (✓) in the box next to each behavior that best describes how commonly your cat does each of the behaviors described below.

Does your cat	All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time	Does not apply
Leave household articles (furniture, drapes, clothing, plants, etc.) alone.	☐	☐	☐	☐	☐	☐	☐
Eat small amounts calmly at intervals throughout the day.	☐	☐	☐	☐	☐	☐	☐
Drink small amounts calmly at intervals throughout the day.	☐	☐	☐	☐	☐	☐	☐
Use the litterbox.	☐	☐	☐	☐	☐	☐	☐
Get along with people in the home.	☐	☐	☐	☐	☐	☐	☐
Get along with other pets in the home.	☐	☐	☐	☐	☐	☐	☐
Remain calm when left alone.	☐	☐	☐	☐	☐	☐	☐
Stay relaxed during normal, everyday handling (grooming, petting).	☐	☐	☐	☐	☐	☐	☐
Calm down quickly if startled or excited.	☐	☐	☐	☐	☐	☐	☐
React calmly to everyday events (telephone or doorbell ringing).	☐	☐	☐	☐	☐	☐	☐
Play well with people.	☐	☐	☐	☐	☐	☐	☐
Play well with other family cats.	☐	☐	☐	☐	☐	☐	☐
Show affection without acting clingy or annoying.	☐	☐	☐	☐	☐	☐	☐
Tolerate confinement in a carrier (including travel).	☐	☐	☐	☐	☐	☐	☐
Groom entire body calmly.	☐	☐	☐	☐	☐	☐	☐
Use scratching posts.	☐	☐	☐	☐	☐	☐	☐
Play with toys.	☐	☐	☐	☐	☐	☐	☐

Comments: anything else your cat regularly does or does not do that you think might be helpful for us to know about?

FIGURE 13.52 (*Continued*)

Diet

The role of diet in controlling FIC and urethral plugs is somewhat controversial. Although many feline diets have been acidified and, in some cases, magnesium restricted "for urinary tract health," there is no proven benefit of this practice. Struvite crystals do not damage normal urinary tract epithelium, and their presence does not appear to be the cause of cystitis. Nevertheless, the

feeding of canned moist diet has been shown to lower incidences and recurrence of FIC. While it is clear that the ingestion of a wet food diet decreases urine osmolality and, therefore, concentration of noxious substances, other factors may be involved. The feeding of a wet food involves a different type of interaction between the owner and the pet. Bowls need to be washed, cans opened, food scooped and prepared, and finally, the cat is presented with its meal. This can be contrasted with scooping and "dumping" of a dry kibble. Whether it is the moisture content of the food, the ritual involved, or both, the feeding of a wet food diet is important in reducing recurrence of FLUTD.

It is important, not to "switch" diets, especially in cats accustomed to a dry kibble food. The stress associated with an abrupt diet change has the potential to trigger further episodes of cystitis or, worse, anorexia and hepatic lipidosis. Rather, the new diet should be offered alongside the cat's usual food, and the pet should be allowed to choose between them. Most cats will eventually choose the wet food. If the cat will only eat dry food, then a change should not be instituted.

The eating environment should be analyzed for potential stress. Many cats prefer to eat alone where they will not be disturbed by other animals, sudden movement, or unexpected noises. Other cats seem to be more social and may enjoy companionship during their meals. The goal is to minimize stress and maximize the pleasure of the dining experience for the individual cat.

Pheromones

Pheromones are chemical messengers that convey information between members of the same species. Cats release several pheromones from facial scent glands, and they deposit these pheromones by rubbing their heads on objects, including their human companions, when they feel safe. A synthetic analog (Feliway®, Ceva Santé Animale, France) is available as both a room diffuser and spray. While studies examining the use of this product in cats with cystitis are lacking, there is evidence that this product may decrease marking and scratching behavior in multicat households, as well as increase grooming and eating in hospitalized patients. It has been suggested that the spray can be applied to the area in which the cat is inappropriately urinating or that an entire room can be treated with a plug-in diffuser.

Drug Therapy

Amitriptyline (Elavil®), is a tricycle antidepressant drug with antianxiety, analgesic, and anti-inflammatory properties. Although some small studies have shown no benefit from the use of amitriptyline for the treatment of FLUTD, others have demonstrated a significant benefit from its use. In one study, 100% of obstructed cats which received no treatment other than amitriptyline recovered. Not only does amitriptyline decrease anxiety, provides analgesia both peripherally and in CNS, it has been shown to be a potent urethral relaxer. Recommended dosage is 1 mg/kg q.24 h. Like all oral medications for cats, compounding into a liquid should be considered if pills are problematic.

Prazosin (Minipress®) is an alpha-blocker that may decrease urethral spasms. At this time, there are no controlled studies to support or refute its usage; however, empirical observations suggest it may be helpful. It is dosed at 0.5 mg per cat (not kg) p.o. q.24 h.

As FLUTD is associated with significant discomfort, analgesics should be provided. Butorphanol, an opioid analgesic, appears to provide satisfactory pain relief. Robenacoxib (Onsior®), a nonsteroidal anti-inflammatory drug, may also be helpful in controlling discomfort. Some have had success with gabapentin (5 mg/kg p.o. q.24 h.).

While the exact cause of FLUTD is unknown, a multifaceted approach combining environmental enrichment, diet, pheromones, and pharmacology appears to give many patients relief. In cases in which symptoms cannot be controlled, a penile urethrostomy may be required. Because of the risk of incontinence, the required anatomic modification, and high lifelong risk of infection, this should only be considered when other possible alternatives have been exhausted.

Prognosis

While most cats will respond to a combination of environmental modifications, pheromones, and pharmacology, some may still require penile urethrostomy; however, surgery fails to address the underlying issue.

UROLITHIASIS

Definition/Overview

Common uroliths in dogs and cats include struvite and calcium oxalate, while ammonium urate and cystine are less common (Tables 13.16 and 13.17).

Etiology

Urine is a complex solution made up of dissolved substances, some of which have a tendency to precipitate out of solution, while others actively inhibit precipitation by increasing solubility. For example, as the concentration of calcium in urine increases, there is an increased risk of it binding to oxalate and forming crystals and stones; however, citrate in the urine binds to calcium and makes it unavailable. If we look at Figure 13.52, there is a region on the chart called the solubility product. If urine were only made up of substances that tend to precipitate out of solution, then this would be the maximum saturation that could be achieved. However, the presence of inhibitors like citrate allows urine to achieve a metastable supersaturated state. Under normal circumstances, there is a balance between precipitators and inhibitors, and urine exists in this metastable state; however, if there is an excess of precipitators or a shortage of inhibitors, crystals and uroliths can form. In some cases, urine pH can also directly impact the solubility of these solutes.

TABLE 13.16 Uroliths in dogs

	Struvite	Calcium oxalate	Urate	Cystine
Age	2–9 years*	5–12 years	1–5 years	1–7 years
Breed	Min. Schnauzer, Min. Poodle, Bichon Frise, Cocker Spaniel	Min. Schnauzer, Std. Schnauzer, Lhaso Apso, Yorkshire Terrier, Min. Poodle, Shi Tzu, Bichon Frise	Dalmatian, English Bulldog, Min. Schnauzer, Yorkshire Terrier, Shi Tzu	English Bulldog, Dachshund, Bassett Hound, Newfoundland
Sex – Female – Male	>80%	>5 years**	>6 years**	Majority
Urinalysis – PH – Crystals – Culture – Serum	≥7.0 Struvite *Staph. intermedius*	≤7.0 Calcium oxalate ↑ Ca2+†	≤7.0 Urate ↓ Albumin†† ↓ BUN (urea)†	≤7.0 Cystine
Radiography	Large, >2 cm smooth surface	Medium size spiked surface	Small rounded	Small rounded
Opacity	2+–4+	4+	0–2+	1+–2+

* If less than 1 year old, very high chance of struvite.
** Higher probability if in this age category.
† Only rarely found.
†† In portosystemic shunts.

TABLE 13.17 Uroliths in cats

	Struvite	Calcium oxalate	Urate
Age* – 1–4 years – >10 years	79% 60%	21% 40%	Rare
Breed	Any	Burmese Himalayan Persian	
Sex – Male – Female	65% 75%	35% 25%	
Urinalysis – PH – Crystals – Culture – Serum	≥7.0 Struvite *Staphylococcus intermedius*	≤7.0 Calcium oxalate ↑ Ca2++†	≤7.0 Ammonium urate ↓ Albumin†† ↓ BUN
Radiograph	Discoid‡ Ovoid/ Smooth‡‡	Spiked surface	Rounded
Opacity	2+–4+	4+	0–2+

* If less than 1 year old, usually due to urease-producing infection.
† Only rarely found.
†† In portosystemic shunts.
‡ Usually sterile.
‡‡ Associated with urease-producing infection.

Pathophysiology

Struvite

In dogs, the most common urolith is struvite (magnesium, ammonium, phosphate). These stones are associated with urease-producing bacteria (*Staphylococcus intermedius*, *Proteus mirabilis*, *Pseudomonas* spp., *Klebsiella* spp.). Urea is plentiful in the urine, and urease splits it to form

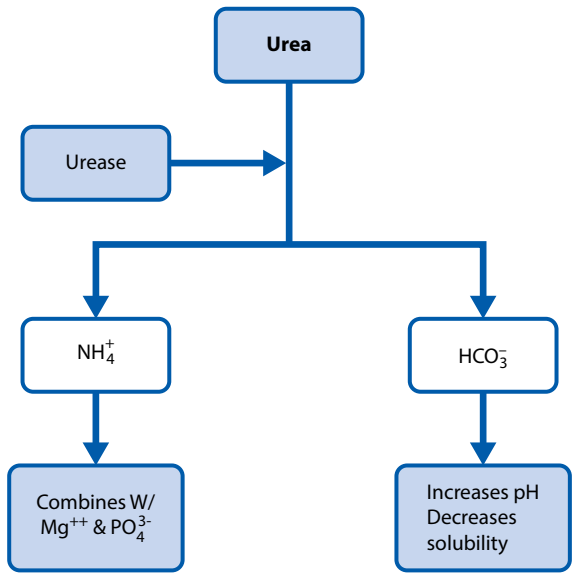


FIGURE 13.53 Bacterial urease splits urea, which is plentiful in urine, to form ammonium and bicarbonate. Ammonium combines with magnesium and phosphate while the bicarbonate raises the urine pH. The change in pH decreases the solubility of the ammonium–magnesium–phosphate complex, leading to the formation of struvite crystals and stones.

ammonium and bicarbonate (Figure 13.53). Ammonium combines with magnesium and phosphate, while the bicarbonate raises the urine pH. The change in pH decreases the solubility of the ammonium, magnesium, phosphate complex, leading to the formation of struvite crystals and stones. The anatomic configuration of the female makes urease-producing infections more common than in males.

In contrast to canines and people, struvite uroliths found in young, healthy cats are usually not associated with urinary tract infections. Although the exact pathophysiology is not well understood, diet, breed, sex, and urine pH all seem to play a role.

Calcium Oxalate

The second most common canine urolith is calcium oxalate. The formation of these stones can be the result of excessive calcium/oxalate excretion or an absence of precipitation inhibitors. Although most cases are idiopathic, possible causes of excessive calcium excretion into urine should be investigated. Increased calcium in the urine can be result of excessive kidney loss or increased renal excretion due to elevated blood calcium levels. Elevated blood levels can be secondary to (1) increased intestinal absorption, (2) hyperparathyroidism, (3) paraneoplastic syndromes, (4) granulomatous disease, or (5) calcitriol toxicosis. While it was once thought that urine pH had a great effect on calcium oxalate formation, it is now generally accepted that urine acidity plays only a minor role.

Serum ionized calcium levels should be measured in all patients who present with calcium oxalate uroliths or crystals. This information when combined with serum levels of calcitriol, PTH, and parathyroid hormone-related peptide (PTHrP) can be helpful in identifying the underlying cause of calcium oxalate formation (Table 13.18). For example, calcium oxalate uroliths occur in dogs secondary to hyperparathyroidism. In these patients, excessive PTH results in osteoclastic reclamation of bone and excessive formation of calcitriol (25-hydroxyvitamin D) by the kidney. Calcitriol increases intestinal absorption of calcium. These two actions result in elevations in blood calcium concentrations. In the kidney, excessive amounts of calcium are passed through the glomerulus. Although PTH simulates renal calcium reabsorption, the filtered calcium overwhelms the kidney's resorptive capacity, resulting in hypercalciuria and stone formation.

TABLE 13.18 Causes of canine hypercalcemia can often be determined by measuring calcium, parathyroid hormone (PTH), calcitriol, and parathyroid hormone-related peptide (PTHrP)

	Ca++	PTH	Calcitriol	PTHrP
Intestinal	E	L	L	O
Leakage	N	N	N	O
Hyperparathyroid	E	E	E	O
Paraneoplastic	E	L	E	E
Granulomatous	E	L	E	O
Calcipotriol	E	L	E	O

E, elevated; L, low; N, normal; O, zero.

TABLE 13.19 Causes of feline hypercalcemia can often be determined by measuring ionized calcium, parathyroid hormone, and parathyroid hormone-related peptide

	Ionized Ca++	PTH	PTHrP
Idiopathic	High	Normal/high	O
Cancer	High	Low	High
Primary	High	High*	O

Note: Since idiopathic hypercalcemia can present with only slightly increased total calcium, it is recommended that ionized calcium be used for screening.

* Primary hyperPTH can have PTH values ranging from normal to high. Any normal PTH with increased PTH concentrations is inappropriately elevated.

Leakage hypercalciuria is a failure of the renal tubules to resorb filtered calcium despite the presence of adequate PTH. As calcium is lost, PTH is released from the parathyroid gland, mobilizing calcium from bone, and stimulating formation of calcitriol. Although calcium is lost into the urine, serum levels are normal due to the actions of PTH and calcitriol. Even though leakage hypercalciuria can occur as a primary condition, it should be noted that hyperadrenocorticism (Cushing's disease) and steroids can both promote leakage hypercalciuria and urolith formation.

Although many cases of feline calcium oxalate are idiopathic, all patients should be screened for idiopathic hypercalcemia, malignancy hypercalcemia, and primary hyperparathyroidism. Since increases in total calcium can be underwhelming in some of these conditions, ionized calcium should be tested in all patients with calcium uroliths. If high, PTH and PTHrP levels should be measured. Based on these three parameters, the likely cause of the hypercalcemia can be determined (Table 13.19).

Cats with idiopathic hypercalcemia may have only slight elevations in total calcium, while ionized calcium can be dramatically affected. While at least half of affected cats will have no clinical signs, others will experience weight loss, signs of inflammatory bowel disease, constipation, anorexia, and oxalate stones. Besides removing the calcium oxalate stones, these patients should be fed a high-fiber, alkaline-urine-forming diet. While many will respond to high-dose prednisolone (5–10 mg per cat q.24 h.) bisphosphonates (e.g., alendronate) may be a better alternative. Alendronate can be given 10 mg per cat once a week. The dose then can be adjusted (5–20 mg per cat) based on ionized calcium rechecks at 8 weeks and then monthly. As alendronate can cause esophagitis, the pill should not be split or crushed and always followed with 5 mL of tap water.

Urate

Urate stones are the third most common urolith in dogs and account for 8% of canine urinary calculi. A genetic predisposition (autosomal recessive) has been

documented in Dalmatians and is suspected in English Bulldogs. Urate uroliths are observed in a number of other breeds. While the mechanism of urate stone formation in these dogs is unclear, Yorkshire Terrier, Shih Tzu, and Miniature Schnauzer appear to be overrepresented. Urate stone formation has also been associated with hepatic dysfunction, especially hepatic portal shunts.

In most dogs, dietary purines are metabolized in a series of steps to the highly soluble allantoin (Figure 13.54). This process, which takes place in the liver, involves converting purines to hypoxanthine. Through the action of xanthine oxidase, hypoxanthine is converted to xanthine and then uric acid. Uric acid, which is poorly soluble, is then converted to the highly soluble allantoin through the enzymatic action of uricase. Although Dalmatians possess all the necessary enzymes to convert purines to allantoin, it appears that a defective cell membrane transport system decreases hepatic metabolism of uric acid, and large amounts of uric acid are then presented to the kidney. The resulting hyperuricosuria may not completely explain the urolith formation, as not all Dalmatians with increased urate excretion are affected. It is likely that other factors, including urine pH and a decrease in the production of crystallization inhibitors, play a role. The fact that most Dalmatians that present for urate stones are male is likely due to anatomic differences (e.g., decreased urethral diameter) between the sexes.

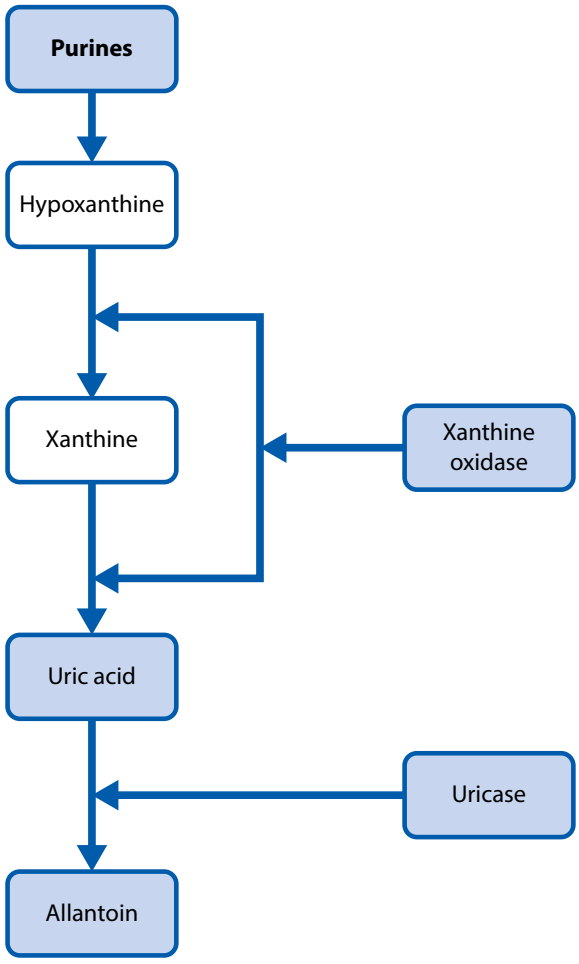


FIGURE 13.54 Dietary purines are metabolized in a series of oxidative steps to the highly water soluble allantoin. In some patients, the process is interrupted, leaving large amounts of the poorly soluble uric acid.

Urate uroliths have been observed in cats. There does not appear to be a breed predilection. Most urate uroliths occur in younger cats and may occur as a secondary to liver disease or portal vascular anomaly; however, most appear to be idiopathic.

Canine Cystine

In the United Sates, cystine urolithiasis is uncommon and accounts for only 1%–2% of all uroliths; however, the incidence may be higher elsewhere. Cystine uroliths have been reported in more than 100 different breeds of dogs, and more than 90% of these stones occur in male intact patients.

In the kidney, cystine is freely filtered by the glomerulus and then reabsorbed in the proximal convoluted tubule. In affected dogs, there is a defect in the proteins needed for cystine reabsorption, and excessive amounts of the poorly soluble amino acid are excreted in the urine. Four different genetic mutations have been identified affecting several different breeds. For example, in Newfoundland dogs, the condition is inherited as an autosomal recessive condition, while in Australian Cattle dogs, it is autosomal dominant. In most dogs (>90%), the condition appears to be testosterone responsive, and castration significantly reduces cystinuria. DNA testing is available to determining which form of the disease is affecting a patient (PennGen®).

Clinical Presentation

Clinical signs vary with the location of the uroliths. Nephroliths may cause sublumbar pain and hematuria, but they are often associated with no clinical signs. Bladder uroliths cause signs of lower urinary tract inflammation with hematuria, pollakiuria, and stranguria. Urethral uroliths in male dogs cause stranguria and intermittent incontinence with a full bladder. In both dogs and cats, they can cause complete urethral obstruction.

Differential Diagnosis

Lower urinary tract inflammation (hematuria and proteinuria), trauma, neoplasia, UTI, idiopathic cystitis (cats)

Diagnosis

Presence, number, size, and location of uroliths are usually determined by radiographic and/or ultrasound examination (Tables 13.16 and 13.17). As size and radiolucency can vary substantially, ultrasound has proven to be more diagnostically useful than radiographs.

Likely, mineral composition of uroliths can be predicted on the bias of clinical data, including the age, breed, sex, radiographic density and shape of the uroliths (Figure 13.55a, b), composition urine crystals (Figures 13.56–13.59), urine pH, and bacterial culture

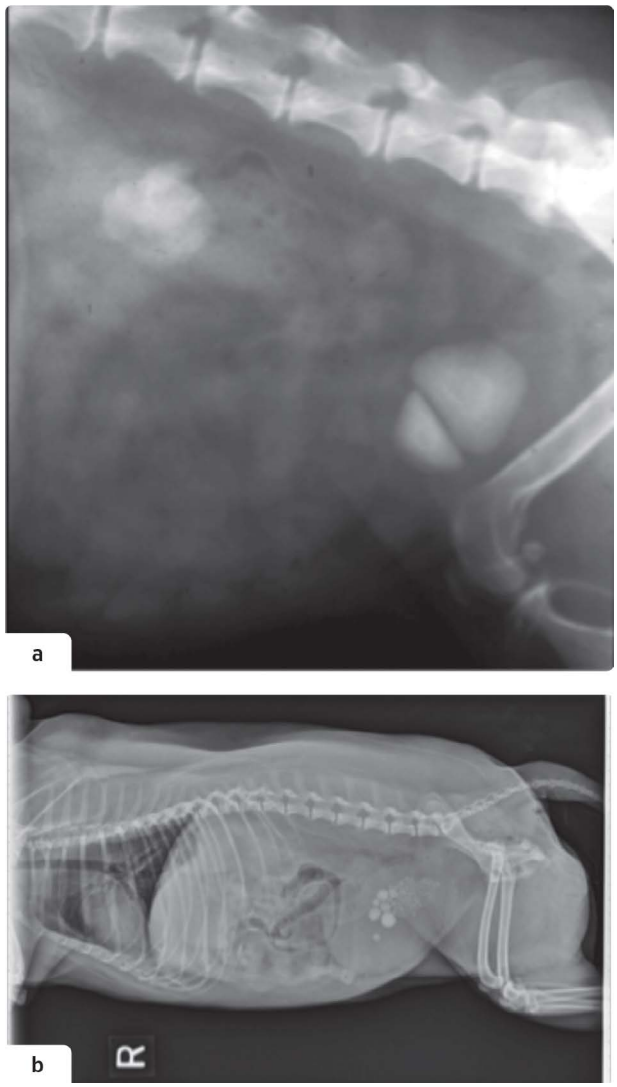


FIGURE 13.55 Although struvite uroliths are classically described as being large with flattened edges between the stones **(a)**, they can appear as many small stones **(b)**, making predicting the composition of the uroliths based on clinical data challenging. In addition, uroliths of a mixed composition are not uncommon; therefore, whenever possible, uroliths should be submitted for analysis.

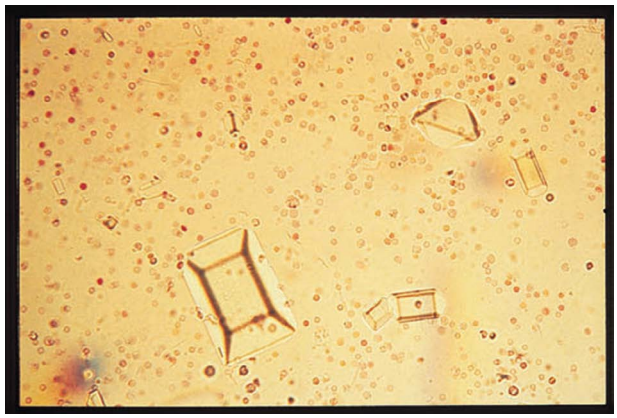


FIGURE 13.56 Appearance of crystals in urine corresponding to the common uroliths: struvite. (*Courtesy of D.F. Senior.*)

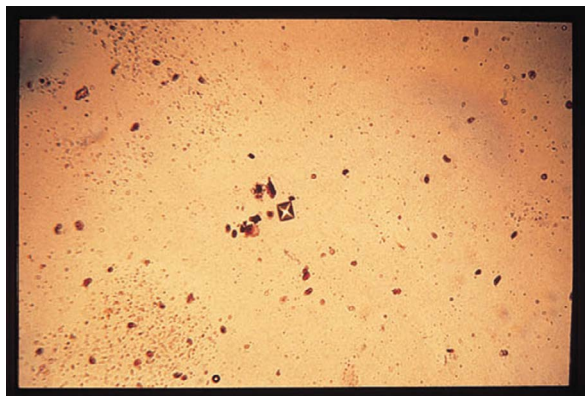


FIGURE 13.57 Appearance of crystals in urine corresponding to the common uroliths: calcium oxalate dihydrate. (*Courtesy of D.F. Senior.*)



FIGURE 13.58 Appearance of crystals in urine corresponding to the common uroliths: ammonium urate. (*Courtesy of D.F. Senior.*)

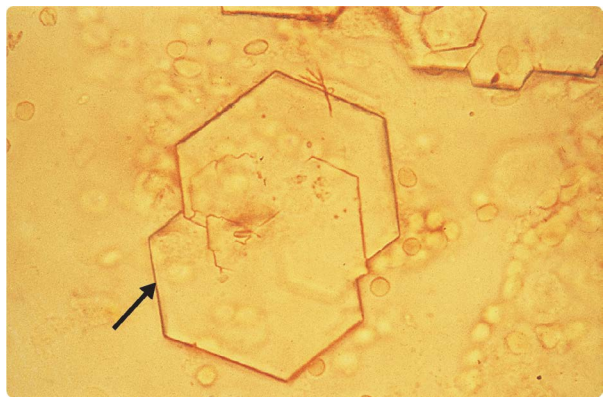


FIGURE 13.59 Appearance of crystals in urine corresponding to the common uroliths (arrow): cystine. (*Courtesy of D.F. Senior.*)

of the urine; however, actual mineral composition can only be determined by quantitative analysis of recovered uroliths. These tests, which include optical crystallography, x-ray diffraction, and infrared spectroscopy, are only performed at specialty laboratories and should be performed on every patient.



FIGURE 13.60 Lateral abdominal radiograph of a patient with a subcutaneous bypass (SUB). The proximal end of the device is in the kidney. The distal end is positioned within the urinary bladder. This restores the flow of urine from kidney to the bladder without addressing the obstructed ureter. The port, located in the ventral abdomen, allows for flushing and collecting of urine samples. These are typically placed using fluoroscopy.

Management

Depending on their location in the urinary tract, there are different ways to treat uroliths. Stones located in the kidney (nephroliths) are usually left untreated unless they obstruct the ureter, at which point most would require surgical intervention. Although an attempt can be made to dissolve nephroliths in dogs, only 20%–30% are composed of struvite. The rest are likely calcium oxalate. Virtually all feline nephroliths are calcium. Stones that become lodged in the ureter (ureterolith) represent a surgical emergency because in a matter of days they can lead to hydronephrosis and irreversible kidney damage. Traditionally, these have been surgically removed; however, today options such as ureteral stents and subcutaneous ureteral bypass devices (Figure 13.60) have become possible.

Struvite, urate, and cystine uroliths are all amenable to being dissolved (Figure 13.61); however, in male patients, these is always a risk of urethral obstruction. Removal of tiny stones can be attempted with catheter-assisted retrieval. Small stones may be removed with urohydropropulsion or endoscopically utilizing a stone basket (Figure 13.62). Larger stones can be fragmented with a laser and removed endoscopically. Once removed, all stones should be submitted for analysis. While diagnostic imaging and urinalysis can provide information about the possible composition of the stone (Tables 13.16 and 13.17 and Figures 13.56–13.59), only a proper stone analysis can provide definitive information regarding stone composition.

Preliminary: Urine obtained by cystocentesis submitted for culture and sensitivity.

Initiate therapy: Start oral antimicrobial drugs based on urine culture and sensitivity results and begin feeding commercially available struvite dissolving diet.
Antimicrobial therapy must continue for duration of dissolution therapy.

Every 30 days: Physical examination, urinalysis, abdominal radiographs. If pH is >7.0, suspect resistant infection and submit urine for culture and sensitivity. Adjust antimicrobial as indicated.

Continue protocol: Continue therapy for 30 days after the ÿrst follow-up radiographic examination that shows no evidence of uroliths.

FIGURE 13.61 Canine struvite uroliths dissolution flowchart.

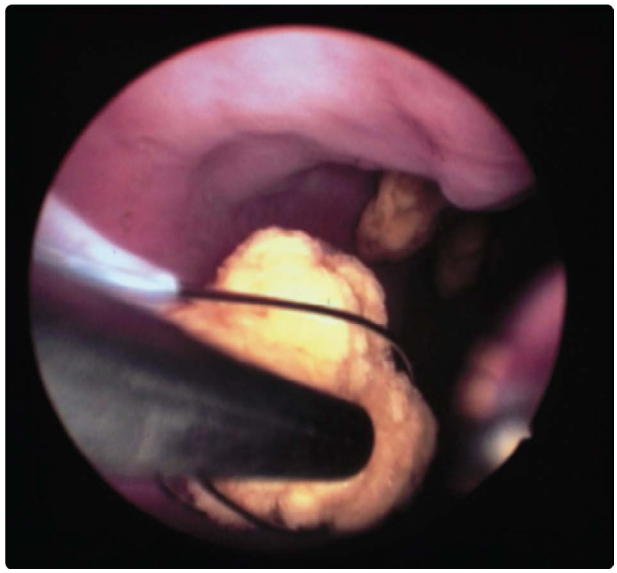


FIGURE 13.62 Urolith removed with a urethroscope and retrieval basket.

Canine Struvite Uroliths

Struvite uroliths can be dissolved over time; however, this carries the risk of urethral obstruction in males. A discussion with the owner about the relative risks and benefits of medical and surgical management should occur before deciding on a therapy. The owner should be made aware that in dogs the dissolving process takes many months.

Dissolution of struvite uroliths involves a combination of antimicrobial and dietary therapy. Appropriate antimicrobial selection can only be made on the basis of a urine culture and sensitivity. The urine must be obtained by cystocentesis and plated in a timely fashion. Since bacteria are often sequestered and protected in the layers of the stone, antibiotic therapy must be continued throughout the entire dissolution process. There are several commercially available struvite-dissolving diets. These diets tend to be low in protein and acidify the urine. At home, the owner should periodically test urine pH with a dipstick. If the pH is greater than 7.0, a resistant urinary tract infection should be suspected, and a urine sample, obtained by cystocentesis, should be submitted for culture. The patient's progress should be evaluated monthly by performing abdominal radiographs and a urinalysis.

Inhibition of struvite formation requires prevention of alkaline urine; therefore, the urinary tract must be free of infections. At-home monitoring can be performed by periodically measuring urine pH. The presence of

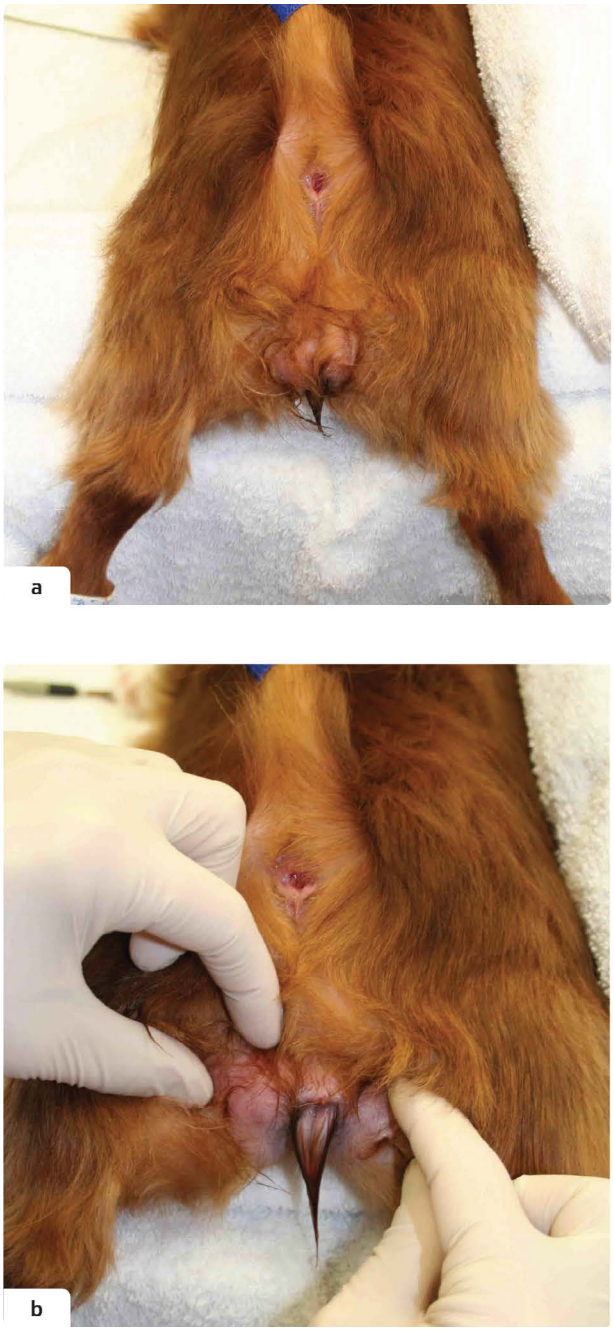


FIGURE 13.63 (a, b) Dog with an involuted vulva. Note how the extent of the involution is not apparent until a complete genital examination is performed.

alkaline urine indicates that a urine culture is necessary. Dogs with recurrent UTIs despite the resolution of uroliths should be evaluated for structural abnormalities that may predispose the patient to UTIs. We have found that most of these cases involve an involuted vulva (Figure 13.63a, b).

Feline Struvite Uroliths

Feline struvite uroliths can be dissolved by feeding a diet that is both restricted in magnesium, phosphorous, and protein and induces aciduria. There are several commercial diets which are formulated to accomplish struvite dissolution is cats. Unlike dogs, complete dissolution of stones can be often accomplished in just days to weeks. Although one might assume there is a high risk of urethral obstruction, this is actually quite rare. In cases where the composition of the stone is unknown, an attempt should always be made to dissolve the stone first.

Canine Calcium Oxalate

Calcium oxalate uroliths cannot be dissolved and must be removed using urohydropropulsion, a stone basket, surgery, or lithotripsy. One of the most important steps in preventing calcium oxalate crystals and uroliths is to increase water intake, which can be accomplished by feeding a canned diet. The optimum diet composition to prevent calcium oxalate urolith formation is unknown. Previously, it had been recommended that diets be low in protein and sodium restricted; however, recent epidemiologic studies have challenged this approach. Currently recommended diets include Royal Canin S/O, Hill's u/d, and Hills w/d. Despite appropriate diet therapy, as many as 50% of dogs will have recurrence within 3 years.

After calcium oxalate stone removal, the owner should purchase a refractometer and urine dipsticks. Urine should be checked weekly to be certain urine specific gravity remains less than 1.020 and pH is 7.0–7.5. Radiographs should be taken every 4 months so that stones can be detected while they are small enough to be removed by stone basket, catheter-assisted retrieval, or urohydropropulsion.

Thiazide diuretics have been shown to decrease urinary calcium excretion and should be considered in dogs with persistent calcium oxalate crystalluria or recurrence of uroliths despite appropriate diet therapy (hydrochlorothiazide 2 mg/kg p.o. q.12 h.). Citrate is a urolith inhibitor that forms complexes with calcium and increases its solubility. In people, oral potassium citrate ingestion increases urine pH and increases the amount of citrate in the urine; however, the benefit of potassium citrate supplementation in dogs is unclear. In dogs, oral potassium citrate does not result in a significant change in urine citrate concentration. Nevertheless, some still recommend supplementation (25–50 mg/kg p.o. q.12 h.).

Feline Calcium Oxalate

Cats with elevations in ionized calcium should be treated appropriately for any underlying condition. Once the hypercalcemia is addressed, the amount of calcium spilling into the urine will abate, and they should not continue to form uroliths. For idiopathic urolith-producing patients, there are two diets formulated for the prevention of these stones. These diets contain potassium citrate and induce a urine pH of approximately 7.0. Neither has been evaluated in actual calcium oxalate-forming cats; nevertheless, cats consuming c/d Multicare (Hill's Pet Nutrition) and SO (Royal Canin) do appear to have decreased urine calcium oxalate saturation.

Canine Urate

Although urate uroliths can be medically dissolved, there is a significant risk of urethral obstruction in male dogs. A discussion with the owner about the relative risks and benefits of medical and surgical management should occur before selecting a therapy. Dissolution should not be attempted in dogs with known liver disease.

The dissolution of urate uroliths involves dietary changes, medical intervention, and urine modification. Reduction of urate excretion can be achieved by restricting total protein and by replacing high-purine-content proteins (e.g., fish) with low-purine-content proteins (e.g., eggs). Feeding a protein-restricted diet can dilute urine by decreasing the urea available for the medullary concentration gradient of the kidney. A canned diet increases water intake and can further decrease urine concentration. Hills u/d, i/d Sensitive Canine and Purina HA Hydrolyzed have all be successfully employed. Allopurinol, a xanthine oxidase inhibitor, prevents the conversion of soluble xanthine to the insoluble uric acid (see **Figure 13.54**). Although a variety of adverse reactions have been reported in humans, the most commonly reported adverse effect in dogs is the formation of xanthine uroliths. This is usually seen when high-protein diets are consumed in conjunction with the medication. For this reason, long-term use is not advised.

Prevention of urate uroliths recurrence is best accomplished through a combination of low-protein diet and urine alkalinization. Prophylactic treatment with allopurinol is not recommended. Urate urolith formation is inhibited in alkaline urine as the concentration of ammonium ions needed for stone formation decreases. The target pH range is 7.0–7.4. Low-protein diets favor an alkaline pH; however, if further urine alkalinization is needed, potassium citrate (40–90 mg/kg p.o. q.12 h.) can be utilized. A urine pH of 7.5 or higher should be avoided, as this may favor the formation of calcium phosphate and struvite uroliths. Response to medical therapy can be evaluated by checking periodic monitoring of urine pH (7.0–7.4), specific gravity (<1.015), and serum BUN (<10 mg/dL).

Canine Cystine

Although cystine uroliths can be medically dissolved (1–3 months), there is a significant risk of urethral obstruction. For this reason, dissolving them should never be attempted in male dogs (>97% of cases). Since the majority of cases are likely testosterone responsive, the patient should be either DNA tested and then castrated or castrated with no further testing.

Prevention of cystine uroliths in non-testosterone-response dogs involves dietary changes, medical intervention, and urine modification. Reduction of cystine excretion can be achieved by restricting total protein. Feeding a protein-restricted diet can also dilute urine by decreasing the urea available for renal medulla. Further urine dilution can be achieved by feeding a canned diet. Thiol-containing drugs catalyze the conversion of the poorly soluble cystine to more soluble compounds. N-(2-mercaptopropionyl) glycine (Thiola®, Mission Pharmacal) 20 mg/kg p.o. q.12 h. is commonly used for this purpose. Side effects, including aggression, myopathy, proteinuria, anemia, and thrombocytopenia, may limit its use. Cystine urolith formation is inhibited in alkaline urine. The target pH range is 7.0–7.4. Low-protein diets favor an alkaline pH; however, sometimes further urine alkalinization is needed. Potassium citrate (40–90 mg/kg p.o. q.12 h.) can be utilized. A urine pH of 7.5 or higher should be avoided, as this may favor the formation of calcium phosphate and struvite uroliths. Response to medical therapy can be evaluated by periodic at home checking of urine pH (7.0–7.4) and specific gravity (<1.015).

TUMORS OF THE LOWER URINARY TRACT

Definition/Overview

Tumors of the lower urinary tract are relatively rare, representing less than 2% of all canine neoplasms and an even lower percentage of feline neoplasms. Most are malignant, and transitional cell carcinoma (TCC) is by far the most common. Other neoplasms seen less frequently include squamous cell carcinoma, adenocarcinoma, undifferentiated carcinoma, rhabdomyosarcoma, and fibroma.

Etiology

Scottish Terriers have an 18-fold increased risk of developing transitional cell carcinoma, while Shetland Sheepdogs and Beagles have a 4-fold increased risk. A link between lawn herbicide and pesticide exposure and the development of TCC has been established. In cats, the tumor types are more varied with different primary cell types involved. As many as 20% of bladder tumors in cats may be benign.

Pathophysiology

Transitional cell carcinomas spread by direct extension through the wall of the bladder or urethra to adjacent tissue and draining lymph nodes. At diagnosis, about 40% have undergone metastasis, most commonly to regional lymph nodes, the lungs, and ventral lumbar vertebrae; however, ureteral and urethral obstructions are the most common life-limiting complications. Secondary UTIs are common, a development that can intensify clinical signs.

Clinical Presentation

Affected animals present with signs of lower urinary tract inflammation, including pollakiuria, dysuria, stranguria, and hematuria. Urethral obstruction may be evident in patients with urethral involvement. On physical examination, the bladder wall may be thickened, and a mass may be palpable. For urethral tumors in dogs, a portion or all of the urethra may be thickened on rectal palpation.



FIGURE 13.64 Example of a retrograde urethrogram in a patient with urethral obstruction due to transitional cell carcinoma. The arrow indicates an area of filling defect.

Differential Diagnosis

Abnormal micturition: UTI, urolithiasis, behavioral disturbances, urethral stricture, granulomatous urethritis, neurologic disorders, cystitis.

Diagnosis

Historically, TCC has been diagnosed based on a combination of diagnostic imaging (Figure 13.64), urinalysis findings, and diagnostic catheterization (suction biopsies). Each of these has limitations. More recently, two genetic mutations associated with approximately 95% of TCC cases have been identified, and a test has been made commercially available (CADET® BRAF-PLUS). This test, which is both sensitive and specific, uses a specialized free-catch urine system which is totally noninvasive. Unlike earlier tests, it is not affected by other urinary tract conditions.

In cases where urinary tract neoplasia is suspected but the CADET test is negative, samples for histopathologic/cytologic examination can be obtained by either cystoscopy or diagnostic catheterization (Figure 13.65). Because of the risk of spreading the neoplasia, fine-needle aspirates should not be attempted. Diagnostic catheterization is performed by placing a side-hole catheter in the urethra while using rectal palpation or ultrasound to guide the catheter tip into the affected area. Suction is then applied using a syringe so that the catheter adheres to the urethral wall, and abnormal tissue is drawn inside the lumen of the side hole. Then, the catheter is forcibly removed while continuing to apply suction. When available, urethroscopy and cystoscopy can be rewarding procedures. Not only do they allow visual inspection of the urethra and bladder, but they also facilitate tissue biopsies.



FIGURE 13.65 Example of simple equipment needed for effective urethral suction biopsy. The patient is sedated and a catheter inserted into the urethra using rectal palpation to guide the catheter tip into the affected area. Suction is applied using the syringe and the catheter is forcibly removed.

Management

The success of surgical intervention is limited by the late stage at which the diagnosis of tumors of the lower urinary tract is generally made. The mainstay of therapy is composed of piroxicam (0.3 mg/kg p.o. q.24 h.) alone or in combination with chemotherapy. Urethral stenting may be utilized in patients presenting with or developing a urethral obstruction with this therapy.

Prognosis

Piroxicam has an 18% reported overall response rate and 35% when used in combination with chemotherapeutic agents. Commonly used drugs include doxorubicin, cyclophosphamide, mitoxantrone, cisplatin, and carboplatin. Radiation therapy has also been successfully employed.

Urethral and prostatic involvement is associated with a worse prognosis due to the likelihood of urinary obstruction. Urethral stenting can provide palliative relief of obstructed urethras (Figures 13.64 and 13.66). Control of concurrent UTI and treatment with an anticholinergic such as propantheline (7.5–15 mg p.o. q.8–12 h.) to reduce bladder spasm can alleviate some of the urge incontinence experienced by affected dogs.

CYSTIC DISEASE

Definition/Overview

Polycystic kidney disease (PKD) is a bilateral condition that has been reported in Persian cats, Cairn Terriers, West Highland White Terriers, and Australian Bull Terriers. Rare solitary renal cysts can be seen in otherwise normal cats and dogs. Perirenal pseudocysts have also been described in cats.



FIGURE 13.66 The patient after placement of a urethral stent.

Etiology

PKD has a genetic basis with autosomal-dominant inheritance in Persian cats and autosomal recessive inheritance in Cairn and West Highland White Terriers. As many as 40% of Persian cats are carriers.

Pathophysiology

The precise changes in the nephron wall that lead to PKD are not known. A prevailing theory is that a genetic mutation leads to apoptosis of the renal parenchyma. This allows cystic epithelial cells to proliferate, which creates multiple, often large cysts.

Persian cats can appear normal as kittens and only develop pronounced renomegaly and CKD as adults. In the single report of PKD in Cairn Terriers, dogs developed clinical renal disease as very young puppies. The cysts of PKD can become infected. The cause of perirenal pseudocysts in cats is unknown, and most affected animals are diagnosed in CKD.

Clinical Presentation

Animals with PKD or perirenal pseudocyst develop extreme bilateral renomegaly with concurrent signs of CKD. Affected Persian cats can be any age on initial presentation, but in Cairn and West Highland White Terriers, affected animals are usually very young. Solitary renal cysts are most often diagnosed as an incidental finding.

Differential Diagnosis

Renomegaly, neoplasia, hydronephrosis, amyloidosis, feline infectious peritonitis.

Diagnosis

In Persian cats, an ultrasound performed at 16 weeks has been reported to have a sensitivity of 75% and a specificity of 100%, while an ultrasound performed at 36 weeks of age has a sensitivity of 91% and a specificity of 100%. Cairn Terrier PKD is characterized by the presence of cysts in the liver and kidney, while West Highland White Terriers develop PKD as puppies.

Once bilateral renomegaly is recognized on physical examination, ultrasound examination can differentiate between PKD, solitary cysts, and perirenal pseudocysts. In PKD, the cysts are multiple, of variable size, and throughout the parenchyma of the kidney (**Figure 13.67a, b**), whereas in perirenal pseudocysts the renal capsule is extremely distended, completely surrounding the kidney with fluid (**Figure 13.68**).

Management

No specific treatment is available to manage cats with PKD or perirenal pseudocyst other than support for their concurrent CKD. Antibiotics to control secondary pyelonephritis may prevent some of the malaise suffered by cats with PKD.

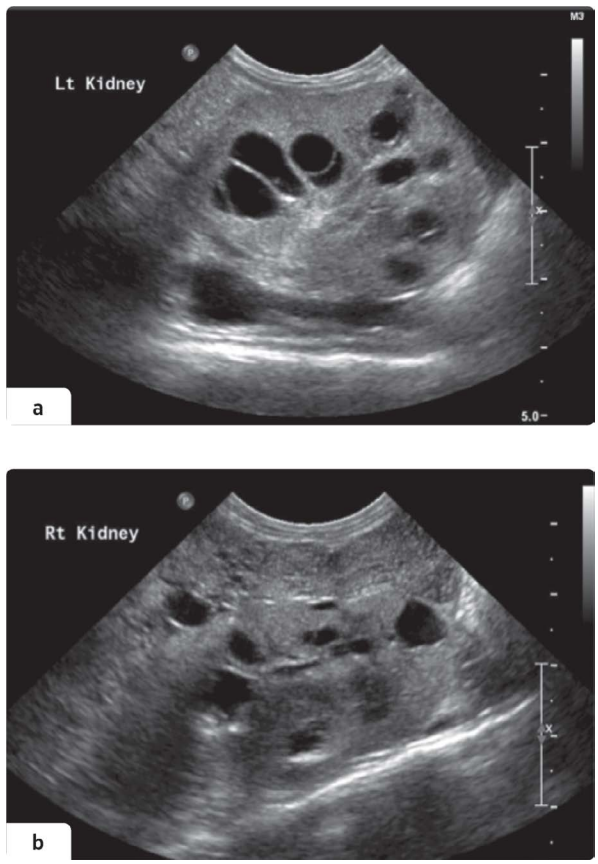


FIGURE 13.67 (a, b) Ultrasonograms of a Persian cat (age unknown) with polycystic kidney disease. (*Courtesy of R. Baumruck.*)

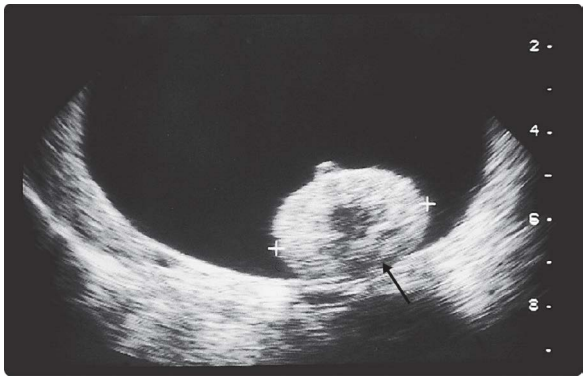


FIGURE 13.68 Ultrasonographic appearance of the kidney (arrow) and the surrounding cystic structure in a cat with a perirenal pseudocyst. (*Courtesy of AM Grooters; from* Compendium on Continuing Education for the Practicing Veterinarian*, 1997, 9:1226, with permission.*)

Prognosis

PKD is an insidious disease without effective treatment. Although clinical signs of CKD can be managed, long-term prognosis is poor.

RENAL TUMORS

Definition/Overview

Primary kidney tumors are rare and account for less than 2% of all canine cancer. Moreover, they are usually tumors that have metastasized from a remote site. The most common histologic types in dogs include renal tubular cell carcinoma, transitional cell carcinoma, and renal cell papilloma. Carcinoma, sarcoma, fibroma, hemangiosarcoma, lymphoma, and nephroblastoma have also been reported. In cats, lymphoma is the predominant renal neoplasia.

Etiology

The large renal blood supply results in the kidney being the site of distant metastases from primary tumors elsewhere in the body.

Pathophysiology

Tumors cause pain, hematuria, hydronephrosis (if they obstruct urine outflow), and displacement of normal renal tissue, which can lead to CKD. Early metastasis by the time of initial presentation is usual. Paraneoplastic syndromes have been described, including polycythemia and hypertrophic osteopathy. A hereditary multifocal renal cystadenocarcinoma of German Shepherd Dogs is accompanied by cutaneous nodules (dermatofibrosis).

Clinical Presentation

At presentation, affected animals usually exhibit anorexia and weight loss. Dogs and cats with nonlymphomatous renal tumors can present with red-brown urine that appears the same color both at the beginning and the end of urination. In addition, pollakiuria, stranguria, and urgency are not usually observed. Unilateral renal enlargement and pain may be evident on abdominal palpation. Unilateral tumors do not cause CKD.

In dogs with renal lymphoma, renal involvement can be diffuse, so both kidneys can be enlarged. Gross hematuria is not common, and evidence of the tumor can usually be detected involving other organs. In cats, lymphoma usually causes "lumpy" bilateral renomegaly. In both dogs and cats, the diffuse bilateral nature of renal lymphoma generally leads to CKD.

Differential Diagnosis

Renomegaly: Hydronephrosis, amyloidosis, feline infectious peritonitis, cystic disease.

Diagnosis

Abdominal radiographs show an irregularly enlarged kidney, and areas of mineralization may be visible. While an intravenous urogram can be used to find abnormal blood perfusion or distortion of the collection system, ultrasonographic imaging can readily detect the abnormal tissue (Figure 13.69). Cytologic evaluation of the urine has proven unreliable, so only a fine-needle aspirate or biopsy can provide a definitive diagnosis. Thoracic radiographs and an abdominal ultrasound should be performed to rule out metastasis of a renal tumor or a primary tumor in another organ.

Management

Treatment of discrete renal tumors is by surgical resection (Figure 13.70).

Prognosis is poor because of the late stage at which these tumors are generally diagnosed. However, nephroblastoma is less metastatic than other tumors, and nephrectomy can be curative. Usual treatments for lymphoma are indicated, and renal function can show some improvement if remission is achieved.



FIGURE 13.69 Renal mass in the right kidney later confirmed to be anaplastic carcinoma.

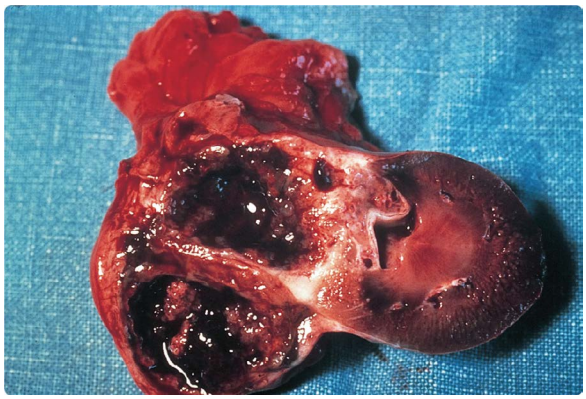


FIGURE 13.70 Gross specimen showing a unilateral renal carcinoma following surgical resection. (*Courtesy of D.F. Senior.*)

URINARY TRACT INFECTION

Definition/Overview

A urinary tract infection (UTI) is defined as the presence of bacteria in urine in a patient with related clinical signs. Such signs can include urgency, inappropriate urination, dysuria, pollakiuria, stranguria, and urinary incontinence. At one time, the simple presence of bacteria in the urine (subclinical bacteriuria) justified the use of antibiotics. In both people and animals, subclinical bacteriuria is no longer considered a pathologic state that requires treatment; therefore, proper antimicrobial stewardship dictates that we not treat these cases.

Etiology

UTIs develop when bacterial number and virulence are sufficient to overcome host defenses, or a disease state alters the host defense mechanisms.

Pathophysiology

The urinary tract and urine have a number of defense mechanisms, which prevent bacterial colonization. Urinary tract defenses include a tight sphincter, frequent forceful voiding, a long urethra, a glycosaminoglycan coating, regular shedding of epithelial cells, and urinary secretion of immunoglobulin and cytokines. Characteristics of urine that prevent bacterial colonization include an inhospitable pH, high urine osmolality (especially cats), and urinary inhibitors of bacterial adherence. When there is loss of normal defense mechanisms or an overwhelming inoculation of pathogenic bacteria, the urinary tract can become infected. If there is an inflammatory response to the bacteria, we can see clinical signs associated with a UTI. Rectal and genital bacteria are thought to serve as a reservoir for infection. Although more than 20 different species bacteria can be found colonizing this area, only seven account for the vast majority of UTIs (Table 13.20).

TABLE 13.20 Frequency of bacterial isolates from urinary tract infection in dogs (%)

Microorganism	%
Escherichia coli	26–67
Staphylococcus spp.	11–19
Proteus mirabilis	3–32
Enterococcus/Streptococcus spp.	3–22
Klebsiella pneumoniae	2–8
Pseudomonas aeruginosa	2–4
Enterobacter cloacae	2–6

Clinical Presentation

Clinical signs are dependent on whether the upper urinary tract, the lower urinary tract, or both are affected. Lower urinary tract infections can have any combination of urgency, hematuria, inappropriate urination, dysuria, pollakiuria, stranguria, and urinary incontinence. Most of these signs are due to inflammation of the bladder and/or urethra. It is important to note while infections involving the lower urinary tract can cause pollakiuria, they cannot cause polyuria. When the upper urinary tract is involved, signs consistent with acute kidney injury and septicemia may predominate.

Although a mucopurulent or bloody discharge is sometimes seen at the distal end of the penis or vulva, physical exam findings in patients with UTIs are usually unremarkable. Intact male dogs may exhibit pain on rectal palpation suggesting prostatic involvement. Patients with pyelonephritis may exhibit signs of back pain.

Differential Diagnosis

Lower urinary tract inflammation: Trauma, neoplasia, urolithiasis, idiopathic detrusor instability.

Diagnosis

Urinary tract infections can be divided into two general categories: (1) Uncomplicated, also called sporadic bacterial cystitis, and (2) complicated or recurrent bacterial cystitis. Uncomplicated cases are those first time UTIs in which no underlying predisposing condition can be identified. Complicated cases include those with a predisposing condition, a history of recurrent history of UTIs, and intact male dogs. Predisposing conditions include systemic diseases (e.g., renal disease, hyperadrenocorticism, diabetes mellitus, hyperthyroidism), structural abnormalities (e.g., vulvar malformations, uroliths, tumors, PKD, etc.), and immunosuppressive medications.

The incidental finding of bacteriuria in an asymptomatic patient should not trigger a diagnostic workup or treatment. Subclinical bacteriuria is not a pathologic condition requiring antimicrobials. Diagnostic workup for an uncomplicated UTI should include a thorough physical examination, urinalysis, and culture.

Diagnostics for complicated cases should focus on possible underlying conditions and include a thorough physical examination, diagnostic imaging, CBC, serum chemistry, urinalysis, and culture. While abdominal radiographs are commonly performed, ultrasound may have more diagnostic value as it is more sensitive and specific for finding uroliths, discovering structural abnormalities, and detecting pyelectasia.

The cornerstone of diagnosing and treating urinary tract infections is a urine culture. In addition, widespread antibiotic resistance makes antimicrobial susceptibility testing essential. Interestingly, as more than 50% of all urine samples submitted for culture fail to grow bacteria, clinical signs commonly associated with UTIs are not specific.

Urine should be collected aseptically by cystocentesis. Often, patients with UTIs will experience pollakiuria resulting in a small urinary bladder, making cystocentesis difficult. In these cases, ultrasound can be helpful in sample collection. When cystocentesis is not possible, urine may be collected by catheterization, although in female dogs and all cats, sedation would be required. Midstream urine collection as is performed in people is generally not acceptable because of the likelihood of sample contamination.

In most cases, urine collected for culture will need to be sent to a diagnostic laboratory. Although in-hospital culture kits exist, none provide reliable information on antimicrobial sensitivity, severely limiting their utility. Urine should be refrigerated immediately after collection, as samples left at room temperature can experience an exponential increase in bacterial growth, potentially amplifying contaminates and leading to death of pathogenic bacterial. Results from samples refrigerated more than 24 hours should be treated with skepticism as both false positive and false negative results are possible.

Antimicrobial susceptibility based on the minimum inhibitory concentration (MIC) provides essential information for selecting an appropriate antibiotic therapy. Results are often reported as (S)ensitive, (I)ntermediate, and (R)esistant. In the MIC test, isolates of the patient's uropathogen are incubated with different dilutions of an antibiotic. The minimum concentration of the antibiotic that will inhibit the growth of the bacteria represents the bacteriostatic dose. If the achievable urine concentration of the antibiotic can be expected to be four or more times the MIC, then this drug would be an acceptable choice.

Management

In uncomplicated cases, treatment with amoxicillin, or trimethoprim-sulfamethoxazole can be initiated while waiting for the results of susceptibility testing. Antibiotic therapy should be reevaluated once susceptibility results become available. While earlier recommendations called for administration of antimicrobials for 10–14 days, it is now generally recognized that shorter courses, such as 5 days, are just as efficacious. The use of NSAIDs to decrease lower urinary tract inflammation should be considered. In cases where a urine culture is unavailable or declined by owners, empirical treatment can be attempted with these same antibiotics. Other classes of antimicrobials such as fluoroquinolones should never be empirically used.

In complicated cases, it is important to address underlying conditions. Endocrine disorders such as hyperadrenocorticism, diabetes mellitus, and hyperthyroidism must be regulated in order for UTIs to be adequately controlled. A recessed vulva (see **Figure 13.63**) is a common malformation that contributes to many UTIs in female dogs. This can be surgically corrected. Immunosuppressive medications should be reduced to the lowest effect dose. Repeated courses of antibiotics without correcting the underlying problem are likely to result in multidrug-resistant infections.

In intact male dogs, UTIs can involve the prostate, and only certain antibiotics can penetrate this organ. If appropriate antibiotic therapy is not selected, the urinary tract can be repeatedly re-infected by sequestered bacteria. Antibiotic selection needs to be guided by the results of antimicrobial susceptibility testing as well as by considering which drugs are likely to penetrate the prostate. Macrolides, lincosamides, sulfonamides, chloramphenicol, and fluoroquinolones all seem to be reasonable choices.

Despite appropriate therapy and a failure to diagnosis a predisposing underlying cause, persistent and recurrent UTIs occur. One strategy to prevent reinfection is oral administration of methenamine hippurate (Urex®) (500 mg p.o. q.12 h. dog; 250 mg p.o. q.12 h. cat). In the presence of acidic urine (pH ≤5.5) methenamine is converted to formaldehyde. Ammonium chloride can be used to acidify the urine (65 mg/kg p.o. q.8 h. in dogs; 20 mg/kg p.o. q.12 h. in cats). Although controversial, long-term, low-dose antimicrobial treatment can also be used in the treatment of recurrent UTIs. Patients are given a full course of antimicrobial based on sensitivity test results for 3–4 weeks. Treatment is then continued for at least 6 months by giving 50% of the regular daily dose at night after the patient has voided.

Prognosis

Most UTIs are easily treated, and the prognosis is quite good.

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CHAPTER

14

Disorders of the Nervous System and Muscle

Simon R. Platt

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DISORDERS OF THE BRAIN

Introduction

Diseases of the forebrain (cerebrum and thalamus) are very complex and may affect the whole of the central nervous system (CNS). In veterinary medicine, the clinical symptoms of brain dysfunction can be relatively mild despite being often associated with a severe lesion. Dogs and cats with forebrain dysfunction may exhibit clinical signs that include altered mental status (obtundation more likely than stupor or coma), behavioral changes, circling in a wide arc, head-pressing, visual impairment, focal and/or generalized seizure activity, and hemi-inattention (unilateral hemineglect) syndrome. Conscious proprioceptive deficits with a normal to near-normal gait are characteristic of forebrain dysfunction. Neck pain may be appreciable in some patients with structural brain lesions. Lesions from the midbrain (mesencephalon) through the medulla (myelencephalon) may lead to altered mental status (stupor or coma more likely than with forebrain lesions), proprioceptive and gait abnormalities, deficits in cranial nerves (CNs) III–XII, and central vestibular dysfunction.

Neurodiagnostic Investigation

Depending on the localization of the disease, appropriate diagnostic tests should be performed to rule in or out each disease on the differential diagnosis list. Sometimes the underlying disorder is evident, such as with cranial trauma; however, all too often animals with brain disease can present a diagnostic challenge. If the animal presents in a coma, emergency evaluation of airway patency and vital signs, including cardiac function and respiration, should be undertaken, as for animals with head trauma. The important aspects of the evaluation of animals with brain disease include:

- Response to noxious stimulation
- The presence of voluntary motor movement
- Posture (i.e., decerebrate rigidity)
- Pupillary reactivity to light
- Eye movements (physiologic nystagmus)
- Segmental spinal reflexes

This evaluation is very similar to that of the patient with severe head trauma, and in some respects, the modified Glasgow Coma Scale (GCS) system may be useful, although it has not been universally utilized or validated. Unless the diagnosis is established from the history (e.g., toxin ingestion), further testing is usually necessary:

- Routine laboratory analysis is essential—the minimal acceptable information should include packed cell volume (PCV), total protein concentration, blood urea nitrogen (BUN), electrolytes, and glucose concentrations.
- Urinalysis and urine production rate should be assessed, which may necessitate urethral catheterization.
- Liver function tests.
- Thoracic and abdominal radiographs may be useful to supplement physical examination findings.
- Cerebrospinal fluid (CSF) analysis is indicated primarily to confirm an inflammatory lesion. Although such analysis is rarely specific, when it is assessed in conjunction with the patient's signalment, history, neurologic signs, and the results of other diagnostic tests (such as serologic assays), it can help to better define the underlying etiology. If there is evidence or even a suspicion of increased intracranial pressure (ICP) (anisocoria, lack of pupil

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response to light, reduced or absent physiologic nystagmus, decreased or absent response to noxious stimulation), diagnostic imaging should be performed prior to cisterna magna or lumbar puncture, which risks promoting further herniation. In these cases, reducing the ICP using mannitol (0.5–2.0 g/kg IV) should be considered.

- Advanced imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI) are strongly indicated to assess the integrity of the intracranial structures.
- An electroencephalogram (EEG) records the electrical activity associated with forebrain structures. An EEG is rarely specific, and with certain cerebral conditions, it also lacks sensitivity. Although rarely used as a diagnostic tool, electroencephalography can provide confirmation of brain death (flat or isoelectric EEG). However, other factors, such as patient body temperature, concurrent drug administration, and cardiac function, must be considered before brain death is diagnosed.

VASCULAR DISEASE

Definition/Overview

Cerebrovascular disease refers to any abnormality of the brain caused by a pathologic process compromising blood supply. Pathologic processes that may result in cerebrovascular disease include occlusion of the lumen by a thrombus or embolus, rupture of a blood vessel wall, a lesion or altered permeability of the vessel wall, and increased viscosity or other changes in the quality of the blood. Stroke or cerebrovascular accident (CVA) is the most common clinical presentation of cerebrovascular disease and is defined as a sudden onset of nonprogressive focal brain signs secondary to cerebrovascular disease. Cerebral microbleeds (CMBs) are small, well-defined, rounded, intraparenchymal hemorrhagic lesions with a maximum ≤5 mm diameter and no known history of head trauma.

Etiology

Vascular disturbances of the nervous system can arise due to a loss of adequate blood supply (ischemia/infarct) or hemorrhage into the nervous tissue. The initial process is focal in the majority of cases. However, it is possible with a disturbance in systemic perfusion that there is a multifocal, diffuse hemorrhagic process in the brain with a subsequent multifocal course. Vascular damage to the nervous system can be due to various different causes such as neoplasia, endocrine diseases, CNS infections, atherosclerosis, carcinogenic emboli, vasospasm, hematologic disturbances, vasculitis, hyperviscosity syndrome, hypertension, coagulopathy, disseminated intravascular coagulation, or sepsis. Hypertension, diabetes mellitus, hypothyroidism, and hyperadrenocorticism have been identified as concurrent systemic disorders in dogs with CMB. The majority of CMBs in dogs are found in the cerebral cortex.

Pathophysiology

Ischemia means the reduction of the blood flow to a level that is not compatible with normal function. An infarct is a large and continual reduction in the blood flow resulting in tissue necrosis. Hypoxia/ischemia initially particularly affects the most sensitive elements of the tissue and then subsequently disturbs all the tissue components. The main mechanism of cell damage found in an infarct is a reduced energy metabolism. Dogs with brain infarction are frequently (55%) detected with a comorbidity predisposing to CVA; chronic kidney disease (24%) and hyperadrenocorticism (18%) being most commonly encountered. Cats documented with ischemic brain infarcts have been affected by hypertrophic cardiomyopathy, neoplasia, and hyperthyroidism.

Spontaneous intracranial hemorrhage is caused by a bleed within the brain or in its immediate surroundings without accompanying trauma. A brain hemorrhage can be epidural, subarachnoidal, intraparenchymal, or intraventricular. Epidural or subdural hemorrhages are always associated with cranial trauma. Although not well documented, hypertension appears to play a role in the development of primary intraparenchymal hemorrhage in the dog and cat. Secondary intraparenchymal hemorrhages are associated with reperfusion disturbances after infarcts, congenital arteriovenous malformations, intracranial tumors, and coagulopathies. The damage to the brain is the result of compression or destruction of the surrounding brain tissue. In addition, reduced blood flow to the brain, increased ICP, and obstructive hydrocephalus can be the consequence of an intracranial hemorrhage. In cats with hemorrhagic brain infarcts, significant liver pathology and nephritis have been identified in 100% and 25% of cases, respectively. *Angiostrongylus vasorum* is a lungworm detected in much of Europe and Canada which can cause thrombocytopenia and/or dysfunction of coagulation factors, resembling chronic disseminated intravascular coagulation (DIC).

Clinical Presentation

Cavalier King Charles Spaniels and Greyhounds have been suggested to be breeds predisposed to CVA. Generally, cerebrovascular diseases start suddenly and have a nonprogressive course. The brain dysfunction due to an infarct is usually focal. The neurologic deficits depend on the size of the lesion and are usually asymmetrical. The forebrain symptoms are mainly seizures, possibly in clusters, with contralateral visual and proprioceptive deficits. Behavioral changes are common and involve compulsive pacing, disorientation, and sudden attacks of anxiety or aggression. Ipsilateral circling or head tilt can often be seen.

CMBs occur in up to 10% of dogs undergoing brain MRI, being more common in older (median age 13 years) and smaller (median weight 8.7 kg) dogs. Small (toy and miniature) Poodles and Shih Tzus are most frequently affected with CMBs. Dogs with CMBs appear to present more frequently for vestibular signs and more commonly have proteinuria.

Hypertensive encephalopathy has been reported in dogs and cats. It is associated with either an acute (>30 mmHg from resting level) or a sustained (>180 mmHg) elevation in systolic arterial blood pressure. The clinical signs reflect involvement of the prosencephalon and include seizures, altered mentation, loss of consciousness, and blindness. In addition, signs may also relate to dysfunction of the CNS structures of the caudal fossa and include altered mentation, vestibular or cerebellar ataxia, and abnormal nystagmus. Ocular changes suggestive of hypertension, such as retinal hemorrhage, retinal detachment, and hyphema, may also be observed.

Differential Diagnosis

Head trauma, neoplasia, CNS inflammation.

Diagnosis

Complete blood count (CBC), biochemistry profile, coagulation tests, and urinalysis are helpful in excluding renal disease, sepsis, hyperviscosity syndrome, or coagulopathy. Assessment of systemic blood pressure at several time points is vital. Endocrine evaluations may be necessary if an endocrine association is suspected based on clinical evaluation of the patient. Thoracic and abdominal imaging is important to rule out cavity neoplasia. Electrocardiography and an ultrasonographic investigation of the heart may be necessary to diagnose heart disease, although this is a rare association in veterinary medicine.

The most useful specific diagnostic methods are imaging techniques such as CT or MRI. Abnormal changes in patients with brain infarcts can be visualized with CT within a few hours. These changes depend on the age of the lesion and are normally shown as a slightly hypodense region. An increase in contrast can occur after a few days in the periphery of the lesion and reflects the capillary proliferation. CT is a sensitive method of imaging acute hemorrhages. These appear as hyperdense regions, which become more demarcated over the next 72 hours and attain a constant pattern after roughly 4 weeks.

In MRI, an infarct is hypointense in T1-weighted sequences and hyperintense in T2-weighted sequences (**Figure 14.1a–e**). These changes can already be seen an hour after the start of the infarct, meaning that MRI is more sensitive for the visualization of an infarct than CT. In comparison, the depiction of a hemorrhage with MRI is more complicated and depends on the age of the lesion. As infarct and hemorrhage can occur at the same time, CT is often preferred in the acute stages to differentiate between these two different types of disease.

Management

Treatment of dogs with ischemic events to the brain is largely supportive. The aim of the treatment is to ensure an adequate oxygen supply to the tissue to treat neurological problems and the causative disease.

Oxygen supplementation is often enough in many cases. Hypovolemia should be treated with fluids, although administration of large volumes of crystalloids should be avoided as this causes a worsening of cerebral edema and can increase the ICP. Diazepam (0.5–1.0 mg/kg IV) and barbiturates (phenobarbital 2–5 mg/kg p.o. q.12 h.) can be used to control seizure activity and reduce the brain metabolism.

The prognosis for dogs with focal brain infarcts is variable, but most have a guarded to fair prognosis for recovery of partial or full function. In a single study with a total of 22 dogs with presumed CVAs, 23% died within 30 days; however, those that survived this period had a median survival time of 505 days. The long-term prognosis in cats with CVAs is currently unknown.

ANOMALOUS/DEVELOPMENTAL DISORDERS

CONGENITAL HYDROCEPHALUS

Definition/Overview

Hydrocephalus is the term used to describe a condition of abnormal dilatation of the ventricular system within the brain. It can be further subdivided into obstructive and nonobstructive types. Ventricular dilatation occurs with some frequency in dogs and cats due to a variety of intracranial disease processes. Some breeds are predisposed to congenital hydrocephalus, including Chihuahuas, Pomeranians, Yorkshire Terriers, English Bulldogs, Lhasa Apsos, Toy Poodles, Cairn Terriers, Boston Terriers, Pugs, Pekingese, and Maltese.

Etiology

Hydrocephalus can result from:

- Obstruction (intraventricular or extraventricular) of the ventricular system (e.g., brain tumor)
- Increased size of the ventricles due to loss of brain parenchyma (hydrocephalus *ex vacuo*)
- No obvious cause (congenital)
- The overproduction of CSF associated with a choroid plexus tumor (rare)
- Obstruction of CSF flow in cats as a result of ependymitis and vasculitis associated with CNS infection with feline coronavirus (which causes feline infectious peritonitis [FIP])

Pathophysiology

Diffuse ventricular enlargement suggests congenital ventricular dilatation or obstruction at the level of the lateral apertures or foramen magnum. Focal ventricular enlargement suggests focal obstruction or loss of parenchymal cells. It is not uncommon to have asymmetrical bilateral lateral ventricle enlargement. Animals

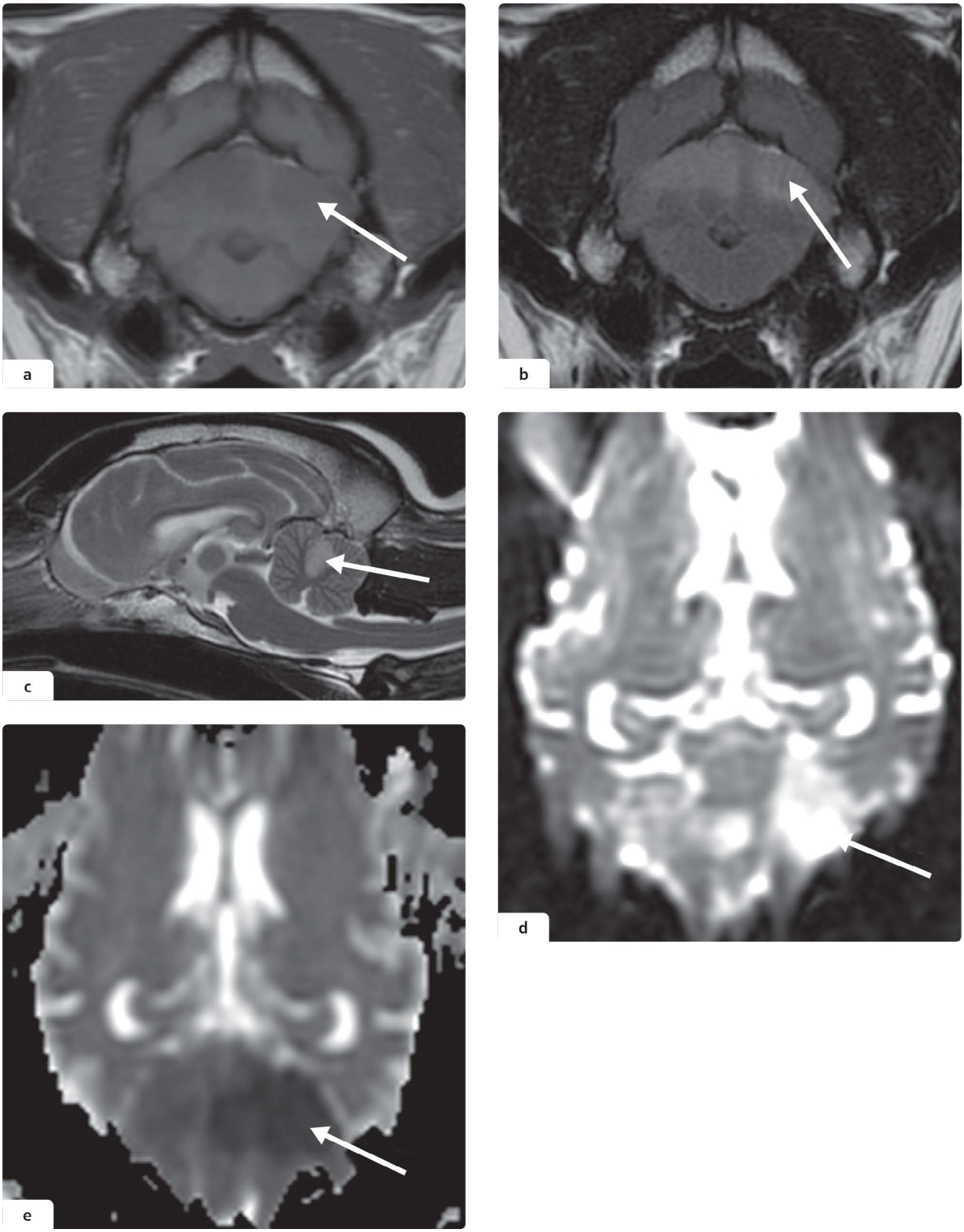


FIGURE 14.1 MR images of a 7-year-old mixed-breed dog with an ischemic stroke (arrows). **(a)** T1-weighted transverse image at the level of the cerebellum demonstrating a large hypointense lesion (arrow). **(b)** T2-weighted transverse image at the same level demonstrating the lesion as hyperintense. **(c)** Midline sagittal T2-weighted image demonstrating the well-demarcated hyperintense lesion within the cerebellum. **(d)** Dorsal plane diffusion-weighted image demonstrating the lesion as hyperintense. **(e)** At the same level, an apparent diffusion coefficient map demonstrates the lesion as a signal void.

with an asymmetrical appearance of the ventricles should be critically evaluated for focal obstruction of, or impingement on, the ventricular system due to mass effect. Elevation of ICP associated with hydrocephalus can occur in cases of acute severe obstruction to CSF flow or chronically enlarged ventricles with little cortical mantle remaining to absorb pressure.

Initial pathologic changes are found in the ependyma at the angles of the lateral ventricles. Loss of integrity of the ependymal surface allows water to leak into the periventricular white matter, causing edema. Further enlargement of the ventricles causes direct damage to the white matter due to compression. Treatment needs to be considered prior to damage affecting the cerebral cortex.

Clinical Presentation

Hydrocephalus can result in clinical signs due to loss of neurons or neuronal function and/or alterations in ICP and all of its consequences. Clinical signs of hydrocephalus can reflect the anatomic level of disease involvement or can represent a diffuse disease process. The severity of the clinical signs is not necessarily dependent on the degree of ventricular dilatation but rather on a host of concurrent abnormalities, including the underlying disease process, associated ICP changes, intraventricular hemorrhage, and the acuity of ventricular obstruction. In animals with severe hydrocephalus, the compressed layer of cortex is prone to tearing either spontaneously or with minor trauma, causing a sudden onset of focal signs of forebrain disease.

In young dogs prior to ossification of the cranial sutures, hydrocephalus may contribute to abnormalities of skull development such as a thinning of the bone structure, a dome-shaped or bossed appearance to the head (Figure 14.2), or a persistent fontanelle.

A ventral and/or lateral strabismus has been noted in humans and animals with hydrocephalus. This is sometimes referred to as the "setting sun sign." Confusion remains as to the underlying reason for this clinical finding. It has been suggested that this appearance is associated with skull deformity and distortion of the orbits. Others suggest that because this abnormality can be improved with shunting of the lateral and third ventricles, the strabismus is associated with pressure on the mesencephalic tegmentum.

As a result of the involvement of the forebrain and brainstem structures in hydrocephalus, alterations in awareness and cognition are common. Many congenitally affected animals may appear less intelligent than normal and be difficult to house train. In addition to alterations in consciousness, aggression, circling, and paresis may also be seen. Central visual dysfunction can occur with compression of the optic radiations and occipital cortex. Seizures have been reported to be a common clinical sign in dogs and cats with internal hydrocephalus due to various causes, affecting between 16% and 33% of cases. However, the prevalence of seizures as a clinical sign in dogs and cats with idiopathic internal hydrocephalus after ruling out additional brain diseases was 1.7% based on a study of 98 dogs and 23 cats.

Occasionally, when hydrocephalus is associated with fourth ventricle enlargement, there may be pronounced vestibular dysfunction.

Differential Diagnosis

Lissencephaly, hepatic (metabolic) encephalopathy.

Diagnosis

The diagnosis of hydrocephalus is aided by information obtained from a variety of imaging and electrophysiologic studies.

Ultrasonography can be used to diagnose hydrocephalus (Figure 14.3). This is most readily accomplished when a fontanelle is present, as it provides an acoustic window (ultrasound waves do not adequately penetrate the skull). In general, correlation between the degree of ventricular enlargement and clinical signs is poor. CT is often useful for defining ventricular size. The ventricular system is usually readily identifiable due to its relatively dark signal in comparison with the parenchyma. CT evaluation also affords the ability to examine the majority of the ventricular system as well as additional intracranial structures. MRI also affords evaluation of the ventricular system (Figure 14.4). It is



FIGURE 14.2 A 2-year-old Cavalier King Charles Spaniel with a domed skull due to its underlying hydrocephalus.



FIGURE 14.3 Ultrasound of the cerebral cavity reveals extensive ventricular volume as a hypoechoic (dark) signal within the more hyperechoic parenchyma.

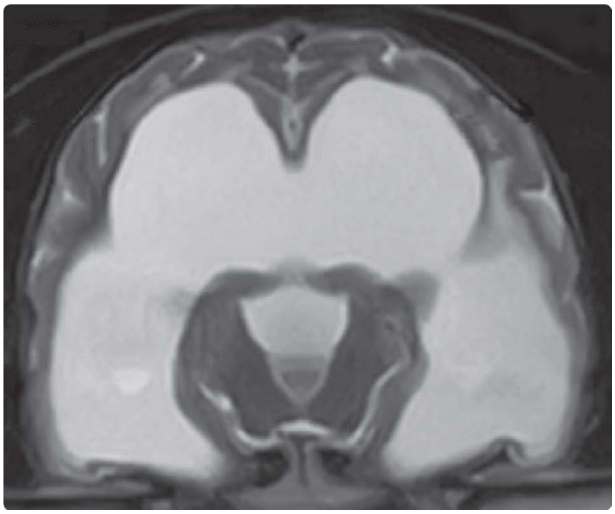


FIGURE 14.4 T2-weighted transverse MR image at the level of the brainstem depicts large lateral ventricles hyperintense to the surrounding parenchyma.

now recognized that many toy breeds that are predisposed to hydrocephalus also have anomalies such as Chiari-like malformations, which can potentially complicate their management and are only detected on MRI. Ventriculomegaly may be misdiagnosed as relevant internal hydrocephalus and interpreted to be the cause of clinical signs in dogs affected by other less conspicuous diseases. A ventricle–brain size ratio of above 0.6 calculated with MRI is used to determine whether there is clinically relevant internal hydrocephalus or asymptomatic ventricular enlargement (ventriculomegaly) in dogs, together with several other structural abnormalities. These other MR imaging findings associated with clinically relevant hydrocephalus include an elevation of the corpus callosum, dorsoventral flattening of the interthalamic adhesion, periventricular edema, dilation of the olfactory recesses, thinning of the cortical sulci and/or the subarachnoid space, and disruption of the internal capsule adjacent to the caudate nucleus.

Management

Although the prognosis for resolution of hydrocephalus is uncertain, there are several medical and surgical options that may be beneficial. The choice of treatment is generally dictated by physical status, age of the animal, and cause of the hydrocephalus. Medical treatment may include general supportive care and drugs to limit CSF production and reduce ICP. Surgical treatment is designed to provide drainage of CSF from the brain to another site for absorption. Glucocorticoids are often used for medical treatment. Prednisone may be given (0.25–0.5 mg/kg p.o. q.12 h., then gradually reduced at weekly intervals to 0.1 mg/kg p.o. q.48 h.). This dose is continued for at least 1 month, after which time it is discontinued, if possible. Some animals can be adequately managed with long-term glucocorticoid administration at low doses. If no clinical benefits are observed within 2 weeks, or if side effects develop, other forms of therapy should be tried. Acetazolamide (a carbonic anhydrase inhibitor) is thought to reduce CSF pressure by decreasing CSF production. Its effectiveness in treating hydrocephalus is inconsistent. Omeprazole has also been administered for the treatment of clinical signs related to hydrocephalus; however, positive outcomes are also inconsistent.

Surgery is generally required for those animals that do not improve within 2 weeks, if deterioration occurs during corticosteroid therapy, or if there is an obstructive cause such as a tumor that cannot be resected. As a successful outcome may be more likely in animals that have minimal clinical signs, surgery may be appropriate in animals with a VB (height of ventricle to height of brain) ratio >60%, although, few owners are willing to undergo the expense and risk of shunt placement if their dog appears healthy. Ventriculoperitoneal shunts are most commonly used in small animals. The shunts have not been proven to be more effective than medical management, but only surgical treatment offers the possibility of long-term control of the clinical signs. Complications of shunt placement occur in approximately 20% of cases and are most likely during the first 6 months after shunt placement.

CHIARI-LIKE MALFORMATION SYNDROME

Definition/Overview

Chiari-like malformation syndrome (CLMS) is the canine analog of Chiari type 1 malformation of people. Although only recently described in dogs, CLMS appears to be a very common neurologic disorder in this species. This disease is almost exclusive to small breed dogs, with the Cavalier King Charles Spaniel (CKCS) being the most overrepresented. Other breeds commonly encountered with CLMS include Brussels Griffon, Miniature/Toy Poodle, Yorkshire Terrier, Maltese, Pug, Pomeranian, and Pekingese. Brachycephalic cats, especially the Persian, can have CLMS.

Etiology

The disorder is a congenital malformation of the suboccipital bone, leading to overcrowding of the caudal fossa and compression of the cervicomedullary junction at the level of the foramen magnum. There is convincing evidence in the CKCS breed that CLMS is a heritable disease, although the exact mode of inheritance has not been determined.

Pathophysiology

Progressive alterations in pressure dynamics between the intracranial and spinal compartments are believed to be responsible for the development of clinical signs of CLMS. Although aberrant pressure dynamics due to obstruction of CSF pathways at the level of the foramen magnum are generally agreed to cause syringomyelia in CLMS, the exact mechanism of this development is

unknown, and there are multiple theories proposed to explain it. Newer theories suggest that the syringomyelia fluid is actually derived from extracellular fluid from the cord itself, either driven into the central canal via a pulse pressure wave from behind the foramen magnum obstruction and/or drawn into the central canal via a centrifugally directed hydrostatic pressure force within the spinal cord. Common to all theories of syrinx development in CLMS is the causative factor of obstruction of normal CSF flow at the foramen magnum. Pain related to CLMS is thought to relate to failure to equilibrate intracranial pressure due to obstruction of CSF pathways. Intracranial pressure is affected by the systolic pulse, venous drainage, the balance between CSF production and absorption, and microgravitational effects; for example, when being lifted rapidly or with head position. Classically in humans, pain in CM is exacerbated by Valsalva, a brief increase in intrathoracic pressure, for example when coughing or with abdominal straining.

The clinical sign of scratching activity is believed to be due to the syrinx interfering with spinothalamic tracts and/or dorsal horn neurons, resulting in abnormal sensations (dysesthesia/paresthesia). Scoliosis (torticollis) is most likely due to asymmetric syrinx damage to sensory proprioceptive neurons innervating cervical musculature. An alternative, less likely, hypothesis is syrinx damage to lower motor neurons (LMNs) innervating cervical musculature.

Clinical Presentation

Most dogs with CLMS are presented for evaluation as young adults between 3 and 6 years of age. However, the age range for this disorder is very broad, ranging from <6 months to more than 12 years of age. Dogs that are presented at <2 years of age often have more severe clinical signs than older dogs. Signs of canine CLMS include vocalization on posture change or on lifting, spinal pain, head and ear rubbing or scratching, aversion to touch, refusal or difficulty jumping or climbing stairs, exercise intolerance/reduced activity, sleep disruption, and behavioral change.

Scratching activity and neck discomfort are due to the presence of an associated syrinx in the cervical spinal cord and often are exacerbated by stress or excitement and physical contact with the neck/shoulder region (e.g., collar).

Diagnosis

Consistent findings on MR imaging indicative of CLMS are attenuation/obliteration of the dorsal subarachnoid space at the cervicomedullary junction and rostral displacement of the caudal cerebellum by the suboccipital bone (Figure 14.5). Other common MRI findings in CLMS include syringomyelia (usually C2 level caudally), herniation of the caudal cerebellum through the foramen magnum, and a "kinked" appearance of the caudal medulla. In the absence of concurrent disease processes, CSF analysis is usually normal; occasionally, a mild mononuclear pleocytosis may be apparent.

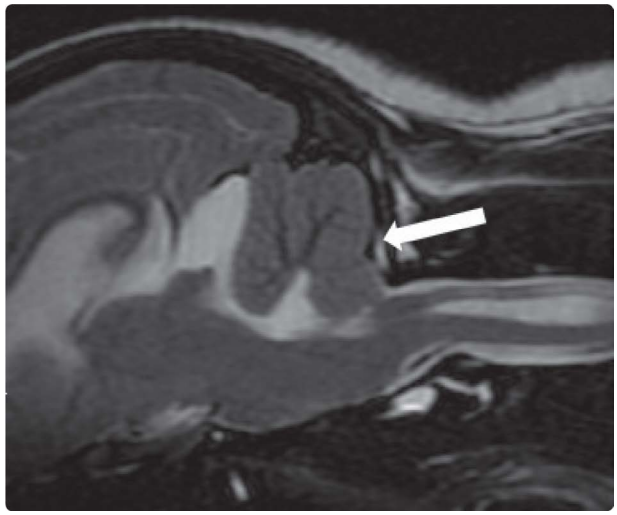


FIGURE 14.5 T2-weighted sagittal MR image of the brain and skull of a Brussels Griffon dog; the arrow points to a hypoplastic occipital bone, which is causing compression and herniation of the cerebellum through the foramen magnum, classic for Chiari-like malformation in dogs.

Management

Treatment of CLMS can be divided into medical and surgical therapy. Medical therapy generally falls into three categories: Analgesic drugs (implies relief of dysesthesia/paresthesia also), drugs that decrease CSF production, and corticosteroid therapy. By far, the most useful drug available for relief of the scratching activity associated with syringomyelia is pregabalin (2–4 mg/kg p.o. q.8–12 h.). There is poor evidence that pain associated with CLMS will improve with prescription of carprofen alone. There is some evidence of improvement with combination of carprofen and gabapentin. Orally administered opioid drugs are sometimes helpful in alleviating neck and head pain in CLMS dogs. A number of drugs aimed at decreasing CSF production have been used in CLMS patients in an effort to diminish the CSF pulse pressure. They include omeprazole (a proton pump inhibitor), acetazolamide (a carbonic anhydrase inhibitor), and furosemide (a loop diuretic). Corticosteroids are often used in medical management of CLMS. An initial anti-inflammatory prednisone dose of 0.5 mg/kg p.o. q.12 h. is often effective in controlling clinical signs. In most cases of CLMS, medical therapy will diminish the severity of clinical signs, but resolution is unlikely. The preferred surgical procedure for treatment of CLMS in dogs is foramen magnum decompression.

Prognosis

Clinical signs will progress in approximately 75% of dogs, and approximately 15% will be euthanized because of CLMS. However, despite progressive signs, many dogs with signs of pain and phantom scratching respond to medical management and are considered by their owners to have an acceptable quality of life.

Although syrinx width increases over time, the rate of increase is not constant. Many syringes appear to rapidly expand within months (or even days) and then can remain remarkably unchanged over years having achieved a hydrodynamic equilibrium.

INTRACRANIAL ARACHNOID CYST (DIVERTICULUM)

Definition and Overview

Intracranial arachnoid cyst (IAC) (also termed intra-arachnoid cyst) is a developmental brain disorder in which CSF is thought to accumulate within a split of the arachnoid membrane. All reported canine cases have been in the caudal fossa. Because IAC is typically associated with the quadrigeminal cistern in dogs, these accumulations of fluid are often called quadrigeminal cysts in this species. The vast majority of reported IAC cases in dogs have been small breeds, with a predominance of brachycephalic dogs.

Etiology

The cause of this developmental anomaly is unknown.

Pathophysiology

It is believed that some aberration of CSF flow from the choroid plexuses during development forces a separation within the forming arachnoid layer, eventually leading to the creation of an IAC. The mechanisms by which an IAC continues to expand with fluid are unknown. Fluid may be secreted by the arachnoid cells lining the cyst cavity.

Clinical Presentation

There is a wide age range at clinical presentation for dogs with IAC (2 months to 10 years), with an approximate average age of 4 years. The most common clinical signs seen with IAC are forebrain (including seizure activity) and/or central vestibular (cerebellovestibular) dysfunction. Dogs may also present with a primary complaint of neck pain. They can be incidental findings.

Differential Diagnosis

Hydrocephalus, congenital portosystemic shunt, hepatic encephalopathy, infectious CNS disease, toxicities.

Diagnosis

Diagnosis is typically made via CT or (preferably) MRI (Figure 14.6). IACs can also be visualized using ultrasound imaging (via foramen magnum, temporal window, and/or persistent bregmatic fontanelle), especially in younger dogs. The characteristic appearance of an IAC is a large, well-demarcated, fluid-filled structure, isointense with the CSF spaces and located between the caudal cerebrum and rostral cerebellum. Because IAC may be an incidental finding, it is important to rule out concurrent inflammatory disease (i.e., by using CSF examination).

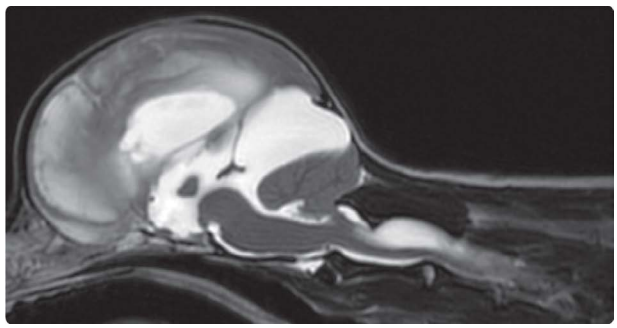


FIGURE 14.6 Sagittal T2-weighted midline brain MR image of a 2-year-old toy breed dog with a large cyst dorsal to and compressing the cerebellum and brainstem.

Management

Medical treatment for IAC is identical to that described for congenital hydrocephalus (see mentioned in the text earlier) (e.g., corticosteroids, diuretics, anticonvulsants if indicated). Dogs with an IAC tend to respond initially to medical therapy, but the response is often temporary. Surgical management of IACs is typically either achieved via cyst fenestration or cystoperitoneal shunt placement.

DEGENERATIVE DISEASES

INHERITED NEURODEGENERATIVE DISEASES

Definition/Overview

Neurodegenerative diseases can affect any part of the nervous system and commonly result in dysfunction of the brain. Examples include multisystem neuronal degeneration of Cocker Spaniels, spongiform degenerations in Labrador Retrievers, Samoyeds, Silky Terriers, Dalmatians (cavitating leukodystrophy), mixed-breed dogs and Egyptian Mau kittens, and multisystemic chromatolytic neuronal degeneration in Cairn Terriers.

Etiology

The likely etiology for many of these diseases is genetic, although it has not been elucidated in most of them.

Pathophysiology

Storage diseases are due to an inborn error of metabolism and the absence of a vital enzyme necessary to break down endogenous body substances. These substances then accumulate within the neuron or other cells associated with the nervous system and eventually cause cellular dysfunction (Figure 14.7). The numerous storage diseases of small animals have been reviewed in detail in other publications.

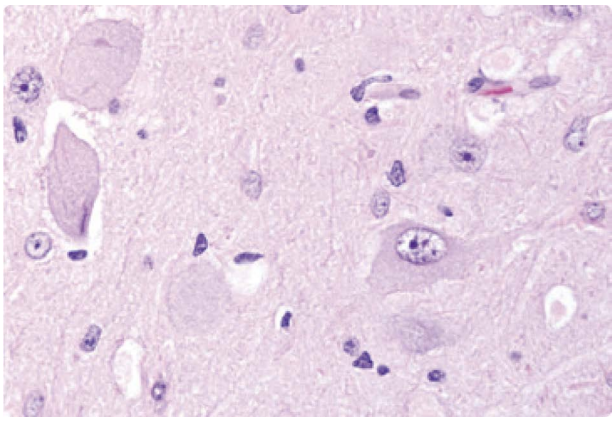


FIGURE 14.7 Intracytoplasmic storage material in the majority of the neurons of the trigeminal ganglion of a dog with GM2 storage disease. The tissue is stained with hematoxylin and eosin.

Clinical Presentation

The majority of degenerative diseases involving the nervous system result in clinical signs early in life, usually with an onset at <1 year of age. Many are breed related and presumed inherited. Clinical signs are slowly progressive with severe alterations in consciousness occurring relatively late in the disease course. Most diseases cause multifocal neurologic signs, and many affect the cerebellum.

Differential Diagnosis

Hydrocephalus, congenital portosystemic shunt, hepatic encephalopathy, infectious CNS disease, toxicities.

Diagnosis

Antemortem diagnosis requires biopsy of the affected tissue. Determination of the lysosomal enzyme activity within the brain and other cells may be helpful but is not universally clinically available.

Screening blood and urine for accumulation products indicative of inborn errors of metabolism may suggest the presence of a lysosomal storage disease and, in some cases, can be diagnostic. Depending on the disease, abnormal accumulations may be evident within cells (particularly macrophages) on buffy coat blood smears and in biopsy samples from the liver, spleen, lymph nodes, bone marrow, or nerves. Screening tests performed on fresh urine samples should include evaluation for the following analytes:

- *Urinary organic acids:* The accumulation of organic acids within the body fluids (particularly urine) is indicative of inborn errors of metabolism such as L-2-hydroxyglutaric aciduria in Staffordshire Bull Terriers.
- *Urinary oligosaccharides:* The accumulation of mannose-containing oligosaccharides in cats is indicative of mannosidosis. The accumulation of high-molecular-weight oligosaccharides in dogs and cats is indicative of GM1 and GM2 gangliosidosis, and of fucosidosis in English Springer Spaniels.
- *Urinary glycosaminoglycans:* The accumulation of dermatan sulfate is indicative of mucopolysaccharidosis (MPS) I, II, VI, and VII. The accumulation of heparin sulfate is indicative of MPS IIIA and IIIB.

Where the signalment and neurologic signs are suggestive of one or more lysosomal storage diseases, and where the underlying enzyme defect is known for those diseases, then an enzyme analysis can be performed against known normal control animals. A reduction in the level of enzyme activity is indicative of that particular lysosomal storage disease. Washed white blood cells or cultured skin fibroblasts are usually the most appropriate cell source and can be assayed either fresh or fresh-frozen.

Characteristic MRI changes may be apparent with some canine and feline genetic diseases, although the changes are rarely specific for a single disease. The lesions usually appear bilaterally symmetrical (e.g., as seen with L-2-hydroxyglutaric aciduria in Staffordshire Bull Terriers) and often result in a decrease in the apparent size of the cerebellum. Fucosidosis in English Springer Spaniels and some of the gangliosidoses can also result in notable MRI abnormalities.

Management

Currently, there is no effective treatment for degenerative diseases of the CNS. Symptomatic therapy, such as anticonvulsants and antianxiety drugs, can help alleviate clinical signs, but these diseases are inevitably progressive. Often, helping the owner decide when to elect euthanasia for a dog affected by a slowly progressive brain disease is the most challenging aspect of these diseases.

COGNITIVE DYSFUNCTION SYNDROME

Definition/Overview

Cognitive dysfunction syndrome (CDS) affects older dogs (>8 years of age) and cats which typically show chronic progressive behavioral abnormalities. The prevalence of CDS in dogs 11–12 years old is estimated to be approximately 28% and is 68% in dogs 15–16 years of age. In addition to advancing age, other reported risk factors for developing CDS include sex (females at highest risk, spayed/neutered at higher risk than intact dogs) and body size (smaller dogs at higher risk than larger dogs); however, some reports have not found associations between sex or body size and the likelihood of developing CDS. Idiopathic epilepsy (IE) has recently emerged as a risk factor for CDS in dogs.

Etiology

There is no specific etiology identified for this condition.

Pathophysiology

The normal aging brain progressively atrophies with increases in oxidative damage, inflammation, glutamate-mediated excitotoxic damage, and other types of neuropathology that ultimately result in neuronal dysfunction and cognitive decline. In dogs, the frontal lobe volume decreases, ventricular size increases, and there is evidence of meningeal calcification, demyelination, increased lipofuscin and apoptotic bodies, neuroaxonal degeneration, and a reduction in the number of neurons. Dogs between 13 and 15 years of age have approximately 30% less neurons in the hilus of the dentate gyrus when compared to 3- to 5-year-old dog, with other studies showing that there is reduced neurogenesis in the mature brain, and noradrenergic neurons in the locus coeruleus of cognitively impaired dogs and cats are significantly reduced.

Similar to the early stages of Alzheimer's disease (AD) in humans, diffuse beta-amyloid (Aβ) plaques may develop in the brain in aging dogs, but canines do not develop full-blown neurofibrillary tangles, which is the second neuropathologic characteristic of AD. Aged dogs do, however, show the accumulation of several phosphorylated tau epitopes that are consistent with AD in humans. Proteomic studies have revealed a significant increase of hyperphosphorylated tau in synaptosomes of CDS dogs compared with non-CDS dogs, suggesting that cognitive decline in dogs maybe related to the tau synaptic impairment and neuroinflammation. Tau phosphorylation is also seen in the aging cat brain and has been more frequently associated with the presence of seizures in this species.

In the dog, Aβ deposition occurs earliest in the prefrontal cortex and later in the temporal cortex, hippocampus, and occipital cortex. Beagles that show learning and memory impairments in a laboratory setting with systematic cognitive tests also show higher levels of Aβ plaques than those old dogs without cognitive impairments. Soluble forms of Aβ called Aβ oligomers have recently been identified in humans with AD and are considered highly toxic, impairing synaptic function, and strongly associated with cognitive dysfunction. Aβ is typically observed in cats older than 10 years, but Aβ deposition seems to be different from that of dogs and humans, as well as being poorly correlated with cognitive decline in this species.

Cerebrovascular amyloid angiopathy (CAA) is the deposition of Aβ in association with the cerebrovasculature. The occipital cortex seems to be particularly vulnerable to CAA in the aged dog brain, which may compromise the blood–brain barrier, disrupt vessel wall viability, and cause microhemorrhages. Aged dogs may also show lacunar infarcts of the caudate nucleus and thalamus, with most dogs showing no causative metabolic, endocrine, or hypertensive disease, and these lesions increase in number with advancing age.

Clinical Presentation

Classic signs of CDS are summarized by the acronym DISHAA, which refers to disorientation; alterations in interactions with owners, other pets, and the environment; sleep–wake cycle disturbances; house soiling; and changes in activity and anxiety levels. Although a decline in activity might be reported, laboratory studies suggest that increased locomotor activity and decreased immobile time are associated with greater cognitive impairment. In addition, signs of fear, phobias, and anxiety, which are commonly reported by owners of senior pets, might also be considered a component of CDS. Finally, memory deficits, which are some of the first recognizable signs of cognitive impairment in humans, have been identified early in the process of brain aging in both dogs and cats. Therefore, learning or memory deficits in aged dogs and cats would also be a sign of CDS.

Differential Diagnosis

Brain tumor, cerebrovascular disease, metabolic encephalopathy, hypertensive encephalopathy.

Diagnosis

Cognitive disorder is diagnosed by excluding other causes of the behavioral abnormalities. However, due to the nonspecific clinical signs associated with this clinical syndrome, it is difficult to make a definitive diagnosis. An extensive evaluation for other causes of intracranial signs in older dogs should be undertaken. Additionally, multitargeted approaches that combine owner-evaluated questionnaires with neuropsychological tests can be most effective in screening cognitively affected dogs from normally aging dogs.

Recent investigations have supported the use of MRI-assessed interthalamic adhesion thickness, interthalamic adhesion thickness/brain height ratio, and interthalamic adhesion thickness/brain height ratio/lateral ventricle to brain height ratio for quantifying brain atrophy in dogs with cognitive dysfunction. However, decreases in interthalamic adhesion size are not specific for cognitive dysfunction and have been reported sporadically in other disorders that can cause brain atrophy.

Leukoaraiosis, bilaterally symmetrical, periventricular T2, and fluid-attenuated inversion recovery (FLAIR) hyperintensities in white matter, has also been identified brains of elderly dogs in conjunction with signs of brain atrophy. The lesions are isointense on pre- and postcontrast T1W imaging and contiguous to the lateral ventricles, with a variable degree of extension into the adjacent subcortical white matter. The lesions are suspected to be caused by Wallerian degeneration, demyelination, and accompanying gliosis but may also represent a local degeneration of the regional blood–brain barrier (BBB).

Management

Recent work suggests that simple preventive measures against CDS may be generally advisable in pet dogs and cats as they near middle age rather than waiting until obvious clinical signs are present. Environmental enrichment can have positive effects on behavioral health and

quality of life in pets and is likely to improve cognitive function. Inconsistency in the management of the senior pet's environment (especially for cats) can cause stress and negatively impact health and behavioral well-being. As sensory, motor, and cognitive function decline, new odor, tactile, and/or sound cues may help the pet better cope with its environment. Canine studies have shown that mental stimulation is an essential component in maintaining quality of life and that continued enrichment in the form of training, play, exercise, and novel toys can help to maintain cognitive function.

Diets rich in antioxidants have been useful in slowing age-related behavioral changes. A nutrient blend consisting of antioxidants, B vitamins, fish oil and l-arginine has been shown to have cognition improving effects in dogs and retard aging-induced decline in learning, memory, and executive function. Similar positive results have also been seen in cats using this nutrient supplementation. Another strategy is a diet containing medium-chain triglycerides (MCTs), which are converted to ketone bodies by the liver. Since a decline in cerebral glucose metabolism and reduced energy metabolism are associated with cognitive decline, MCT-induced ketone bodies provide an alternate energy source that can be used by the brain.

Selegiline, also known as L-deprenyl, is a selective and irreversible inhibitor of monoamine oxidase B. It may enhance dopamine and other catecholamines in the cortex and hippocampus and has been shown to improve signs consistent with CDS in dogs. This drug also may be neuroprotective possibly by reducing free radical production and/or increasing enzymes that scavenge free radicals such as superoxide dismutase and catalase.

Antidepressant and antianxiety medications may be beneficial in the symptomatic management of some animals. Melatonin is best given to dogs 30 minutes before bedtime. Diphenhydramine, phenobarbital, or trazodone can also promote sedation. For the dog or cat that has difficulty settling at night but then sleeps well, situational use of anxiolytics can be helpful. Benzodiazepines have rapid onset, are generally short acting, and have sedative effects at the higher end of the recommended dosage range. Since pain may contribute to unsettled sleep or night waking, gabapentin or pregabalin can be added both as an adjunctive therapy for pain management and for its behavioral calming effects. For senior pets with generalized anxiety, noise phobias, or separation anxiety, buspirone or selective serotonin reuptake inhibitors like fluoxetine and sertraline may be considered because of their low risk of side effects. Recent evidence suggests that the anticonvulsant drug levetiracetam is effective in improving cognitive function and decreasing hyperexcitability.

METABOLIC DISEASES

Numerous metabolic abnormalities may alter cerebrocortical and brainstem function. Liver disease (hepatic encephalopathy), renal disease (renal encephalopathy), pancreatic disease (pancreatic encephalopathy), glucose abnormalities (hyperglycemia or hypoglycemia), electrolyte abnormalities (sodium, potassium, chloride, calcium, magnesium), cardiovascular diseases (resulting in ischemia and hypoxia), and acid–base abnormalities are examples of metabolic diseases. Endocrine abnormalities (thyroid hormones and cortisol) may also affect consciousness.

HEPATIC ENCEPHALOPATHY

Definition/Overview

When liver function is compromised due to organ failure, hepatic microvascular dysplasia, or portosystemic shunting, CNS signs quickly ensue.

Pathophysiology

Hepatic encephalopathy occurs when numerous putative neurotoxins reach the brain without being metabolized as a result of passing through an abnormally functioning liver. Suspected toxins include neurotransmitters (e.g., gamma-aminobutyric acid [GABA] and glutamate), aromatic amino acids, and ammonia.

Clinical Presentation

Animals with hepatic encephalopathy are most often admitted for seizures, ptyalism (especially in cats), and mentation changes, which range from behavioral abnormalities to coma. Signs of hepatic dysfunction, such as weight loss, polydipsia, anorexia, and vomiting, may be present. These animals are often sensitive to the administration of benzodiazepines and barbiturates, as both these types of drugs are metabolized by the liver. Overzealous administration of these drugs may result in stupor and coma due to CNS depression.

Differential Diagnosis

Hydrocephalus, inflammatory CNS diseases, toxicity, other metabolic encephalopathies.

Diagnosis

The diagnosis of hepatic encephalopathy (HE) is supported by abnormal liver function studies such as bile acid testing and resting ammonia levels. Other associated abnormalities may include microcytic red blood cells; low albumin, cholesterol, glucose, and urea concentrations; and elevated liver enzymes if there is parenchymal damage. The preferred imaging studies to confirm a diagnosis of portosystemic shunt include mesenteric portography, abdominal ultrasonography, and per rectal scintigraphy. Transcranial color-coded duplex ultrasonography and MRI have also been used to characterize the brain tissue of animals with hepatic encephalopathy. MRI examinations performed in animals with HE have revealed changes such as cortical atrophy and bilaterally symmetric T1-hyperintensities

within the lentiform nuclei, presumably due to manganese accumulation

Management

Treatment of hepatic encephalopathy aims to:

- Treat the underlying liver disease
- Treat any associated seizures
- Reduce the level of hematogenous neurotoxins (e.g., ammonia) or factors that can increase ammonia production (e.g., metabolic alkalosis, hypokalemia, gastrointestinal [GI] bleeding)

A diet of high-quality, low-quantity protein can help to minimize ammonia production in the gut. Lactulose (0.5–1.0 mL/kg p.o. q.8 h.) is frequently used to assist with this aim, as it reduces the amount of colonic ammonia produced and "traps" ammonia by creating an acidic environment within the gut. Lactulose can also be administered as an enema to comatose patients (1–2 mL/kg q.4–6 h. until loose stool is seen). In addition, neomycin (20 mg/kg p.o. q.8 h.), ampicillin (22 mg/kg p.o. q.8 h.), or metronidazole (7.5 mg/kg p.o. q.8 h.) can be given to reduce the number of urea-splitting bacteria in the colon. Potassium bromide can be used in these cases but requires load-dosing to rapidly attain steady-state levels. The ideal anticonvulsant to use is levetiracetam (p.o., IM, or IV). Seizures following surgical ligation of portosystemic shunts can be especially severe and difficult to effectively treat. Cautious use of a constant rate infusion of diazepam or midazolam may be used for status epilepticus in this situation; however, it can be difficult to dose due to the underlying alterations in liver function. Reduced dosages titrated to effect can be helpful but require vigilant patient monitoring and assessment.

HYPOGLYCEMIA

Definition/Overview

The neurons in the brain require glucose for energy metabolism. A decrease in the availability of glucose to the brain neurons can cause a constellation of clinical abnormalities.

Etiology

Decreases in the blood glucose level alter intracranial neuronal function.

Pathophysiology

Hypoglycemia can occur secondary to insulinoma, liver disease, hypoadrenocorticism, glycogen storage diseases, insulin overdose in diabetic animals, toxicity (e.g., xylitol), infectious diseases, and extrapancreatic neoplasia. Toy breeds and neonates may become hypoglycemic during times of stress. Some dogs that undertake significant exercise (e.g., hunting dogs) and young animals with metabolic stresses (such as caused by a parasitic infestation) are also at risk of developing hypoglycemia.

Clinical Presentation

Hypoglycemia can cause a variety of neurologic signs, including anxiety, a ravenous appetite, lethargy or depression, tremors, seizures, and coma. Exercise or fasting may precipitate signs. The speed with which the glucose concentration changes influences signs to a certain extent. A sudden drop in the blood glucose level causes a sympathetic discharge, hence anxiety and hunger, whereas a chronically low glucose concentration causes lethargy. Central blindness is a frequent finding in animals that present with hypoglycemic seizures. This can be a permanent residual deficit if severe damage has occurred.

Differential Diagnosis

Hydrocephalus, inflammatory CNS diseases, toxicity, other metabolic encephalopathies.

Diagnosis

Serum glucose concentrations <3.3 mmol/L (<60 mg/dL) accompanied by consistent neurologic signs are suggestive of significant hypoglycemia. If the glucose level decreases slowly, some animals can tolerate a lower concentration (<2 mmol/L; <35 mg/dL) without serious clinical problems. Imaging can be used to demonstrate the presence of a pancreatic mass, which may be one of several types of pathology, including insulinoma (beta cell carcinoma).

Management

Treatment depends on the underlying cause. Feeding multiple small meals can help dogs with insulinomas. Direct correction of hypoglycemia is indicated in emergency situations. Syrup can be applied to the gums when IV access is not available (e.g., by owners). It should be noted that if the suspected diagnosis is insulinoma, giving large amounts of glucose, either in the form of a large meal or IV, can sometimes cause a further increase in insulin release into the circulation and exacerbate the problem.

ELECTROLYTE DISTURBANCES

SODIUM ABNORMALITIES

Definition/Overview

Both hypernatremia and hyponatremia may affect the CNS and result in abnormalities of mentation.

Etiology

Any cause of an abnormal sodium concentration will result in neurologic dysfunction. Hypernatremia is most extreme in animals with abnormalities of thirst and drinking, which may also be associated with hypothalamic disease.

HYPERNATREMIA

Pathophysiology

Hypernatremia is synonymous with hyperosmolality and can lead to shrinkage of the brain parenchymal cells, which in turn can cause stretching of the small intracranial blood vessels and hemorrhage. After 2–3 days, the brain attempts to compensate for the altered extracellular sodium level by producing osmotically active intracellular substances (idiogenic osmoles). Thus, overly rapid correction of chronic hypernatremia can cause sudden swelling of the brain parenchyma and ultimately be fatal.

Clinical Presentation

The clinical signs of hypernatremia include lethargy and irritability progressing to ataxia, tremors, myoclonus, seizures, blindness, coma, and death.

Differential Diagnosis

Hydrocephalus, inflammatory CNS diseases, toxicity, other metabolic encephalopathies.

Diagnosis

Demonstration of an abnormal electrolyte level in the presence of an encephalopathy, which improves with appropriate correction, confirms the diagnosis.

Management

Guidelines for the treatment of sodium abnormalities have been suggested but are crude. Appropriate therapy is based on replacement of the water deficit (calculated using the following equation) in conjunction with addressing the underlying cause:

$$\text{Water deficit (l)} = 0.6 \times \text{bodyweight(kg)} \times (\text{patient's sodium concentration/normal sodium concentration} - 1)$$

However, calculations such as this are only used as a guide to begin therapy. With chronic serum sodium abnormalities, cautious fluid therapy with frequent monitoring for neurologic deterioration is imperative. In an animal with established hypernatremia, the water deficit should be corrected either orally or by fluid therapy administered conservatively over 2–3 days. An isotonic maintenance fluid (such as lactated Ringer's solution) should be used, initially at 1.5 times the normal maintenance rate. Serum sodium concentrations should be monitored every 4–6 hours and the rate of fluid therapy administration adjusted up or down accordingly. If the serum sodium concentration is lowered too rapidly, cerebral edema may result, with a clinical deterioration in consciousness. With slow-onset hypernatremia (occurs over 48 hours or more), the maximal daily decrease with treatment should not exceed 0.5 mEq/h or 8–12 mEq/L per 24 hours.

HYPONATREMIA

Pathophysiology

Hyponatremia is synonymous with hypo-osmolality and can result in swelling of the brain parenchymal cells with subsequent edema. After 2–3 days, the brain tries to compensate for this by actively extruding osmotically active intracellular components. As with hypernatremia, rapid correction of hyponatremia can be fatal.

Clinical Presentation

The clinical signs of hyponatremia include lethargy, nausea, and vomiting progressing to seizures, coma, and death.

Differential Diagnosis

Hydrocephalus, inflammatory CNS diseases, toxicity, other metabolic encephalopathies.

Diagnosis

Demonstration of an abnormal electrolyte level in the presence of an encephalopathy, which improves with appropriate correction, confirms the diagnosis. T2-weighted and FLAIR MR images of the thalamic area of the brain reveal characteristic bilateral hyperintense abnormalities. These abnormalities are often focal and oval.

Management

Appropriate therapy is based on correction of the sodium deficit (calculated using the following equation) in conjunction with addressing the underlying cause:

$$\text{Sodium deficit (mEq/l)} = 0.6 \times \text{bodyweight(kg)} \times (\text{normal sodium concentration} - \text{patient's sodium concentration})$$

As for hypernatremia, cautious fluid therapy and frequent monitoring are paramount. Too rapid correction of established hyponatremia can result in thalamic lesions. When hyponatremia has occurred over a period of >24 hours, treatment is adjusted so that the maximal increase does not exceed 0.5 mEq/L/h or 8–12 mEq/L per 24 hours.

NEOPLASTIC DISEASES

Definition/Overview

Brain tumors most commonly affect older dogs and cats. Brain tumors may arise primarily from the brain or surrounding tissues, extend into the brain from adjacent structures, or metastasize to the brain from another location in the body. Tumors result in clinical signs either through primary mechanical damage or as a

consequence of secondary pathophysiologic events such as edema and hemorrhage.

The median age of dogs diagnosed with a brain tumor is reported to be 9 years (range: 4–13 years). The most commonly affected breeds include Golden Retrievers, Labrador Retrievers, Boxers, Collies, Bulldogs, and Boston Terriers. The median age at the time of diagnosis of brain tumors in cats is reported to be 11.3 years (± 3.8 years).

Pathophysiology

Tumors of the intracranial space may be primary (arising from tissues in the intracranial space) or secondary (arising from tissues adjacent to the intracranial space or from metastasis). Primary intracranial tumors include:

- *Meningiomas:* The most common brain tumors in dogs and cats. These tumors arise from the arachnoid layer of the meninges, originating at the periphery of the brain parenchyma and expanding inwards.
- *Gliomas:* Arise from the supporting cells of the brain parenchyma. These include astrocytes and oligodendrocytes forming astrocytomas, oligodendrogliomas, and the extremely malignant glioblastoma multiforme. Brachycephalic breeds such as Boxers and Boston Terriers may be more often affected with these tumors.
- *Ependymomas:* Arise from the ependymal lining of the ventricular system.
- *Choroid plexus tumors (CPT):* Arise from areas where the choroid plexus is concentrated (the lateral, third, and fourth ventricles).
- *Pituitary gland tumors:* Macroadenomas may enlarge dorsally from the sella and compress the diencephalon. Neurologic impairment can be surprisingly minimal. The relative size of the tumor cannot be predicted from the endocrine test result.

Secondary intracranial lesions arise as a result of metastasis or direct extension from extraneural sites. Numerous tumors in older animals metastasize to the brain, including hemangiosarcomas, lymphomas, and mammary gland and other carcinomas.

Clinical Presentation

Most canine brain tumors affect the forebrain. The most common presenting complaint in these cases is seizures. Seizures are sometimes the only sign of a structural intracranial abnormality, with the remainder of the neurologic examination findings being normal. This is particularly true with more rostral and olfactory lobe lesions. Otherwise, the clinical signs associated with tumors affecting the brain depend on the location within the brain, brainstem, or cerebellum. Disorientation, circling, ataxia, depression, and CN signs can variably be seen.

Most feline intracranial neoplasia affects the forebrain. The most common neurologic signs include altered consciousness (depression, stupor, or coma), circling, seizures, ataxia, and behavioral changes.

Differential Diagnosis

CNS inflammatory diseases such as granulomatous meningoencephalomyelitis (GME) and those due to infections.

Diagnosis

Advanced imaging modalities, such as CT and MRI, are most commonly used to investigate cases of suspected neoplasia (Figure 14.8a–h).

Accurate presumptive diagnoses of the general tumor type (meningioma, glioma, or CPT) can be made extrapolated from MRI features in 70% of dogs with primary brain tumors.

CT-guided, freehand needle biopsy of brain tumors has been reported in dogs with intracranial lesions to obtain a histologic diagnosis prior to treatment. Although CT-guided, freehand needle biopsy is a relatively safe procedure, the diagnostic yield can be variable.

An MRI-compatible stereotactic brain biopsy system has recently been validated for use in dogs. This modified frameless stereotactic system has been shown to have acceptable precision for obtaining biopsy samples and has been used successfully in a clinical setting.

CSF analysis is often not helpful for the definitive diagnosis of a brain tumor and, in some instances, can even be misleading. Typically, CSF in dogs with a brain tumor contains an increased level of protein without a concurrent pleocytosis (albuminocytologic dissociation). However, in a significant proportion of these cases, cellular changes consistent with inflammation are present and, interpreted alone, may falsely suggest a primary inflammatory disease. Occasionally, CSF in a dog with a brain tumor is normal. The presence of neoplastic cells in the CSF is specific; however, it is a very rare finding.

Management

Treatment for brain tumors in dogs depends on tumor type, location, natural history of the tumor, associated morbidity/mortality with the treatment modality, and cost. While studies of brain tumor treatment in dogs and cats exist in the veterinary literature, many have incomplete diagnoses, nonstandardized treatment protocols, lack of a control population, and different tumor types being grouped together to increase overall case numbers. These problems make it difficult to make definitive statements regarding treatment efficacy.

Glucocorticoid therapy provides minimal supportive care for patients with brain tumors, although its use can often be necessary and helpful. The aims of glucocorticoid treatment are to control the secondary conditions of acquired hydrocephalus and peritumoral edema and to reduce ICP. Clinical signs in many patients improve following the initiation of steroid treatment, which may give some indication of tumor invasion and what could be achieved with surgery.

Surgery is ideal for superficially located, encapsulated, relatively small benign tumors, of which

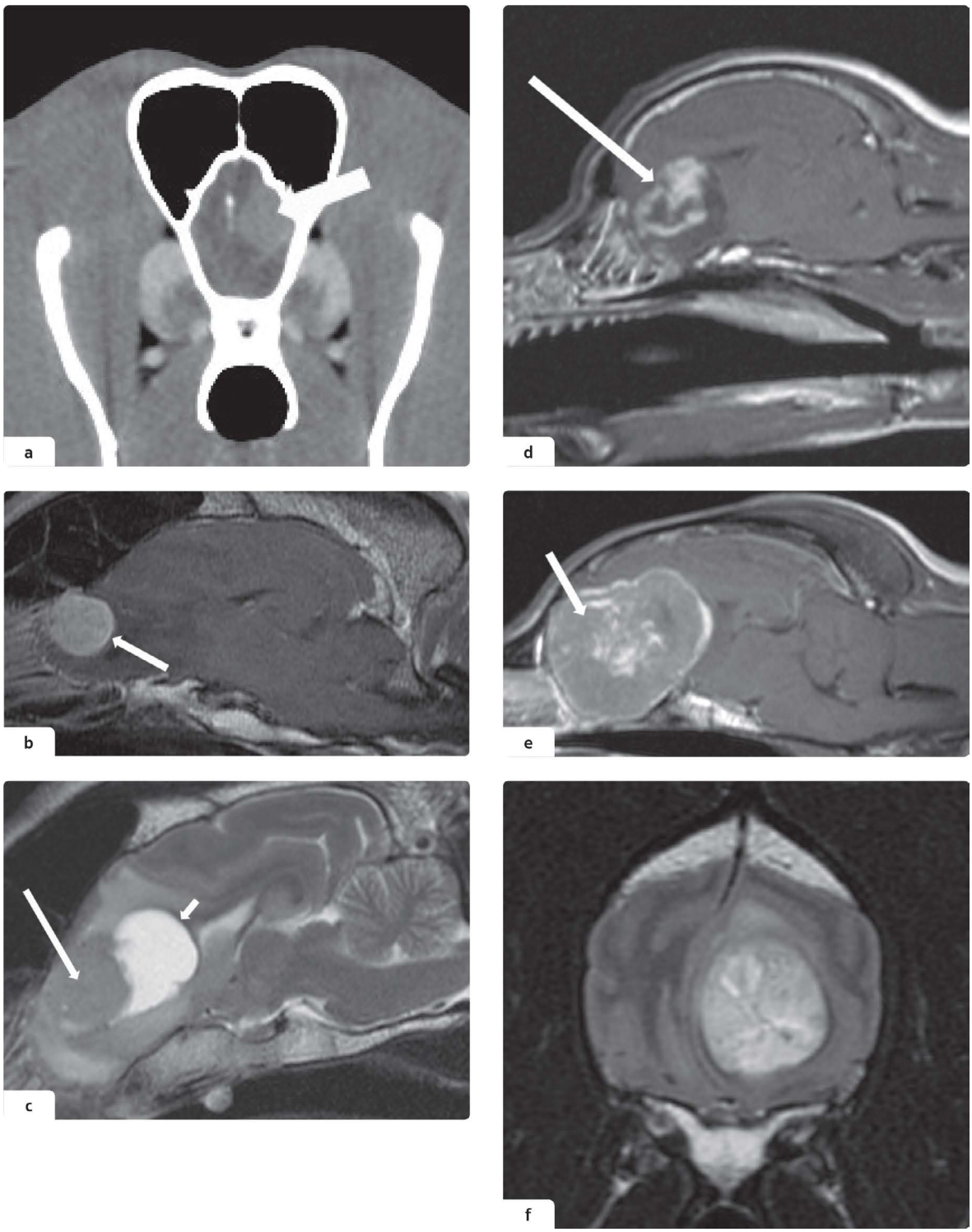


FIGURE 14.8 **(a)** Postcontrast transverse CT brain scan at the level of the olfactory bulbs and frontal sinuses. A well-defined, contrast-enhanced lesion can be identified (arrow), which was confirmed to be meningioma on histopathology following resection. **(b)** T1-weighted postcontrast midline sagittal brain MR image depicting a homogeneously enhancing lesion in the olfactory bulb (arrow), characteristic for a meningioma. **(c)** T2-weighted midline sagittal brain MR image depicting an isointense to hyperintense lesion in the olfactory bulb (long arrow), which is accompanied by a cystic component (short arrow), which is well described for meningiomas. **(d)** T1-weighted postcontrast midline sagittal brain image depicting a heterogeneously enhancing lesion in the frontal lobe characteristic for a glioma, which in this case was an astrocytoma. **(e)** T1-weighted postcontrast midline sagittal brain MR image depicting a heterogeneously enhancing lesion in the olfactory bulb and the frontal lobe. The lesion was a nasal adenocarcinoma extending caudally from the nasal cavity. **(f)** T2-weighted transverse brain MR image clearly showing a large well-demarcated, heterogeneously hyperintense lesion causing mass effect (midline shift of the brain). The lesion was confirmed as an oligodendroglioma. (*Continued*)

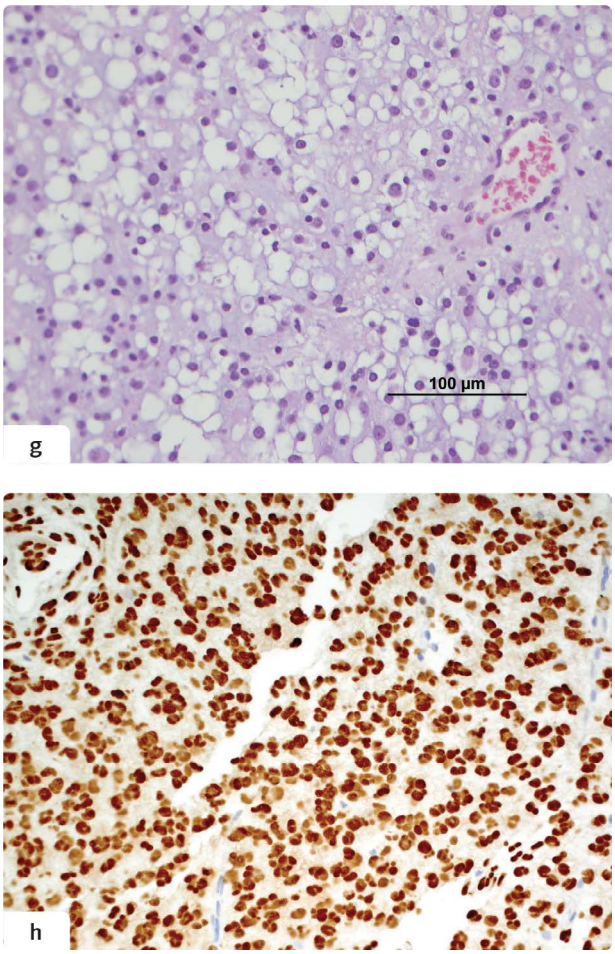


FIGURE 14.8 (*Continued*) (g) The oligodendroglioma shown in (f) is stained with hematoxylin and eosin. **(h)** The oligodendroglioma shown in (f) stains positively immunohistochemically with Olig2.

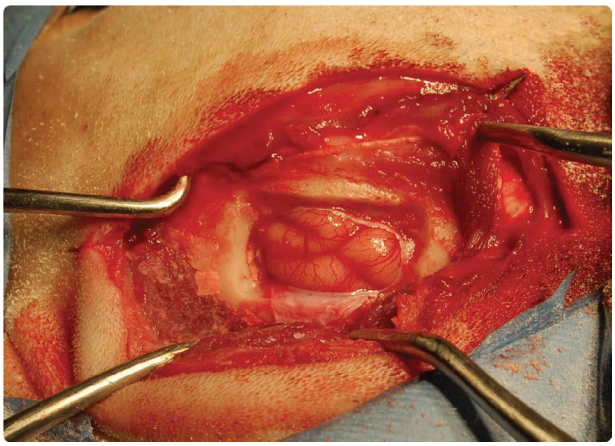


FIGURE 14.9 A lateral rostrotentorial craniectomy is used to approach the parietal lobe of the brain for the purposes of tumor resection.

meningiomas are the most common example (Figure 14.9). Early postoperative neurological deterioration has been reported in up to 45% of dogs, with 11% of dogs experiencing seizures, and non-neurological postoperative complications such as aspiration pneumonia reported in up to 18%. Median survival times reported in dogs following surgery for all types of brain tumor vary but tend to cluster around 140–150 days. For meningiomas, median survival times may be slightly longer (240 days), and there is evidence that improving surgical excision using ultrasonic aspiration or endoscopy does improve survival times. Surgical excision is more readily accomplished in cats, as meningiomas in this species tend to be well encapsulated and easily delineated from normal brain tissue. Studies have determined the median survival time in cats following meningioma resection to be between 22 and 27 months.

Conventional radiation therapy has been shown to be effective for brain tumors in dogs. The main goal of treatment is to administer the highest possible dose to the tumor while minimizing the dose to the surrounding normal tissue. Median survival time in dogs is around 150–350 days. Single fraction stereotactic radiation therapy (SRT) has resulted in a median survival time of over 17 months for dogs with intracranial meningiomas and so should be considered a viable alternative to the fractionated regimens. Stereotactic RT is also effective in prolonging survival in dogs with intracranial gliomas, with similar results to conventional hyperfractionated protocols. Additionally, it appears that patients can be safely treated with multiple rounds of SRT, resulting in improved survival times. Radiation therapy (RT) is effective to reduce pituitary size and the mass effect associated with pituitary tumors but does not appear to affect blood hormone concentrations, necessitating additional medical treatment against hypercortisolism. Radiation generally shrinks the tumor by 25%–50% and may not completely control the neurologic signs associated with a large tumor. Sixty percent of cats with pituitary tumors treated with RT improved, with 50%–60% no longer needing insulin or having improved insulin response and partial or complete remission of neurologic signs. Survival outcomes with stereotactic radiotherapy for dogs with pituitary tumors (MST = 10.3 months) are reportedly shorter than those reported with definitive radiation (MST = 32 months), especially for dogs with hyperadrenocorticism.

Chemotherapy is used as a primary therapy or as an adjunct to surgery in selected instances in animals with brain tumors. Carmustine and lomustine are alkylating agents that have some effectiveness against gliomas. Dogs with intraparenchymal mass lesions (presumptively diagnosed gliomas), dogs treated with lomustine (n = 17, MST 4.5 months) survived significantly longer than dogs receiving palliative care only (n = 23; MST 1 month). Hydroxyurea (30–45 mg/kg p.o. three times a week, with monitoring of the blood cell count for evidence of myelosuppression) is gaining popularity for treatment of meningiomas. There is little to no data available on the effectiveness of chemotherapy for canine or feline brain tumors.

INFLAMMATORY INFECTIOUS CNS DISEASES

Definition/Overview

Encephalitis and infectious diseases often exist concurrently in dogs and cats.

Etiology

Numerous infectious agents have been implicated:

- *Viral:* Distemper, parvovirus, parainfluenza, herpesvirus, feline coronavirus (which causes FIP), West Nile virus, pseudorabies, and rabies
- *Bacterial*
- *Rickettsial:* Rocky Mountain spotted fever and *Ehrlichia*
- *Fungal:* Blastomycosis, histoplasmosis, cryptococcosis, coccidioidomycosis, and aspergillosis
- *Protozoal:* Toxoplasmosis and neosporosis
- *Unclassified organisms:* Protothecosis

Pathophysiology

The specific pathophysiology of the aforementioned infectious diseases in the CNS is discussed in further sections. Inflammation of the structures of the brain (encephalitis) can coexist with inflammation of the meninges (meningitis) and, occasionally, with inflammation of the spinal cord (myelitis).

Clinical Presentation

As a general rule, inflammatory diseases tend to be acute in onset and progressive, with a multifocal or diffuse, often asymmetrical, distribution within the CNS. Neurologic manifestations are quite variable and reflect the location of the inflammatory foci within the nervous system. Central vestibular signs are commonly encountered and can be seen alone or in combination with other neurologic signs. Neck pain can also be present as a manifestation of meningeal inflammation. Animals with CNS infections frequently do not have evidence of systemic involvement. Therefore, the absence of fever, anorexia, and depression and the presence of a normal hemogram cannot be used to exclude the possibility of an infectious etiology in an animal with neurologic signs.

Differential Diagnosis

Sterile causes of CNS inflammatory disease, brain tumor, metabolic and toxic encephalopathies.

Diagnosis

A thorough ophthalmologic examination should be performed in every neurologic case to look for evidence of fundic changes or uveitis compatible with inflammatory disease. Definitive diagnosis of CNS inflammatory disease is typically based on finding an increased total nucleated cell count or an abnormal cell type distribution, with a concomitant increase in protein concentrations, on CSF analysis. In rare instances, normal CSF can be obtained from an animal with confirmed CNS inflammatory disease. This can occur if the inflammation does not involve the meninges or the ependymal lining of the ventricular system, or if the animal has been treated with corticosteroids prior to CSF collection. Elevations in protein concentration can result from breakdown of the blood–brain barrier or intrathecal antibody production. It is likely that both of these mechanisms contribute toward the elevated protein levels recognized with most CNS inflammatory disease. Cytologic evaluation of the fluid provides additional information as to possible causes (Figure 14.10).

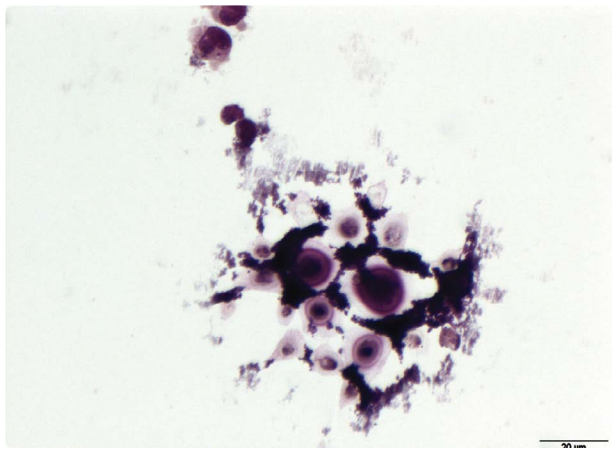


FIGURE 14.10 *Cryptococcus* organisms can be seen in this cytologic analysis from CSF of a dog with seizure episodes. (*Courtesy of R. Di Terlizzi.*)

Additional testing, based on the cytologic evaluation, is performed in an attempt to identify the infectious cause of the inflammation. These tests can include:

- CSF culture for bacterial or fungal organisms
- Serum and CSF antibody or antigen titers
- CSF polymerase chain reaction (PCR) analysis

However, despite extensive testing, an underlying cause for the inflammation is not determined in most cases.

Management

Treatment is aimed at the primary disease process. Treatment with clindamycin (10–15 mg/kg p.o. q.12 h.) and/or trimethoprim/sulfonamide (15 mg/kg p.o. q.12 h.) for potential protozoal infections can be initiated once a diagnosis of encephalomyelitis has been made based on CSF results, while additional test results are pending. If no infectious cause is discovered on additional testing, or the animal does not respond to initial antimicrobial therapy, treatment with corticosteroids should

be initiated. Anti-inflammatory doses are often effective at alleviating the clinical signs, but higher immunosuppressive doses may be required in some instances to appropriately manage the immune-mediated disease. Prognosis is variable and depends on both the cause of the inflammation and the extent and the severity of associated neurologic deficits. Some infections, especially those caused by protozoal and fungal agents, are difficult to eradicate and relapses are common. In addition, residual neurologic deficits can persist despite successful treatment of an infection due to irreversible damage caused by the inciting agent.

RABIES

Definition/Overview

Rabies is caused by an enveloped RNA neurotropic virus of the genus *Lyssavirus* in the family Rhabdoviridae. All warm-blooded animals are vulnerable to infection with rabies, but species susceptibility varies tremendously. Foxes, coyotes, jackals, and wolves are among the most susceptible animals, with skunks, raccoons, bats, and cattle also having a high susceptibility.

Pathophysiology

Infection most often occurs as a result of being bitten by an infected animal with rabies virus in its saliva. The incubation period is influenced by multiple factors, including patient age, bite site, the variant, and the amount of virus inoculated. After IM inoculation, the virus enters the neuromuscular junctions following a variable period (from days to 6 months) of replication in the local tissues. The virus rapidly spreads up the peripheral nerves and then the spinal cord to the forebrain, causing damage to the nervous tissue en route and resulting in progressive nervous system signs.

Clinical Presentation

There are several overlapping phases during the progression of the disease. In dogs, there is usually a prodromal phase (lasts for 2–3 days) during which clinical signs such as apprehension, nervousness, anxiety, and variable fever may be seen. Overall, a significant change in the normal behavior of the animal is noted by the owner. Affected animals can be seen to constantly lick the site of viral inoculation. Cats may also exhibit this prodromal phase, but it more commonly consists of erratic behavior for 1–2 days.

The furious or psychotic form of rabies usually lasts up to a week in dogs and is manifest by cerebral dysfunction with exaggerated responses to sound and touch. Affected animals can bite at imaginary objects or their cage and become extremely irritable. At this stage, they frequently exhibit generalized tonic–clonic seizure activity, during which they can die. Occasionally, dogs can exhibit a predeath paralyzed state. Cats typically develop the furious stage, resulting in unprovoked attacks and appearing "disconnected" from the environment.

The paralytic or dumb form of rabies is often seen within 2–4 days following the onset of clinical signs and is manifest by flaccid paralysis. In both dogs and cats, a bite to the neck or head may more commonly result in CN dysfunction. Dysphonia, dysphagia, excessive salivation, and a dropped jaw may be seen, and these clinical signs are also classed as part of the paralytic form. Coma and death usually follow these signs within 2–4 days.

Differential Diagnosis

Other infectious and sterile causes of CNS inflammatory disease, brain tumor, metabolic and toxic encephalopathies.

Diagnosis

Rabies should always be suspected in any animal presenting with neurologic dysfunction and living in an area known to have a virus reservoir in the local wildlife. Particular concern should be raised for animals that are known to be unvaccinated and that have exhibited clinical signs for <5 days.

There are no antemortem tests sensitive enough to be consistently reliable for confirming a diagnosis of rabies, and there are no hematologic or serum biochemical changes characteristic of the disease. CSF analysis may reveal elevated protein levels and white blood cell count with a lymphocytic predominance. Serologic tests are rarely performed because of the low percentage of animals that have time to develop antibodies. However, a serologic assay can be used to assess vaccine efficacy.

A direct fluorescent antibody assay test of the nervous tissue can be performed on thin touch impression smears and is rapid and sensitive for a definitive diagnosis. The most commonly affected areas on examination are the brainstem, hippocampus, cerebrum, and cerebellum (Figure 14.11). Reverse transcription PCR (RT-PCR) is a relatively new method for rabies diagnosis and is very useful when the sample size is small (e.g., CSF sample).

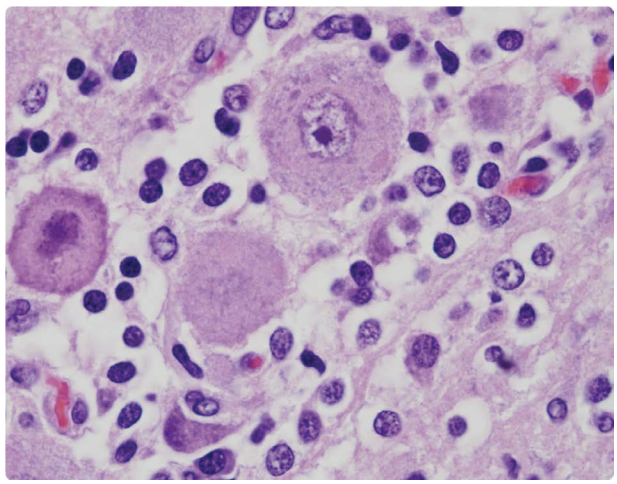


FIGURE 14.11 Intracytoplasmic (pink) inclusion bodies can be seen within the neuronal cells of a dog with rabies virus infection.

Management

There is no specific treatment for this fatal disease. A dog or cat suspected of contracting the disease should be quarantined as recommended by the local health authorities or euthanized and the brain submitted for examination. Exposure of all healthcare providers to the animal and/or its tissues should be restricted.

BACTERIAL MENINGOENCEPHALITIS

Definition/Overview

Bacterial infection is a relatively rare cause of encephalitis in dogs and cats when compared with other species.

Etiology

Bacterial infection of the CNS.

Pathophysiology

Bacterial infection of the brain is usually a consequence of direct extension of infection from the middle ear or sinuses or a penetrating injury to the skull (surgical or traumatic). Hematogenous spread can occur less commonly. Both aerobic and anaerobic infections have been reported. It is possible for the infection to be limited to the extradural or subarachnoid space, especially following bite wounds, in which case the infection can remain localized (intracranial empyema or abscess), and signs might not be so rapidly progressive. Clinical signs are largely the result of the inflammatory reaction that bacteria incite.

Clinical Presentation

Animals can exhibit a variety of signs, including vestibular dysfunction, seizures, cerebellar signs, paresis, cervical hyperesthesia, and coma. Fever is present in approximately 50% of cases at presentation. The signs are usually rapidly progressive and frequently fatal.

Differential Diagnosis

Other infectious and sterile causes of CNS inflammatory disease, brain tumor, metabolic and toxic encephalopathies.

Diagnosis

Routine blood work usually reflects an inflammatory process but can be normal. A urine sample should be cultured if bacterial encephalitis is suspected, and blood cultures are indicated in animals in which there is no obvious source of infection. Imaging of the brain (CT or MRI) is helpful to identify defects in the skull and otitis media/interna (OMI) and can be suggestive of an inflammatory process (Figure 14.12). CSF analysis is the most useful test. Typically, there is a marked elevation in the protein level and total nucleated cell count, and the majority of cells are degenerate neutrophils. Bacteria may be visible in the spinal fluid. However, CSF analysis can be unremarkable or show more nonspecific inflammatory changes. CSF should be cultured if it contains degenerate neutrophils, although it is common for the cultures to be negative.

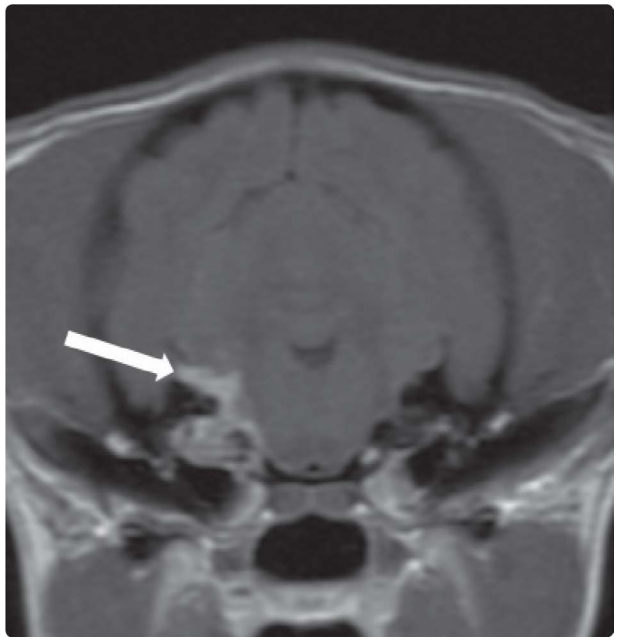


FIGURE 14.12 T1-weighted postcontrast transverse brain MR image at the level of the bullae reveals extension of otitis media/interna into the central nervous system (arrow) in an 8-year-old Yorkshire Terrier.

Management

Treatment with an antibacterial drug that penetrates the CNS should be initiated while waiting for culture results. The most common bacterial isolates are *Escherichia coli*, *Streptococcus*, and *Klebsiella*, but anaerobic infections can also occur. Appropriate drugs include fluoroquinolones and third-generation cephalosporins. Many patients are in a critical condition and need IV fluids and anti-inflammatory drugs. Mechanical ventilation might be necessary in comatose patients. Prognosis is poor in animals with rapidly progressing severe signs. Early appropriate treatment is vital to obtain a good outcome.

CANINE DISTEMPER VIRUS INFECTION

Definition/Overview

Canine distemper is a multisystemic viral disease that causes multifocal CNS dysfunction. It most commonly affects unvaccinated dogs.

Etiology

Canine distemper virus (CDV) is a paramyxovirus that commonly infects the CNS of dogs.

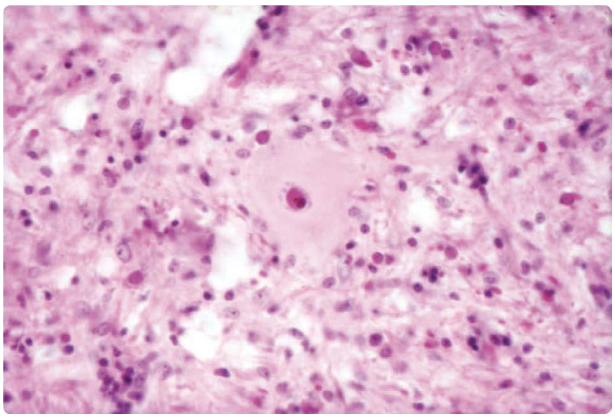


FIGURE 14.13 Intranuclear inclusion material in a neuron of a dog with distemper virus infection. The tissue is stained with hematoxylin and eosin.

Pathophysiology

The presence and severity of the neurologic signs depend on factors such as the age and immunocompetence of the host and the neurovirulence of the virus strain. Many dogs probably develop transient CNS infections without concurrent clinical signs. In the CNS, CDV initially replicates in the neurons and glial cells (Figure 14.13) and can cause both gray and white matter lesions, with one usually predominating. These early degenerative lesions are not characteristically inflammatory. A chronic course of CNS infection results from a late or insufficient immune response to CDV, with characteristic inflammatory demyelinating lesions. Polioencephalomyelopathy has been reported most frequently in immature dogs, while leukoencephalomyelopathy or a combination of both is more common in mature animals.

Clinical Presentation

Presentation can include seizures, visual deficits, vestibular dysfunction, cerebellar signs, paresis, and myoclonus. The presence of myoclonus is most commonly associated with CDV infection but is not pathognomonic, as it has been described with other inflammatory CNS disorders. Neurologic disease associated with CDV infection tends to have a progressive course. Disease can develop in well-vaccinated animals, so previous vaccination history does not exclude the possibility of CDV-associated disease. Systemic signs, such as respiratory and GI involvement, are reported to precede the neurologic signs by 2–3 weeks. However, many dogs have no previous history of disease prior to the onset of neurologic signs. Extraneural signs include conjunctivitis, rhinitis, fever, respiratory signs, GI signs, tonsillitis, cachexia, enamel hypoplasia, and hyperkeratosis of the footpads or nose. These signs are frequently mild. Fundic examination is recommended in all suspected cases, as many dogs have evidence of chorioretinitis.

Differential Diagnosis

Other infectious and sterile causes of CNS inflammatory disease, brain tumor, metabolic and toxic encephalopathies.

Diagnosis

An indirect fluorescent antibody test for viral antigen in conjunctival smears can be positive in many dogs with CNS distemper, regardless of whether the disease is acute or chronic. Viral antigen can also be demonstrated in tracheal washings and urine sediment. Results of CSF analysis are variable. During the acute stage of the disease, an inflammatory response is lacking, and thus, the cell count and protein levels can be normal. In the chronic stage of the disease, lymphocytic pleocytosis is more frequently identified. An elevated CSF titer of antibody against CDV relative to the serum titer is supportive of a diagnosis. Biopsy samples of haired skin from the dorsal neck can be used antemortem for immunohistochemical testing for acute CDV infection. PCR analysis of urine and CSF samples for CDV has proven most useful in the antemortem diagnosis of distemper-associated neurologic disease.

Management

There is no specific treatment for CDV-associated neurologic disease. Overall, the prognosis is poor, especially in cases with rapidly progressive signs. However, some dogs can survive with residual neurologic deficits. Seizures are reported to be an unfavorable prognostic sign as they are often difficult to control with antiepileptic drugs. Consequently, in cases where the neurologic signs are not severe, it is recommended that the animal is provided with supportive care, and the disease progression monitored over 1–2 weeks before considering euthanasia.

FELINE INFECTIOUS PERITONITIS

Definition/Overview

Feline infectious peritonitis (FIP) is a multisystemic viral disease that causes multifocal CNS dysfunction.

Etiology

Feline coronavirus is the causative agent of FIP, which is the most common cause of meningoencephalomyelitis in cats.

Pathophysiology

The disease occurs most commonly in cats <3 years old and from multiple cat households; however, cats as old as 15 years have been diagnosed with the disease. Neurologic involvement is most common with the noneffusive or "dry" form of the disease. Up to one-third of cats with the noneffusive form of the disease have been reported to have either primary neurologic FIP or neurologic signs as part of the overall disease presentation. FIP induces a

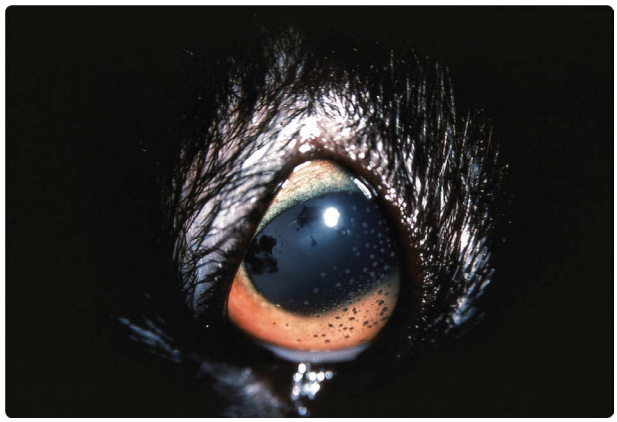


FIGURE 14.14 Ocular feline infectious peritonitis in a cat, showing keratic precipitates. (*Courtesy of Ophthalmology Service, University of Florida.*)

pyogranulomatous and immune complex-mediated vasculitis involving the meninges, ependymal lining, periventricular brain tissue, and choroid plexus of the CNS. Secondary hydrocephalus can be seen due to obstruction of the ventricular system by the inflammation.

Clinical Presentation

Neurologic signs include seizures, cerebellar signs, vestibular dysfunction, and paresis. The disease often has an insidious onset and can lack distinct clinical signs. Affected cats may have concurrent systemic signs, including anorexia and weight loss. Ocular lesions have also been identified, including anterior uveitis, iritis, keratic precipitates (Figure 14.14), retinitis, and anisocoria.

Differential Diagnosis

Other infectious and sterile causes of CNS inflammatory disease, brain tumor, metabolic and toxic encephalopathies.

Diagnosis

Hematological findings can include anemia, leukocytosis, and hyperglobulinemia; however, in some affected cats, no abnormalities are present. Serum tests for anticoronavirus antibodies are often positive, but they have low specificity. In addition, a negative serum titer (i.e., a complete absence of antibody) does not exclude the possibility of FIP-associated neurologic disease because soluble antibodies can form immune complexes and escape detection by standard tests. Advanced imaging of the brain often reveals the presence of ventricular dilatation, and periventricular contrast enhancement can be visible with MRI (Figure 14.15). Results of CSF analysis are variable. The characteristic finding is a marked neutrophilic to pyogranulomatous pleocytosis, with cell counts often in the hundreds, and an associated increase in protein concentration to >200 mg/dL. However, the CSF can be normal, show a mild mononuclear pleocytosis, or have a normal cell count with an elevated protein concentration. Positive CSF titers can be a useful

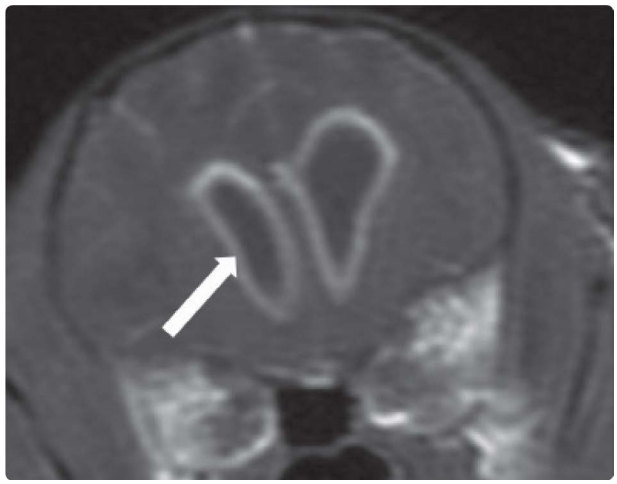


FIGURE 14.15 T1-weighted transverse brain MR image of a 3-year-old Domestic Shorthair cat with feline infectious peritonitis; marked enhancement of the lateral ventricular lining (arrow) is associated with the infection in this cat.

antemortem indicator of neurologic disease. However, positive antibody titers must be interpreted with respect to the integrity of the blood–brain barrier. PCR assays performed on CSF samples have not been shown to be reliable for confirming disease.

Management

Prognosis for cats with CNS FIP is poor. Definitive treatment is not available. The use of immunosuppressive drugs can slow the progression of disease. Recently, treatment with nucleoside analogs have shown clinical efficacy and may result in clearance and long-term resolution of neurological FIP. Treated cats demonstrated resolution of disease defined based on normalization of MRI and CSF findings.

Affected animals should be isolated from other cats to prevent the spread of infection.

TOXOPLASMOSIS AND NEOSPOROSIS

Definition/Overview

Toxoplasmosis and neosporosis are multifocal CNS diseases that are relatively uncommon following systemic infection with *Toxoplasma* or *Neospora*.

Etiology

Toxoplasma gondii is an intracellular protozoan parasite of humans and animals that can cause encephalitis in infected dogs and cats. *Neospora caninum* is a protozoan parasite that is known to cause neurologic disease in dogs but not cats.

Pathophysiology

Ingestion of tissue from infected intermediate hosts is the most common cause of *T. gondii* infection in dogs

and cats. In the case of *N. caninum* infection, dogs are commonly infected in utero, although they can also be infected by ingestion of intermediate host tissue.

Clinical Presentation

Signs of disease are seen most frequently in young or immunocompromised animals and can occur with concurrent CDV infection or FIP. Neurologic signs include seizures, behavioral changes, CN deficits, cerebellar signs, and diffuse neuromuscular disease. A progressive cerebellar ataxia has been described in adult dogs with neosporosis. A characteristic early sign of disease is progressive rigidity of one or more limbs as a result of myositis and neuritis. Concurrent ocular abnormalities can be identified on fundoscopic examination.

Differential Diagnosis

Other infectious and sterile causes of CNS inflammatory disease, brain tumor, metabolic and toxic encephalopathies.

Diagnosis

Imaging can reveal the presence of either solitary or multiple mass lesions in the brain of affected animals. CSF analysis typically demonstrates pleocytosis with a mixed population of neutrophils and the presence of small and large mononuclear cells. Eosinophils can also be seen. With toxoplasmosis, a presumptive diagnosis is based on positive antibody titers in the CSF. However, a positive titer can be seen in animals previously exposed to the organism following nonspecific immune stimulation and, therefore, is not definitive evidence of active disease. Serum and CSF anti-*Neospora* antibody titers are more reliable than serum titers alone. However, for both infections, evidence of a rising titer should be obtained. PCR assays performed on CSF samples can aid in the antemortem diagnosis of these protozoal infections.

Management

Clindamycin and/or trimethoprim/sulfonamide therapy for 3–4 weeks is recommended in animals with CNS protozoal infections. Trimethoprim/sulfonamide can be combined with pyrimethamine (0.5–1.0 mg/kg p.o. q.24 h. for 2 days, then 0.25 mg/kg p.o. q.24 h. for 2 weeks) and a folic acid supplement (5 mg per day p.o.) once the diagnosis has been confirmed. Neurologic signs typically improve with treatment but might not resolve because of permanent damage caused by the organism. In addition, relapses are possible.

CRYPTOCOCCOSIS

Definition/Overview

Cryptococcus neoformans is the most common fungal organism that affects the CNS. It occurs more commonly in cats than in dogs and causes multifocal signs.

Etiology

Cryptococcus is a saprophytic yeast with a worldwide distribution. The organism can be isolated from several sources, although its main reservoir is pigeon droppings.

Clinical Presentation

Nonspecific signs include anorexia, weight loss, lethargy, lymphadenopathy, and pyrexia. Respiratory signs include nasal discharge, sneezing, and coughing. Ocular disease (including anterior uveitis, chorioretinitis, and retinal detachment) can be seen in association with neurologic signs. Neurologic signs often reflect a diffuse or multifocal localization and frequently include altered mentation, CN deficits, and gait abnormalities.

Pathophysiology

Dogs and cats most frequently become infected following inhalation of the organism. Neurologic involvement results from hematogenous spread or local extension of an infection through the cribriform plate.

Differential Diagnosis

Other infectious and sterile causes of CNS inflammatory disease, brain tumor, metabolic and toxic encephalopathies.

Diagnosis

MRI findings are variable and include multifocal or solitary lesions with uniform or peripheral contrast enhancement (**Figure 14.16a, b**). Meningeal enhancement can also be observed. A hemogram can reveal the presence of monocytosis. In animals with extraneural disease, a definitive diagnosis can often be made based on cytology and/or culture of urine, nasal discharge, lymph node aspirates, or cutaneous masses. In addition, these animals often have positive CSF or serum titers for cryptococcal capsular antigen. Diagnosis of CNS cryptococcosis can often be made by cytologic evaluation of the CSF. Neutrophilic, mononuclear, or mixed pleocytosis can be seen, with neutrophilic pleocytosis most common in cats. Eosinophils are frequently present. The encapsulated organism can be seen in cytologic preparations in the majority of cases. The use of India ink, new methylene blue, or Gram stain allows the organisms to be identified more readily (**Figure 14.17**). In cases in which the organism is not observed on cytology, diagnosis can be made either by detecting cryptococcal capsular antigen in the CSF or by culturing CSF samples.

Management

Treatment with amphotericin, fluconazole, or itraconazole is recommended, although overall prognosis

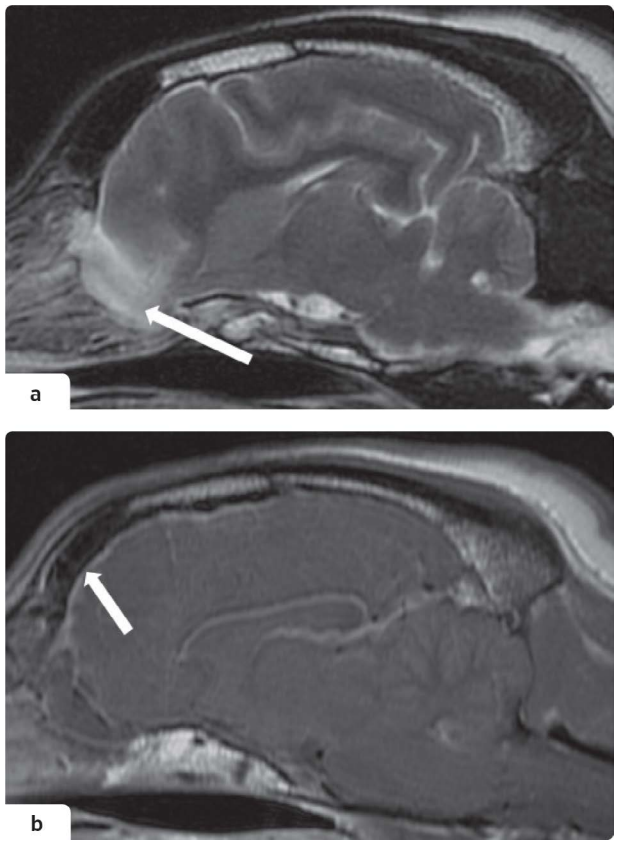


FIGURE 14.16 (a) Midline sagittal T2-weighted MR image of a dog's brain with *Cryptococcus* infection showing a granuloma adjacent to the cribriform plate in the olfactory bulb (arrow). **(b)** Midline sagittal T1-weighted MR image of the same dog reveals marked meningeal contrast enhancement (arrow) compatible with inflammation associated with the fungal infection.

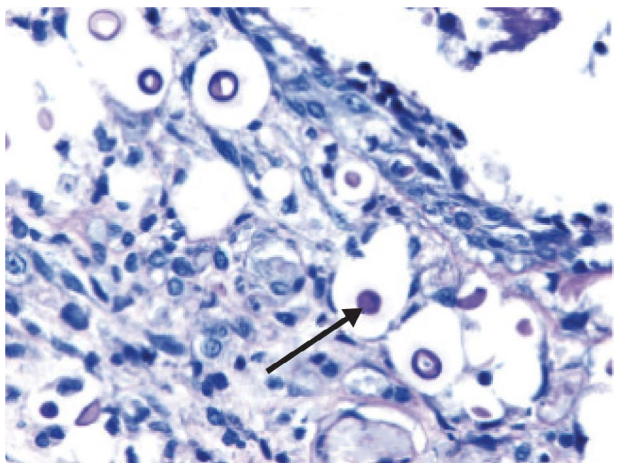


FIGURE 14.17 Brain tissue stained with periodic acid–Schiff to highlight the fungal bodies in purple (arrow), with the capsular area shown in white.

is fair to poor. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be administered when antifungal therapy is initiated to counteract the intense inflammatory reaction that accompanies the killing of *Cryptococcus*. Long-term treatment is required, ranging from several months to years. It is difficult to completely rid the body of the organism, and relapses are common. Treatment should be continued until serum cryptococcal titers are negative or for 2 months beyond the resolution of clinical signs.

INFLAMMATORY NONINFECTIOUS CNS DISEASES

Inflammatory, noninfectious causes of CNS dysfunction in dogs include such diseases as GME and necrotizing encephalitis. These diseases are often grouped together antemortem within the term meningoencephalitis of undetermined origin or MUO.

GRANULOMATOUS MENINGOENCEPHALOMYELITIS

Definition/Overview

GME is an inflammatory disease of unknown etiology that affects the CNS of dogs and, rarely, cats.

Etiology

The etiology is unknown, although infectious, autoimmune, and neoplastic causes have been proposed.

Pathophysiology

Although the cause of GME is unknown, characteristics of the lesion suggest a possible immunologic basis for the disease, and an immune-mediated pathogenesis is suspected.

Clinical Presentation

The disease is most common in middle-aged toy and small breed dogs, with a possible breed predisposition in Poodles and Terriers. Three clinicopathologic forms of the disease are described: (1) An ocular form, which manifests with acute onset of dilated, unresponsive pupils due to optic neuritis; (2) a focal form, which presents with clinical signs suggestive of a single space-occupying mass, with areas of predilection in the pontomedullary region and forebrain; and (3) a diffuse form, which presents with clinical signs suggestive of a multifocal CNS disorder, with the cerebrum, brainstem, cerebellum, and cervical spinal cord most commonly involved. Clinical signs are usually acute in onset and progressive.

Differential Diagnosis

Other infectious and sterile causes of CNS inflammatory disease, brain tumor, metabolic and toxic encephalopathies.

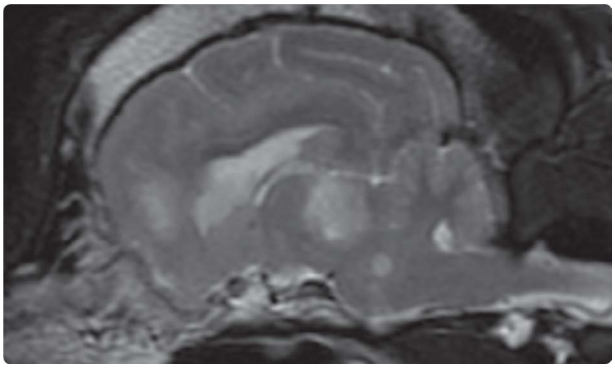


FIGURE 14.18 Sagittal paramedian T2-weighted brain MR image of a 2-year-old French Bulldog demonstrating multifocal hyperintensities confirmed to be GME on histopathology.

Diagnosis

CSF analysis typically reveals a mononuclear pleocytosis with an associated increase in protein concentration. However, both neutrophilic pleocytosis and normal CSF analysis have been reported. A mass lesion may be evident on imaging with the focal form of the disease, while the brain parenchyma can have a patchy, heterogeneous appearance with the diffuse form (Figure 14.18). A definitive diagnosis can only be made histologically on postmortem examination or by biopsy. Antemortem diagnosis is usually presumptive by exclusion of infectious etiologies.

Management

The most commonly prescribed treatment for GME consists of immunosuppressive doses of corticosteroids. Other immunomodulatory drugs are frequently used in combination with corticosteroids and include cytosine arabinoside, cyclosporine, mycophenolate, procarbazine, lomustine, and azathioprine. Radiation therapy has also been recommended as a treatment for dogs with the focal form of the disease. Overall, prognosis is poor, but survival times range from weeks to years. The diffuse form of the disease carries the worst prognosis, with a survival time of weeks to months.

NECROTIZING MENINGO(LEUKO) ENCEPHALITIS

Definition/Overview

Necrotizing meningo(leuko)encephalitis is a chronic progressive neurologic disorder reported in Pugs (Pug encephalitis), Yorkshire Terriers, Chihuahuas, and Maltese. There are also sporadic reports of similar findings in other small-breed dogs, such as the Chihuahua, Pekingese, and Shih Tzu.

Etiology

The etiology of the disease is unknown.

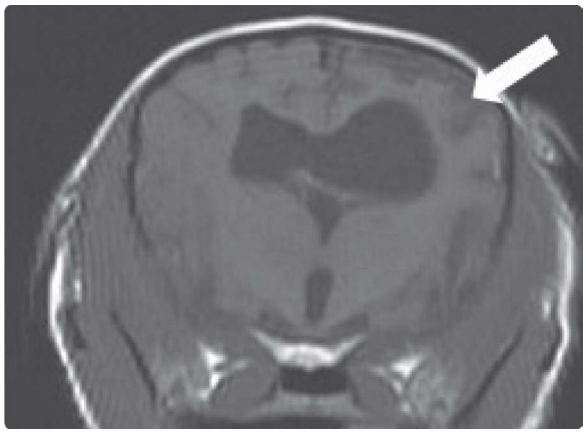


FIGURE 14.19 Transverse T1-weighted brain MR image depicting a loss of subcortical parenchyma (arrow) associated with necrotizing meningoencephalitis in a dog.

Pathophysiology

Infection with an alpha-type herpesvirus has been suggested based on histologic similarities with this type of infection in humans. However, attempts at viral isolation have been unsuccessful. The disease is associated with necrosis and a nonsuppurative meningoencephalitis, predominantly in the cortex. The subcortical white matter is frequently involved (Figure 14.19). Areas of necrosis can also be seen in the brainstem. Recent research suggests that genetics may play a role in disease susceptibility in Pugs.

Clinical Presentation

Pug encephalitis is most commonly seen in juvenile to young adults and causes seizures and other signs of forebrain dysfunction. The disease described in Maltese also has a predilection for the forebrain. The disease in Yorkshire Terriers causes signs of forebrain and brainstem involvement. Chihuahuas with necrotizing meningoencephalitis present with neurologic signs, which include seizures, blindness, mentation changes, and postural deficits. Multifocal loss or collapse of cortical gray/white matter demarcation is identified on MRI. Multifocal asymmetrical areas of necrosis or collapse in both gray and white matter of the cerebral hemispheres are seen on postmortem.

Differential Diagnosis

Other infectious and sterile causes of CNS inflammatory disease, brain tumor, metabolic and toxic encephalopathies.

Diagnosis

CT may reveal a focal hypodense area within the brain parenchyma relating to the area of necrosis. Multifocal, asymmetrical areas of high signal intensity in the brain can be seen on T2-weighted MR images, with variable contrast enhancement of the parenchyma and meninges visible on T1-weighted images. A lymphocytic

pleocytosis is most frequently recognized on CSF analysis. A definitive diagnosis is based on histopathology.

Management

Prognosis is poor, and the disease is typically fatal. Combined immunosuppressive protocols similar to those utilized for the treatment of GME are recommended. As with GME, there is limited information on the efficacy of such treatments in cases of histologically confirmed disease.

NUTRITIONAL DISEASES (THIAMINE DEFICIENCY)

Definition/Overview

Thiamine deficiency is a rare problem in dogs and cats that results in an acute progressive multifocal disease of the brain.

Etiology

Thiamine must be provided in the diet, as dogs and cats are unable to produce it endogenously. Fish is high in thiaminase and feeding an all-fish diet to cats can lead to thiamine deficiency. Overcooking canned food or meat, causing heat destruction of thiamine, has led to thiamine deficiency in dogs. Feeding meat preserved with sulfur dioxide to dogs and cats may also result in thiamine deficiency.

Pathophysiology

Thiamine (vitamin B1) is a necessary cofactor for normal carbohydrate oxidation, and its deficiency results in insufficient adenosine triphosphate (ATP) production in the brain with subsequent neuronal dysfunction and death (if not treated).

Clinical Presentation

Neurologic dysfunction due to thiamine deficiency tends to be acute and rapidly progressive. In both dogs and cats, signs of neurologic dysfunction due to thiamine deficiency typically include vestibular ataxia, decreased mentation (obtundation leading to coma, if not treated), ventroflexion of the head and neck, seizure activity, pupillary dilation with absent menace responses, and head tremors (Figure 14.20a, b). Left untreated, affected animals progress to a comatose state with opisthotonos (decerebrate posture) and ultimately death.

Differential Diagnosis

CNS inflammatory disease, cerebrovascular disease, toxicity.

Diagnosis

Antemortem diagnosis of thiamine deficiency is typically based on characteristic clinical signs of thiamine deficiency in a dog or cat receiving a thiamine-deficient diet. A positive response to thiamine administration also supports the diagnosis. Elevated blood pyruvate and lactate levels and decreased erythrocyte transketolase activity are supportive of the diagnosis, but these tests are rarely done. There are reports of MR imaging in dogs with thiamine deficiency. Similar to other metabolic encephalopathies, bilaterally symmetric brain lesions (hyperintense on T2-weighted images) were evident. In animals that die because of thiamine deficiency, characteristic bilaterally symmetric lesions (petechial hemorrhages) are appreciable throughout the brain at necropsy, especially in the caudal colliculi of the midbrain.





FIGURE 14.20 (a) A 7-year-old Domestic Shorthair cat exhibiting ventroflexion associated with its thiamine deficiency. **(b)** Transverse T2-weighted brain MR image of a dog with thiamine deficiency depicting bilateral hyperintensities associated with the colliculi (arrows).

Management

Treatment of suspected thiamine deficiency is with IM or SC thiamine hydrochloride. Rapid IV injection of thiamine can cause an acute anaphylactoid reaction; therefore, this route of administration is contraindicated. Anaphylactoid reactions are still possible, albeit

more unlikely, with the IM and SC routes. The dosage is 5–50 mg per day for dogs and 1–20 mg per day for cats. If recognized and treated early, prognosis for survival of thiamine deficiency is good. If not treated rapidly in the early period of neurologic dysfunction, prognosis for survival is guarded to poor.

HEAD TRAUMA

Definition/Overview

Severe head trauma is associated with high mortality in animals. The appropriate therapy for head trauma patients remains controversial in veterinary medicine due to a lack of objective information on the treatment of dogs and cats with head injuries. Treatment of affected animals must be immediate if the animal is to recover to a level that is both functional and acceptable to the owner. Many dogs and cats can recover from severe brain injuries if systemic and neurologic abnormalities that can be treated are identified early enough.

Etiology

Common causes of head injuries in cats and dogs include road traffic accidents, falls, kicks, gunshot or pellet wounds, and bites from larger animals. Traumatic injuries to the brain may result from blunt or penetrating insults. Most canine head trauma results from blunt vehicular trauma, while most feline head trauma is associated with crush injury.

Pathophysiology

Head trauma pathophysiology can be divided into primary and secondary injury. Primary injury to the brain cannot be reversed, occurs immediately, and describes the physical disruption of brain tissue. This includes contusions, hematomas, lacerations, and diffuse axonal injury leading to vasogenic edema. The underlying vascular and cellular pathophysiology of head trauma is similar to that described for spinal cord trauma but is complicated by elevations in ICP. This secondary injury is delayed and progressive, potentially providing targets for treatment. In addition to excitatory neurotransmitter release, ATP depletion resulting in cytotoxic edema, intracellular calcium accumulation causing activation of intracellular enzyme systems, and oxygen radical production resulting in lipid peroxidation occur. Traumatic brain injury is associated with a marked inflammatory response. The secondary injury "cascade" is exacerbated by systemic abnormalities present in the patient, which include hypotension, hypoxia, hypoglycemia or hyperglycemia, hypocapnia or hypercapnia, and hyperthermia.

After head trauma, the volume of the brain tissue compartment increases, usually due to edema or hemorrhage. As the brain tissue compartment increases, the CSF and the blood compartments must decrease, or ICP will increase. Compensation for increased brain tissue volume initially involves the translocation of CSF out of the skull. This is followed by decreased production of CSF and, eventually, decreased cerebral blood flow. These compensatory mechanisms prevent increases in ICP for an undetermined period. Once the ability for compensation is exhausted, a further small increase in intracranial volume will result in dramatic elevations of ICP, with the immediate onset of clinical signs. Increases in ICP are often responsible for clinical decline after head trauma. Marked increases in ICP lead to an elevation of mean arterial blood pressure (MABP) and reflex bradycardia (Cushing reflex). In addition to a drop in heart rate coupled with an elevated MABP, other clinical manifestations of ICP elevation include anisocoria, miosis, mydriasis, altered mentation, loss of motor function with the development of vertical nystagmus, and extensor rigidity toward the end stages.

Differential Diagnosis

Cerebrovascular disease, toxicities.

Diagnosis

Imaging of the patient's head is often indicated, especially in animals that fail to respond to aggressive medical therapy or deteriorate after initially responding. Skull radiographs are unlikely to reveal clinically useful information about brain injury but may occasionally reveal evidence of calvarial fractures (**Figure 14.21a–f**). CT is the preferred modality for imaging the head in cases of severe head injury associated with fractures. Even patients with "mild" head trauma can exhibit abnormalities on the CT scan and so the initial decision to image the patient's head should not be based on the neurologic examination alone. CT image acquisition time is faster and often less expensive than MRI, and CT also demonstrates bone detail better than MRI. Several classification methods based on the initial CT findings can be used for predicting prognosis. The recently reported Koret CT score (KCTS) was developed to address these differences. It considers lesions such as cranial vault fractures, areas of brain hyperdensity consistent with hemorrhage, midline shift, ventricular asymmetry, and lesions involving specifically the caudotentorial region, which are commonly identified in dogs following traumatic brain injury (TBI). Each of the mentioned abnormalities is given a score based on its presumed effect on prognosis:

CT parameter	Score assigned
Hemorrhage	1
Midline shift/lateral ventricle asymmetry	1
Cranial vault fracture	1
Any caudotentorial lesion (hypodensity, hemorrhage, fracture)	3
Depressed fracture	1
Sum score	0–7

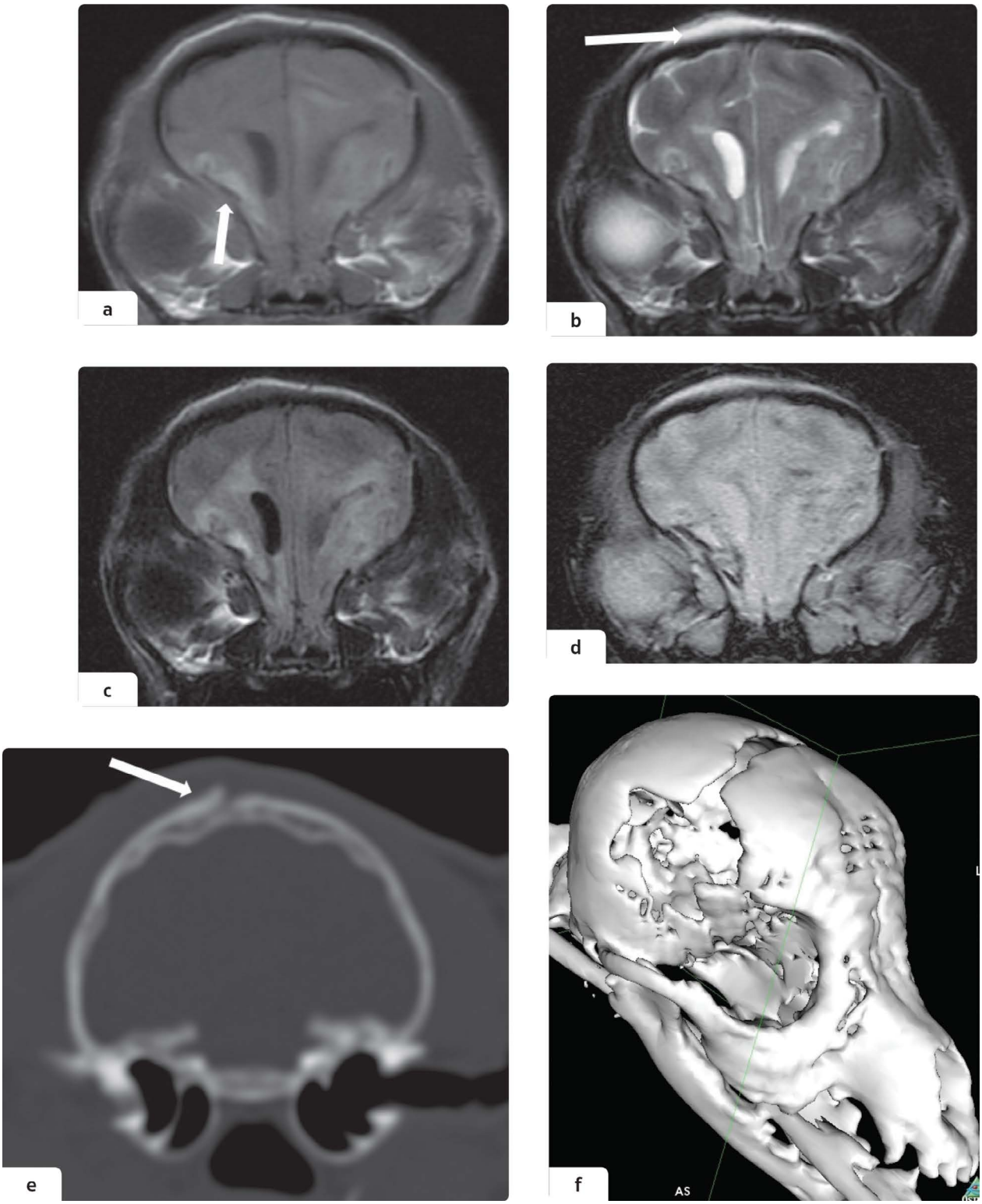


FIGURE 14.21 **(a)** T1-weighted transverse MR image of a dog 24 hours following a head trauma. A linear fracture of the skull associated with the orbit (arrow) can be seen. Multifocal areas of parenchymal damage can be identified within the frontal lobes. **(b)** T2-weighted transverse MR image of the dog in (a). In addition to the parenchymal damage, a focal area of soft tissue damage can be seen on the dorsum of the head as a hyperintensity (arrow). **(c)** T2-weighted FLAIR MR image suppressing free fluid seen on the T2-weighted image and highlighting pathologic hyperintensities alone. **(d)** Transverse gradient echo MR image detailing hemorrhage and bone as black, making both easier to determine in comparison with the other sequences. **(e)** Transverse skull CT scan of a cat following a bite on the head. A small, nondepressed fracture of the skull can be made out (arrow) with this modality, although underlying parenchymal damage is difficult to discern. **(f)** 3D reconstruction of a dog with a depressed skull fracture.

A study of 35 dogs with TBI found a significant negative association between the KCTS and survival for both short (10 days) and long (6 month) terms. A cutoff KCTS score of 3 yielded sensitivities and specificities of 85% and 100% for short-term survival and 83% and 89% for long-term survival, respectively.

MRI has been shown to provide key information relevant to the prognosis based on its ability to detect subtle parenchymal damage not evident on CT imaging. The detection of midline parenchymal shift and ventricular obliteration on MR images is associated with a poor prognosis for survival, based on a recent canine study. Furthermore, lesions of the intracranial structures that may benefit from surgical therapy, such as hematomas and pneumocephalus, can be accurately identified using advanced imaging.

MRI has been shown to provide key information relevant to the prognosis based upon its ability to detect subtle parenchymal damage not evident on CT (**Figure 14.21**). The detection of a midline parenchymal shift and ventricular obliteration on MR images are associated with a poor prognosis for survival

A modified MRI grading system score has been developed for use in veterinary medicine:

Grade 1: Normal brain parenchyma
Grade 2: Lesions only affect the cerebral hemisphere, cerebellar parenchyma, or both without median shift
Grade 3: Same as grade 2 but with median shift
Grade 4: Lesions affecting the corpus callosum, thalamus, or basal nuclei with or without lesions of a lower grade
Grade 5: Unilateral brain lesions in the brainstem with or without lesions of a lower grade
Grade 6: Bilateral brain lesions in the brainstem with or without lesions of a lower grade

A study of 50 dogs demonstrated that a greater area of affected brain parenchyma, a greater degree of midline shift, and a lower modified MRI grade was correlated with poorer clinical outcome follow-up scores and that the MGCS is lower in dogs with evidence of brain herniation. Also in this study, development of post-traumatic epilepsy in dogs was associated with a greater percentage area of brain parenchyma affected on the MR images. Another series of 18 dogs showed that dogs with parenchymal injury affecting the caudal cranial fossa had poorer outcomes (death, euthanasia, or severe persistent neurological deficits).

In cats, a poorer prognosis has been associated with a peripharyngeal pattern of injury and orbital trauma. Additionally, the frequency of bilateral or multifocal parenchymal lesions on T2-weighted imaging, and mass effect, particularly caudal transtentorial herniation, was statistically significantly higher in cats with a poorer outcome.

Cervical spinal radiographs are also advised at the time of any skull imaging to rule out concurrent spinal lesions. As for spinal trauma (see ahead given in the text), thoracic radiographs will help to evaluate for evidence of thoracic and cardiac trauma.

Management

A detailed assessment is important for determining the way in which treatment is tailored to the individual patient. Systemic and neurologic assessment must be undertaken rapidly and continually reassessed. In humans, traumatic brain injury is graded as mild, moderate, or severe on the basis of an objective scoring system (e.g., GCS). A modification of the GCS has been proposed for use in veterinary medicine. The modified scoring system incorporates three categories of the examination (level of consciousness; motor activity; brainstem reflexes), which are assigned a score from 1 to 6, providing a total score of 3–18, with the best prognosis being the higher score.

The most important consideration in head injury is maintenance of cerebral perfusion by treatment of hypotension and elevated ICP.

The basic goal of fluid management of head trauma cases is to maintain a normovolemic to slightly hypervolemic state to ensure an adequate cerebral perfusion pressure. Initial resuscitation usually involves IV administration of hypertonic saline and/or synthetic colloids. Use of these solutions allows rapid restoration of blood volume and pressure while limiting the volume of fluid administered. In contrast, crystalloids will extravasate into the interstitium within an hour of administration, and thus, larger volumes are required for restoration of blood volume. If isotonic crystalloids are chosen for administration (appropriate in mild head trauma), an aliquot of the shock dose (90 mL/kg in the dog and 60 mL/kg in the cat) can be given rapidly and repeated until improved tissue perfusion is achieved. Hypertonic saline administration (4–5 mL/kg over 2–5 minutes; 4 mL/kg of 7.5% or 5.3 mL/kg of 3%) draws fluid from the interstitial and intracellular spaces into the intravascular space, which improves blood pressure and cerebral blood pressure and flow, with a subsequent decrease in ICP. Colloid solutions can be administered after hypertonic saline is used to maintain the intravascular volume, possibly due to retention of fluids in the intravascular compartments, maintaining an intravascular oncotic gradient. The coadministration of hypertonic solutions and colloids is more effective at restoring blood volume than either alone. A dose of 4 mL/kg total of a 1:2 combination of 23.4% hypertonic saline with 6% hydroxyethyl starch (hetastarch) has been recommended.

Osmotic diuretics are very useful in the treatment of intracranial hypertension. Use of mannitol is recommended once vascular volume has been stabilized. Mannitol has an immediate plasma-expanding effect, which reduces blood viscosity, increasing cerebral blood flow and oxygen delivery. This results in vasoconstriction within a few minutes, causing an almost immediate decrease in ICP. The better-known osmotic effect of mannitol reverses the blood–brain osmotic gradient, thereby reducing extracellular fluid volume in both normal and damaged brain. Mannitol should be administered as a bolus over a 15-minute period, rather than as an infusion, in order to obtain the plasma-expanding

effect. Its effect on decreasing brain edema takes approximately 15–30 minutes to establish and lasts between 2 and 8 hours. Doses of 0.5–2.0 g/kg appear to be equally effective in lowering ICP, but the duration of effect is shorter with the lower doses.

Oxygen supplementation is recommended for most acutely brain injured animals. Supplemental oxygen should be administered initially via flow by, as oxygen cages are usually ineffective because constant monitoring of the patient does not allow for a closed system. As soon as possible, nasal oxygen catheters or transtracheal oxygen catheters should be used to supply a 40% inspired oxygen concentration with flow rates of 100 mL/kg per minute and 50 mL/kg per minute, respectively.

CRANIAL NERVE DISEASES

HEAD TILT AND NYSTAGMUS

Definition/Overview

Head tilt and nystagmus are relatively common presentations typically associated with vestibular disease (Figure 14.22). A thorough neurologic evaluation is critical to successful management. By determining the location of the disturbance within the vestibular system, a list of differential diagnoses and a diagnostic plan can be formulated.



FIGURE 14.22 An 8-year-old Domestic Shorthair cat with a left-sided head tilt.

Etiology

For peripheral vestibular disease, OMI, idiopathic vestibular disease, hypothyroidism, toxicity, trauma, and neoplasia should be considered. For central vestibular disease, CNS inflammation, cerebrovascular accident, neoplasia, hydrocephalus, trauma, metronidazole toxicity, thiamine deficiency, and lysosomal storage diseases should be considered.

Pathophysiology

The vestibular system functions to maintain an animal's balance and orientation with respect to gravity. The system detects linear acceleration and rotational movement of the head and is responsible for maintaining the position of the eyes, trunk, and limbs in reference to the position of the head. The sensory receptors for vestibular input are located in the membranous labyrinth of the inner ear. Input from the receptors enters the brain via the vestibular portion of CN VIII, where the majority of fibers terminate in one of four vestibular nuclei. The remaining axons terminate in the cerebellum. Pathways from the vestibular nuclei project to the nuclei of CNs III (oculomotor), IV (trochlear), and VI (abducent) to control eye movements, as well as to other brainstem centers and the cerebellum, cerebral cortex, and spinal cord. A head tilt results from the loss of antigravity muscle tone on one side of the neck. Jerk nystagmus develops from the dysfunction of the pathways responsible for integrating vestibular input with the extraocular eye muscles.

Clinical Presentation

Head tilt is described as a rotation of the head about the first cervical vertebra such that one of the ears is held lower than the other. Head tilt is indicative of vestibular disease and is the most consistent sign of a unilateral vestibular deficit. Nystagmus is a term used to denote the involuntary rhythmic oscillation of the eyeballs. The eye movements have a slow phase in one direction and a rapid recovery in the opposite direction, which can be horizontal, rotary, or vertical in character. Other clinical signs of vestibular dysfunction include ataxia, a wide-based stance, circling, leaning, falling or rolling toward the side of the head tilt, and positional strabismus, where the eye on the affected side deviates ventrally or ventrolaterally when the head is elevated. Animals with acute vestibular disease can present with anorexia or vomiting associated with the disequilibrium.

Differential Diagnosis

The differential diagnoses for an animal with vestibular disease vary considerably depending on whether the vestibular deficits are determined to be central or peripheral in origin. The two most common disease processes that cause central vestibular signs are neoplasia and infection/inflammation, while the two most common diagnoses in animals with peripheral vestibular signs are OMI and idiopathic vestibular disease.

Diagnosis

A CBC, blood chemistry, thyroid panel, and urinalysis should be performed in all animals presenting with vestibular signs. This can be useful for identifying potential inflammatory or metabolic disturbances that might be responsible for the clinical signs, in addition to serving as a general health screen, because further diagnostic testing usually requires anesthesia. Blood pressure measurements should also be obtained, as hypertension can manifest as vestibular dysfunction. An animal found to have peripheral vestibular disease should undergo a thorough otoscopic examination, performed under anesthesia, along with radiographs of the tympanic bullae to assess for OMI. It should be noted that normal radiographs do not rule out OMI. If there is evidence of OMI, a sample of fluid should be obtained via myringotomy and submitted for cytology and bacterial culture. CT and MRI of the tympanic bullae are the most sensitive means of identifying fluid within the middle ear and can be considered in cases posing a diagnostic challenge (Figure 14.23a–c). If the equipment is available, hearing can be assessed using a brainstem auditory evoked response to evaluate for involvement of the cochlear branch of CN VIII. Cats should undergo a thorough pharyngeal examination to check for possible inflammatory polyps. Diagnostic testing in an animal found to have central vestibular disease should include advanced imaging of the brain (preferably MRI) to identify any structural abnormalities. Analysis of CSF collected from the cerebellomedullary cistern can also be helpful. Serologic ± CSF testing for potential infectious agents is indicated where CSF testing shows inflammation.

Management

Treatment options for vestibular dysfunction are determined by the underlying etiology. Supportive care should consist of administering IV fluids to animals that are vomiting and confining the animal to a well-padded area in order to minimize self-trauma secondary to disorientation. Meclizine or maropitant can be given to treat nausea.

PERIPHERAL VESTIBULAR DISEASES

IDIOPATHIC VESTIBULAR DISEASE

Definition/Overview

Idiopathic vestibular disease is a common cause of vestibular disturbance in both dogs and cats.

Etiology

The cause of idiopathic vestibular disease is unknown.

Pathophysiology

Idiopathic vestibular disease is characterized by the acute or even peracute onset of nonprogressive peripheral vestibular signs, which has been associated with inflammation of the membranous labyrinth of the semicircular canals.

Clinical Presentation

The clinical signs most commonly reflect unilateral involvement of the peripheral vestibular system and can be quite severe and acute at onset. Occasionally, bilateral disease is seen, especially in cats. In contrast with many of the other diseases that affect the peripheral vestibular system, facial paresis and Horner's syndrome are not features of idiopathic vestibular disease.

Differential Diagnosis

OMI, ototoxicity, trauma, aural neoplasia, hypothyroidism, nasopharyngeal polyps.

Diagnosis

Diagnosis is based on the presence of a compatible history and physical examination findings and by the exclusion of other causes of peripheral vestibular disease, particularly OMI. Typically, improvement in clinical

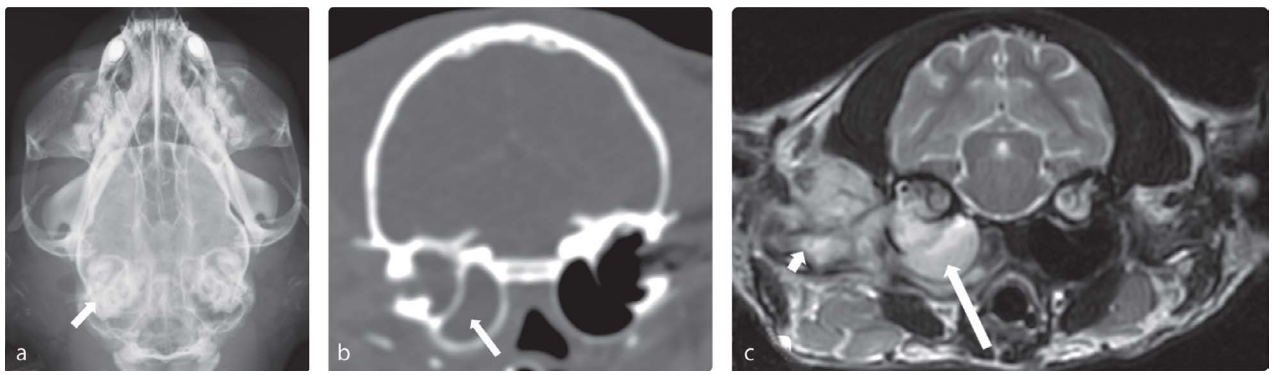


FIGURE 14.23 **(a)** Ventrodorsal radiograph of a cat with a right-sided head tilt. There is increased bone density associated with the osseous bulla on the right side (arrow), compatible with middle ear disease. **(b)** Transverse CT scan of the cat in (a) at the level of the osseous bullae. Soft tissue opacity (arrow) can be seen within both of the cat's middle ear cavities on the right side, accompanied by increased bone density. **(c)** Transverse T2-weighted MR image of the same cat at the level of the bullae confirming abnormal signal within the middle (arrow) and external ear cavities. The cat had a severe otitis media/interna, which had extended from the external ear canal and resulted in peripheral vestibular signs.

signs is seen within 2–3 days without specific treatment, and this can be used to help confirm the diagnosis.

Management

No treatment is recommended aside from supportive care, which consists of administering IV fluids to animals that are vomiting and confining the animal to a well-padded area in order to minimize self-trauma secondary to disorientation. Meclizine or maropitant can be given to treat nausea. Prognosis is good, as the condition resolves on its own within 2–4 weeks in dogs and 4–6 weeks in cats. A mild residual head tilt or ataxia can persist in some animals.

OTITIS MEDIA/INTERNA

Definition/Overview

Otitis media/interna (OMI) is one of the more commonly recognized causes of peripheral vestibular disease in both dogs and cats.

Etiology

OMI is caused by bacterial infection of the middle and inner ear.

Pathophysiology

OMI typically develops as an extension of otitis externa (OE), with common bacterial isolates, including *Staphylococcus intermedius* and *Pseudomonas* spp. OMI can occur in the absence of OE, in which case it is believed to be due to ascent of bacteria from the oral cavity through the auditory tube or hematogenous spread.

Clinical Presentation

Evidence of OE can be apparent on general physical examination. Facial nerve paralysis, neurogenic keratoconjunctivitis sicca, and/or Horner's syndrome can be seen in association with the vestibular signs due to the close association of CN VII and the sympathetic supply with the petrous temporal bone. Disease is most frequently unilateral, but bilateral disease can also occur.

Differential Diagnosis

Idiopathic vestibular disease, ototoxicity, trauma, aural neoplasia, hypothyroidism, nasopharyngeal polyps.

Diagnosis

Diagnosis is based on a thorough otoscopic examination and imaging of the tympanic bullae. Radiography of the tympanic bullae can reveal evidence of fluid density within, and sclerosis of, the bulla. However, radiographs can be normal in some cases, particularly early in the course of disease, and thus, additional imaging techniques such as CT or MRI might be required to provide more sensitive imaging of the bone and soft tissue in the affected area. Any exudate noted in the external ear canal should be removed by gentle saline irrigation to visualize the tympanic membrane. The tympanic membrane is frequently ruptured; if it is intact, it can appear to be bulging into the external ear canal. If fluid is visualized within the middle ear, an attempt should be made to obtain a sample via myringotomy. This can be performed under general anesthesia by inserting a 22-gauge spinal needle or tomcat catheter through the ventral aspect of the tympanic membrane, using an otoscope for guidance. The fluid present can then be gently aspirated into a syringe and submitted for cytology and bacterial culture.

Management

The treatment for bacterial OMI consists of a 4- to 6-week (at least) course of systemic antibacterial drugs. The choice of drugs should be based on the results of culture and sensitivity testing (if samples are successfully obtained via myringotomy). Otherwise, a drug that is effective against the most common causative organisms and penetrates the tympanic bullae (e.g., amoxicillin/clavulanate, a cephalosporin, or a fluoroquinolone) should be chosen. Otic cleansing products should not be used, particularly if the tympanic membrane initially cannot be visualized. If cleansing products escape into the middle ear, they can worsen the vestibular signs and cause deafness. Prognosis is good for resolution of the infection, although neurologic deficits can persist after effective medical therapy due to irreversible damage to the neural structures. Cases that are unresponsive to medical therapy might require surgical drainage and débridement via bulla osteotomy. Occasionally, an infection can extend into the cranial vault, causing central rather than peripheral vestibular signs to predominate. Aggressive management, including surgical drainage of the tympanic bulla and cranial vault via a bulla osteotomy and appropriate drug therapy, can result in a favorable outcome in such cases.

NASOPHARYNGEAL POLYPS

Definition/Overview

Nasopharyngeal (inflammatory) polyps comprise well-vascularized fibrous tissue lined by epithelium. Disease is identified most frequently in cats from 1 to 5 years of age but has been reported in dogs.

Etiology

These benign polyps are usually secondary to inflammation of the Eustachian tube.

Pathophysiology

Nasopharyngeal polyps originate in the auditory tube or the lining of the tympanic cavity and grow passively into the nasopharynx or middle ear of cats and, very

rarely, dogs. OMI can be a complication of auditory tube obstruction by the polyp.

Clinical Presentation

Polyps can cause signs of upper respiratory disease and dysphagia in addition to peripheral vestibular dysfunction. Evidence of otitis externa is often present.

Differential Diagnosis

Idiopathic vestibular disease, OMI, ototoxicity, trauma, aural neoplasia, hypothyroidism.

Diagnosis

Diagnosis is based on visualizing the polyp in the nasopharynx or external ear canal during a thorough pharyngeal and otoscopic examination performed under anesthesia. Radiography can reveal occlusion of the nasopharynx or sclerosis and soft tissue opacity within the tympanic bulla. Advanced imaging can provide additional information on the extent of soft tissue involvement associated with the polyp.

Management

Treatment involves removal of the polyp. Many polyps are attached to the auditory tube by a narrow stalk of tissue, and this can be successfully removed with simple traction. More extensive polyps may require surgical removal via ventral bulla osteotomy. Horner's syndrome is a common postoperative complication following ventral bulla osteotomy but tends to be transient. Overall, the prognosis is good. However, recurrence is possible, especially for polyps removed nonsurgically.

OTOTOXICITY

Definition/Overview

Peripheral vestibular dysfunction can occur secondary to administration of several systemic or topical medications.

Etiology

Systemic administration of aminoglycosides is most commonly associated with ototoxicity.

Pathophysiology

Prolonged therapy for >2 weeks with high doses of the drug are necessary to induce changes in normal animals; however, animals with renal impairment are more susceptible to developing toxicity. Of the aminoglycosides, streptomycin is most often associated with damage to the vestibular system. Due to the potential for ototoxicity, topical otic preparations should never be introduced into the ear when the tympanic membrane cannot be visualized or is found to be ruptured.

Clinical Presentation

Ototoxic agents can affect vestibular function, hearing, or both. Other agents can induce ototoxicity when used topically, the most notable of which are the iodophors and chlorhexidine.

Differential Diagnosis

Idiopathic vestibular disease, OMI, nasopharyngeal polyps, trauma, aural neoplasia, hypothyroidism.

Diagnosis

Diagnosis is based on the acute onset of compatible clinical signs in an animal that has recently been administered an ototoxic agent, in addition to the exclusion of other causes. Deafness can be confirmed with brainstem auditory evoked response testing.

Management

No definitive treatment is possible. Vestibular signs usually improve over time due to resolution of the damage or compensatory mechanisms, but deafness tends to be permanent.

CENTRAL VESTIBULAR DISEASES (SEE ALSO OTHER CAUSES OF BRAIN DISEASE)

METRONIDAZOLE TOXICITY

Definition/Overview

Central vestibular signs have been reported in dogs (and rarely in cats) following administration of metronidazole.

Etiology

Dogs reported to have developed metronidazole toxicity were typically treated with an oral dose of >60 mg/kg per day, although doses as low as 30 mg/kg per day have been incriminated. Metronidazole toxicity has also been reported in cats, but affected animals display signs of forebrain and cerebellar involvement rather than vestibular signs. Toxicity can be seen with lower doses than those reported for dogs.

Pathophysiology

The pathogenesis is poorly understood, but it is hypothesized to be related to the interaction of metronidazole with GABA receptors in the cerebellum and vestibular nuclei.

Clinical Presentation

Initial clinical signs include anorexia and vomiting and can progress rapidly to include bilateral central

vestibular signs with either a symmetrical or asymmetrical generalized ataxia and a positional vertical nystagmus. Head tilt and seizures are observed less frequently. The onset of clinical signs can occur as soon as 3 days after initiating treatment but can also be seen following chronic therapy.

Diagnosis

A history of metronidazole administration and compatible clinical signs should lead to a high suspicion for this disorder.

Management

Treatment consists of discontinuation of the drug and provision of nursing care. In addition, administration of diazepam (0.5 mg/kg IV followed by 0.5 mg/kg p.o. q.8 h. for 3 days has been recommended) has been shown to shorten recovery times in dogs. Recovery is typically seen within 1–3 days in dogs treated with diazepam and within 2–3 weeks in dogs, for which treatment only consists of drug discontinuation and supportive care. As with dogs, clinical signs in cats are reversible with discontinuation of the drug.

DROPPED JAW

Definition/Overview

Weakness of the jaw muscles may manifest as a reduction in voluntary movement of the jaw causing dysphagia or a complete loss of jaw muscle tone and inability to close the mouth (Figure 14.24).

Etiology

The cause of dropped jaw is a bilateral lesion affecting the motor component of CN V (trigeminal nerve). Most commonly this is due to idiopathic trigeminal nerve palsy, which is thought to be a neuritis of unknown cause. Lymphoma and immune-mediated inflammatory diseases are less common differentials that should be considered.

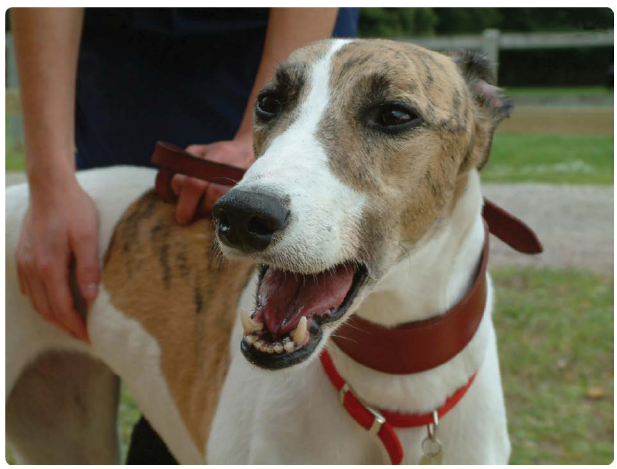


FIGURE 14.24 A 7-year-old Greyhound with an acute onset of dropped jaw.

Pathophysiology

The inability to close the mouth implies a bilateral lesion affecting the motor component of CN V, since a unilateral lesion does not cause sufficient weakness to prevent mouth closure. The bilateral nature of the trigeminal lesion strongly implies that it involves the peripheral nerves rather than the brainstem, since a lesion in the brainstem large enough to affect both trigeminal nuclei would likely be fatal. The motor neurons of CN V are located in the pons near the rostral cerebellar peduncles, and their axons are distributed to the muscles of mastication by the mandibular branch of CN V.

It is important to differentiate a lesion affecting only CN V from one affecting multiple CNs, since both may cause an animal to drool. This can be achieved by examining the animal's ability to use its tongue and swallow food when its mouth is held partially closed. These functions are mediated by CN XII (hypoglossal nerve) and CN IX (glossopharyngeal nerve), respectively, which are not affected by an isolated motor trigeminal neuropathy. Apparent inability to close the mouth must also be distinguished from an unwillingness to close the mouth, which can be caused by painful conditions of the head, such as masticatory muscle myositis, retrobulbar lesions, temporomandibular joint disease, or craniomandibular osteopathy.

Diagnosis

Diagnosis of idiopathic trigeminal neuritis is made largely through recognition of the typical pattern of clinical signs, absence of any other neurologic disease, and allowing a period of time to elapse in which recovery can occur. MRI and CSF can be helpful to rule out other causes.

Management

Treatment of idiopathic trigeminal neuritis is supportive: Helping the animal to eat by offering boluses of soft food and assisting with drinking or the placement of a temporary feeding tube. It has been suggested that holding the mouth partially closed with a muzzle facilitates eating and drinking during recovery. Most animals recover rapidly and are able to eat unassisted within 3 weeks.

ATROPHY OF THE MASTICATORY MUSCLES

Definition/Overview

Masticatory muscle atrophy can occur bilaterally or unilaterally (Figure 14.25). In spite of dramatic muscle atrophy, the ability to close the mouth usually appears

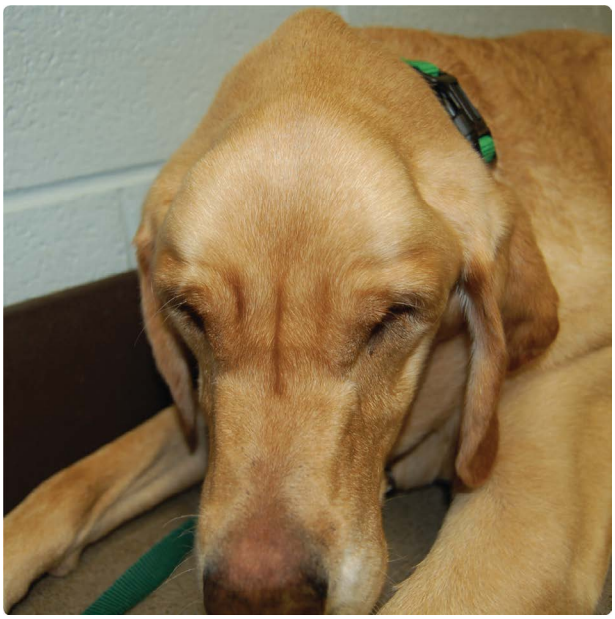


FIGURE 14.25 Bilateral temporal muscle atrophy is seen in this dog with generalized masticatory muscle atrophy.

unimpaired. However, opening the mouth may be very limited in cases in which there has been muscle inflammation and subsequent fibrosis.

Etiology

Masticatory muscle atrophy can result from impaired muscle innervation due to lesions of the motor branch of CN V, diseases of the muscles themselves, or systemic disorders such as cachexia or hyperadrenocorticism (or exogenous steroid administration). Unilateral loss of temporal muscle mass can occur in the absence of any sensory signs; it is recognized that nerve sheath tumors may be responsible. In a recent study of 63 dogs with unilateral masticatory muscle atrophy, presumptive trigeminal nerve sheath tumor (pTNST) was diagnosed in 30 dogs (47.6%); survival time varied from 1 day to 21 months (median, 5 months). Other extra-axial mass lesions were observed in 13 dogs (20.6%); survival time varied from 6 days to 25 months (median, 2.5 months). In 18 dogs (28.6%), no abnormalities were observed on MRI. Neurological signs only progressed in one dog.

Pathophysiology

Bilateral atrophy can be caused by many systemic diseases, most notably cachexia (associated with cancer) and hyperadrenocorticism (associated with exogenous or endogenous corticosteroids). However, bilateral atrophy most commonly occurs as a consequence of masticatory myositis due to the destruction of muscle fibers and scarring, which can occur rapidly. This is an immune-mediated disorder in which antibody-directed inflammation is targeted at the muscles of mastication, including the masseter, temporalis, and pterygoid muscles. The specific antigen is part of the unique myofiber (type 2M) contained within these muscles. There is no gender predisposition documented for masticatory myositis, and breeds noted to have a predisposition include the German Shepherd Dog, Hungarian Vizsla, and Cavalier King Charles Spaniel. Most affected dogs are of large breeds and are often young adults; cats are infrequently affected.

Clinical Presentation

Atrophy of the masticatory muscles can occur unilaterally or bilaterally. Bilateral atrophy is not associated with failure to close the mouth, but some individuals exhibit limited mouth opening (trismus). Third eyelid protrusion may follow severe temporal and masseter muscle atrophy, resulting in enophthalmos (due to loss of muscle support to the orbit), which may be sufficiently severe to impair vision. Swelling of the muscles of mastication can occur in the acute phase of masticatory myositis with trismus and exophthalmos. Palpation of the muscles or attempting to open the jaws may cause pain, and occasionally a "locked jaw" syndrome can result, in which animals are unable to either open or close their mouth. Exophthalmos in the absence of masticatory muscle swelling can result from myositis of the extraocular muscles. Young Golden Retrievers may be predisposed to this unusual disease.

Diagnosis

Detection of a significant concentration of anti-type 2M muscle fiber antibodies confirms masticatory myositis, although by the time the chronic phase is reached, the antibody response may well have subsided. Serum creatine kinase (CK) levels may also be elevated. Muscle biopsy may reveal an inflammatory infiltrate, myofiber necrosis, and phagocytosis. It may also specifically identify antibody localization to the type 2M myofibers. Electromyography often identifies spontaneous abnormalities and should always be performed to evaluate the rest of the musculature in cases where a more generalized myopathy is suspected. CT or MRI is required to diagnose nerve sheath tumors in cases with unilateral masticatory muscle atrophy (Figure 14.26).

Management

Masticatory muscle atrophy as a result of systemic disease does not appear to be reversible but does not often cause significant deficits. Masticatory myositis is treated with immunosuppressive doses of corticosteroids, but some cases of atrophy are too far advanced for this therapy to be effective. The recommended dose of prednisolone is 1–2 mg/kg p.o. q.12 h. for 3–4 weeks, after which the dosage is tapered slowly to achieve the lowest dosage q.48 h. that eliminates the clinical signs. Most dogs treated aggressively in the early stages show a good response to therapy, but relapses are possible. Some cases require the addition of a further immunosuppressive medication, such as

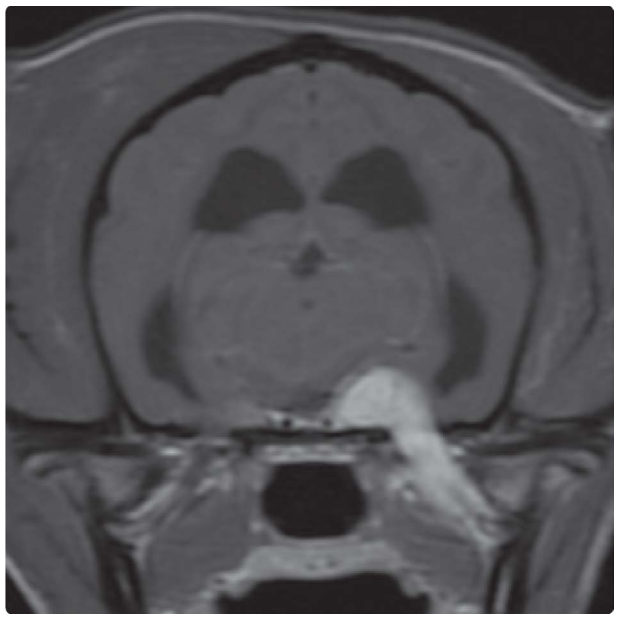


FIGURE 14.26 Transverse T1-weighted postcontrast brain MR image at the level of the brainstem; the hyperintense lesion compressing the brainstem and seen to exit the skull was confirmed to be a trigeminal nerve sheath tumor.

azathioprine. While cases that respond rapidly often have a favorable prognosis, chronic loss of muscle may lead to trismus and permanent dysphagia. Feeding regimens should be discussed with the owner, as even in the early stages of a responsive condition feeding tubes may be necessary, if only to reduce the potential for aspiration pneumonia. Additional therapy such as vigorous physiotherapy of the jaw muscles (by encouraging the dog to chew rawhides or play with tennis balls) is advisable.

FACIAL PARALYSIS

Definition/Overview

Dogs and less commonly cats can present with a drooping of the face due to reduced innervation of the muscles of facial expression. This is most commonly seen as a drooping lip but can also affect the eyelids (Figure 14.27).

Etiology

Facial nerve dysfunction may be due to disease of the peripheral facial nerve caused by OMI, trauma, hypothyroidism, neoplasia of the middle/inner ear, or polyneuropathies. Disease of the facial nerve nucleus in the medulla of the brainstem can result from any disease affecting the CNS. The most common cause of peripheral facial nerve paralysis has been reported to be idiopathic (75% of dogs and 25% of cats with facial paralysis). In addition, facial nerve palsy is sometimes observed in animals with more generalized peripheral neuropathies (e.g., those affecting multiple limbs).



FIGURE 14.27 A 6-year-old female Boxer with left-sided facial paresis.

Pathophysiology

Muscles that control facial expression and maintain the normal appearance of the palpebral fissures and mouth are innervated by the facial nerve. The neuron cell bodies are located in the facial nuclei of the rostral medulla, and axons leave the ventrolateral surface of the medulla ventral to CN VIII (vestibulocochlear nerve). CN VII (facial nerve) enters the petrosal bone through the internal acoustic meatus on the dorsal aspect of CN VIII and emerges from the skull through the stylomastoid foramen. Any disease affecting CN VII along its path can result in facial paresis, which is often seen as an acute-onset disease.

Clinical Presentation

Facial nerve paralysis or palsy may be unilateral or bilateral. Widening of the palpebral fissure and laxity of the facial muscles of expression may be seen. The lip may droop on the affected side, and food or saliva may fall from that side of the mouth. The nasal philtrum can be deviated to the normal side in the early stages, and drooping of the ears may be apparent in some breeds. There are some signs of CN VII dysfunction, for which pet owners may seek veterinary attention, that do not immediately suggest a facial nerve lesion. Owners may observe the third eyelid flicking over the eye. In these cases, the animal substitutes globe retraction (with concomitant third eyelid protrusion) for blinking with the paralyzed lids. Additionally, accumulation of food in cheeks that have poor muscle tone may lead to halitosis.

Loss of the palpebral and corneal reflexes predisposes the animal to exposure keratitis, which can occur subsequent to improper lubrication of the cornea, despite normal tear production. Clinical signs

are usually maximal within 7 days, and recovery can take 3–6 weeks, if it occurs at all. With chronicity, muscle contracture can lead to narrowing of the palpebral fissure, widening of the mouth, and, in unilateral cases, deviation of the nostrils towards the affected side.

Diagnosis

All possible causes of facial paresis and/or paralysis should be excluded before this specific diagnosis of idiopathic facial paresis can be made. A thorough investigation for ear disease should be undertaken in addition to blood tests for hypothyroidism and electromyography to rule out polyneuropathies. MRI may reveal contrast enhancement of the intratemporal facial nerve, which may suggest a poorer prognosis.

Management

There is no effective treatment for the underlying disease, but it is important to ensure that the cornea is adequately lubricated (either by endogenous production or eye drops). The prognosis for idiopathic facial palsy varies. Many animals make a gradual recovery (weeks to months), but some are left with permanent deficits. These deficits may progress to muscle contracture and deform the facial expression permanently. This can be mistakenly interpreted as hemifacial spasm, an uncommon syndrome in dogs and cats.

SPINAL DISORDERS

Clinical Signs of Spinal Cord Dysfunction

The clinical signs associated with spinal cord dysfunction depend on the location, size, and rate of development of the lesion. A small lesion on one side of the spinal cord without a great deal of associated cord swelling (e.g., a slowly growing tumor) will likely cause signs predominantly on the side of the lesion. However, a large lesion or a lesion associated with substantial cord swelling (e.g., an acute disc herniation in the thoracolumbar region) will likely result in bilateral signs of dysfunction. In most spinal cord disorders, bilateral deficits will be observed, but the deficits are often more pronounced on the side of the lesion. Proprioceptive and nociceptive information traveling toward the brain, as well as voluntary motor impulses traveling from the brain, can be affected with spinal cord disease. With progressive spinal cord disease, proprioception is usually the first deficit observed, followed by deficits in voluntary motor ability and finally deficits in the ability to perceive painful stimuli (nociception).

The clinical signs listed in further text for each of the anatomic subdivisions of the spinal cord represent all possible abnormalities that may be encountered with lesions in these respective areas. The clinician may, for example, encounter cases of cervical myelopathy in which severe neck pain is the only clinically detectable abnormality. Alternatively, cases may be encountered with more extensive lesions in the same anatomic location in which the patient is tetraplegic with minimal pain perception to the limbs and having respiratory difficulty. There is a spectrum of possible clinical presentations between these two extreme examples. A topic that is sometimes confusing to clinicians is that of upper motor neuron (UMN) fecal incontinence. Although it is apparently less common than with cauda equina lesions, fecal incontinence may result from cervical or thoracolumbar spinal cord lesions (particularly dorsal lesions, commonly of a cystic nature). This may be due to interruption of ascending information from the rectum to brainstem and cerebral centers responsible for a normal, coordinated defecation reflex, interruption of descending inhibitory influence from such centers on the local spinal cord sacral defecation reflex, or a combination of the two. Since fecal incontinence in these cases does not directly involve the LMNs innervating the anal sphincter musculature or the sensory neurons or nerves innervating the perineum, perineal sensation (in patients with intact pain sensation), as well as anal sphincter tone and perineal reflexes (e.g., anal reflex), are typically normal. The clinical information regarding UMN fecal incontinence in veterinary patients is limited, but it suggests that it may be more responsive to surgical intervention than LMN fecal incontinence. The cauda equina is defined as the nerve roots derived from the cord segments L7 and caudally. Damage to the spinal cord segments supplying the cauda equina will produce the same clinical signs of dysfunction as disruption of the respective nerve roots.

Clinical Signs Related to Disease of C1–C5 Spinal Cord Segments

- Cervical pain (hyperesthesia).
- Proprioceptive deficits ipsilateral to the lesion (forelimb and hindlimb) or all four limbs.
- Voluntary motor deficits ipsilateral to the lesion (forelimb and hindlimb) or all four limbs, varying from paresis to plegia. The paresis or plegia (hemiparesis, hemiplegia, tetraparesis, tetraplegia) is UMN in nature, with normal to hyperactive reflex activity in all limbs.
- Horner's syndrome ipsilateral to the lesion or bilaterally.
- Respiratory difficulty (severe lesions) involving both chest excursions and diaphragmatic movements.
- UMN bladder dysfunction.
- UMN fecal incontinence is possible.
- Nociceptive (pain perception) deficits are possible in all four limbs.

Clinical Signs Related to Disease of C6–T2 Spinal Cord Segments

- Cervical pain (hyperesthesia).
- Proprioceptive deficits ipsilateral to the lesion (forelimb and hindlimb) or all four limbs.
- Voluntary motor deficits ipsilateral to the lesion (forelimb and hindlimb) or all four limbs, varying from

paresis to plegia. The paresis or plegia is classically LMN in nature in the forelimbs (involvement of the gray matter of C6–T2 or the efferent axonal processes from that gray matter) and UMN in nature in the hindlimbs. In some instances (e.g., caudal cervical spondylomyelopathy), caudal cervical lesions may result in obvious signs of UMN paraparesis, with subtle or clinically inapparent forelimb deficits.
- Horner's syndrome ipsilateral to the lesion or bilaterally.
- Decreased or absent cutaneous trunci (panniculus) reflex ipsilateral to the lesion or bilaterally. The deficit is due to impairment of the efferent arm of the reflex arc.
- Respiratory difficulty with severe lesions. The respiratory pattern often differs from that seen with C1–C5 spinal cord lesions. Since the phrenic nerve arises from spinal cord segments C5–C7, there is usually enough phrenic nerve function to provide diaphragmatic movement, but impulses from the medullary respiratory centers cannot effectively traverse the damaged cord segments to stimulate the cell bodies of the intercostal nerves. This is the reason for the "abdominal breathing" pattern seen with severe caudal cervical myelopathies. The thoracic cage moves minimally, if at all, and the exaggerated activity of the diaphragm causes the abdominal contents to move passively.
- UMN bladder dysfunction.
- UMN fecal incontinence is possible.
- Nociceptive deficits are possible in all four limbs.

Clinical Signs Related to Disease of T3–L3 Spinal Cord Segments

- Thoracolumbar pain (hyperesthesia).
- Proprioceptive deficits in the hindlimb ipsilateral to the lesion or both hindlimbs.
- Voluntary motor deficits in the hindlimb ipsilateral to the lesion or both hindlimbs. The paresis or plegia (monoparesis, monoplegia, paraparesis, paraplegia) is UMN in nature, with normal to hyperactive reflex activity in the hindlimbs.
- The forelimbs are neurologically normal (normal proprioception, normal voluntary motor activity). Schiff–Sherrington posture may be seen in the forelimbs and should not be confused with a cervical spinal cord problem. Schiff–Sherrington posture is an anatomic phenomenon, not a prognostic indicator. Depending on the nature of the injury, spinal shock is also a possibility.
- Horner's syndrome is possible with very cranial lesions (T3 spinal cord level) but less likely in comparison with cervical lesions.
- Decreased or absent cutaneous trunci (panniculus) reflex, approximately one to four vertebral levels caudal to the spinal cord lesion. The deficit is due to impairment of the afferent arm of the reflex arc.
- UMN bladder dysfunction.
- UMN fecal incontinence is possible.
- Nociceptive deficits are possible in both hindlimbs.

Clinical Signs Related to Disease of L4–S3 Spinal Cord Segments

- Lumbar pain (hyperesthesia).
- Proprioceptive deficits in the hindlimb ipsilateral to the lesion or in both hindlimbs.
- Voluntary motor deficits in the hindlimb ipsilateral to the lesion or both hindlimbs. The paresis or plegia (monoparesis, monoplegia, paraparesis, paraplegia) is LMN in nature, with a decreased to absent patellar reflex ipsilateral to the lesion or bilaterally. The withdrawal and gastrocnemius reflexes may be normal or decreased, depending on the extent of damage to the L6 spinal segment (L6 contributes to the sciatic nerve).
- A decreased or absent panniculus (cutaneous trunci) reflex may or may not be appreciable one to four vertebral levels caudal to the lesion because the last three or four lumbar spinal nerves do not give off dorsal cutaneous branches.
- LMN bladder dysfunction.
- LMN fecal incontinence is possible. Decreased anal tone is possible.
- Nociceptive deficits are possible in both hindlimbs and the tail.

Neurodiagnostic Investigation

History and findings of physical and neurologic examinations will identify a neurologic problem and assist with neuroanatomic localization and consideration of differentials. The onset (acute or chronic), rate of progression (rapid or gradual), and temporal relation (intermittent and/or episodic, stable or insidious) can be established. A recommended diagnostic approach to spinal cord diseases is as follows:

- CBC, serum biochemistry profile, and urinalysis.
- Thoracic radiographs in animals >5 years of age and after trauma.
- Survey spinal radiographs can assist with recognition of obvious abnormalities such as discospondylitis, luxations, and bone neoplasia. If an abnormality is not seen, advanced imaging and CSF analysis are indicated.
- CSF collection, preferably from the cerebellomedullary cistern and caudal lumbar region (**Figure 14.28a, b**).
- Myelography and epidurography are useful for the detection and characterization of compressive spinal cord lesions (extradural, intradural, and intramedullary) and for determining the extent of the compression (**Figure 14.29**).
- CT is used as a primary method to evaluate the spine or assist with determining lesion extent after myelography.
- MRI is becoming more available to veterinarians in general and specialty practice and is considered the standard of care in the detection of lesions within the spinal cord.

Additional diagnostic procedures include electrodiagnostic evaluation (electromyography and nerve conduction studies), nerve and muscle biopsy, CSF protein electrophoresis, serology, PCR, and exploratory surgery.





FIGURE 14.28 (a) The skin over the caudal skull and cranial cervical column is shaved and prepared in a sterile fashion for a CSF tap at the cerebellomedullary cistern. **(b)** A spinal needle with a translucent hub is used to obtain CSF, and it is allowed to drip into a sterile polypropylene tube.

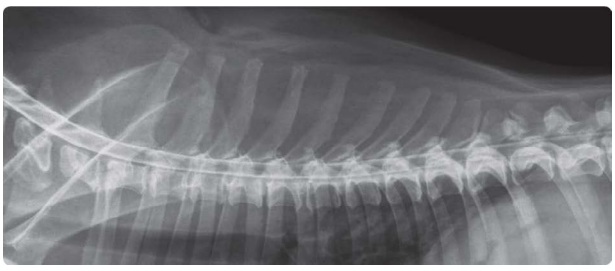


FIGURE 14.29 A lateral cervicothoracic myelogram.

VASCULAR DISEASE

FIBROCARTILAGINOUS EMBOLIC MYELOPATHY

Definition/Overview

Fibrocartilaginous embolic myelopathy (FCEM) is characterized by acute spinal cord infarction caused by embolism of fibrocartilage identical to that of the nucleus pulposus of the intervertebral disc. Acute tetraparesis, paraparesis, monoparesis, or monoplegia can be seen based on the location of the ischemic injury to the cord. Most commonly, this affects large breed dogs. FCEM rarely affects cats.

Etiology

FCEM is caused by embolism of fibrocartilage identical to that of the nucleus pulposus of the intervertebral disc (IVD).

Pathophysiology

Many theories exist as to the pathophysiology for embolization. Entry of disc material into the vascular system and embolization from the point of entry to the arteries and veins of the spinal cord has yet to be elucidated. The gray matter is more severely affected because of its higher metabolic demand. Nonchondrodystrophoid breeds are predisposed, which may relate to the disc being more gelatinous and prone to cause microextrusion. FCEM is frequently recognized in large and giant breed dogs but also affects small- to medium-sized dogs. Purebred dogs that have been documented with FCEM include Miniature Schnauzers, German Shepherd Dogs, Staffordshire Bull Terriers, Labrador Retrievers, and Irish Wolfhounds. FCEM is rare in cats. In dogs, the male-to-female ratio varies in different studies, and the median age in most studies is 5 or 6 years with a wide age range. In cats, males and females are equally represented, with most cats older than 7 years. While FCEM is also described in cats, a separate pathophysiology can also be seen associated with a characteristic clinical presentation, termed "feline ischemic myelopathy" and described in more detail in further sections.

Clinical Presentation

Neuroanatomic localization often is associated with the spinal cord intumescences, but other spinal cord regions can be involved. Thoracolumbar signs are more common than cervicothoracic signs. Clinical signs usually are associated with trauma or exercise. Asymmetrical lesion distribution is a clinical feature due to the distribution of the blood vessels to the spinal cord parenchyma; however, the lesion can be symmetrical. Symmetrical lesions more often are associated with loss of nociception. Spinal hyperesthesia can be present initially but is absent after the onset of ischemia. Maximal neurologic deficits usually occur within the first 24 hours. Dogs

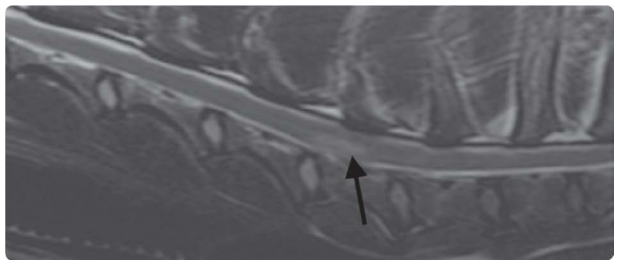


FIGURE 14.30 Sagittal T2-weighted cervical spinal MR image of a 6-year-old Labrador Retriever with a hyperintense lesion within the parenchyma of the spinal cord (arrow), confirmed histopathologically to be associated with a fibrocartilaginous embolus.

with lumbosacral intumescent involvement more often have loss of deep pain perception.

Diagnosis

Diagnosis is based on history, signalment, and clinical signs. Intramedullary spinal cord swelling provides early myelographic evidence of FCEM. MRI is the preferred diagnostic imaging modality for detection of intramedullary lesions and a presumptive diagnosis of FCEM. MRI findings include a focal, sharply demarcated, and often asymmetric intramedullary lesion, which predominantly affects the gray matter (**Figure 14.30**). CSF analysis may reveal abnormalities in severe cases. Dogs that are ambulatory on presentation are more likely to have normal MRI. The severity of neurologic signs has been associated with the extent of longitudinal and transverse lesions on MRI. Diagnosis of FCEM is confirmed by histopathology and documentation of nucleus pulposus in the spinal cord vasculature.

Management

Treatment is with supportive care. As for all spinal cord injuries, physical rehabilitation is important in the process of recovery.

As with other acute myelopathies, outcome is associated with the severity of neurological dysfunction, with a very guarded prognosis attached to dogs with plegia and absent deep pain perception of the affected limbs. It is also notable that persistent neurological deficits are seen in 50%–93% of dogs, with reduced urinary and fecal incontinence also reported in 2.5%–33% of dogs. Prognosis appears to be associated with the size of the spinal cord lesion, with an increased longitudinal and transverse extent of the intramedullary lesion on MRI shown to be associated with a poorer prognosis. Other factors, such as lower motor neuron signs and symmetrical lesions, have also been suggested as negative prognostic indicators. Dog size and severity of clinical signs may also contribute to owners electing for euthanasia, often early in the postinjury period. Although there is more limited data available regarding outcome in cats, the prognosis also appears good with positive outcomes, particularly in the presence of intact deep pain perception.

FELINE ISCHEMIC MYELOPATHY ASSOCIATED WITH HYALINE ARTERIOPATHY

Definition/Overview

This is a recently described condition in older cats, whereby an ischemic myelopathy in the cranial cervical region is thought to be related to hyaline arterial degeneration.

Etiology

The underlying etiology appears to be that of thrombosis secondary to hyaline degeneration of the ventral spinal artery or basilar artery in the region of the cranial cervical spinal cord.

Pathophysiology

Most cases involve an ischemic myelopathy occurring in the cranial cervical spinal cord, resulting from an infarction in the territory of the ventral spinal artery. Given the involvement of the basilar artery, affected cats can also demonstrate ischemic injuries in regions of the brainstem. Many cats are diagnosed with concurrent chronic systemic diseases, such as chronic kidney disease, hypertension, and hypertrophic cardiomyopathy, although the clinical relevance of these diagnoses is unknown.

Clinical Presentation

Clinical signs involve a peracute onset, nonprogressive cervical myelopathy in an older cat of any breed, occurring at an average age of around 14 years. The typical presentation is that of nonambulatory tetraparesis or tetraplegia, with affected cats also often demonstrating marked cervical ventroflexion. Spinal reflexes are usually intact in all four limbs, consistent with a localization to the C1–C5 spinal cord segments, with no spinal pain on examination. In contrast to most cases of FCEM (see mentioned in the text earlier), clinical signs of myelopathy typically affect both sides of the body symmetrically.

Diagnosis

Alongside a high index of suspicion based on the characteristic clinical presentation, a diagnosis is made on the basis of characteristic MRI features. A well-demarcated, intramedullary T2-weighted hyperintense spinal cord lesion is usually evident in the ventral cervical spinal cord, around the level of the C2 vertebra.

Management

As for other ischemic myelopathies such as FCEM, treatment is predominantly supportive with physical rehabilitation to facilitate recovery. The prognosis appears

to be good in most cases, with a return to ambulation in around 6 days on average. However, some cats may develop a chronic relapsing clinical course, so affected cats should be monitored for signs of recurrence in the future. Appropriate management of any concurrent systemic diseases is also an important treatment consideration in these cats.

AORTIC THROMBOSIS AND THROMBOEMBOLISM

Definition/Overview

Thrombosis or thromboembolism affects the terminal aorta and/or the iliac arteries in most dogs and cats, resulting in an acute or chronic onset of pelvic limb dysfunction. Thrombosis is the pathologic formation of a blood clot within a vessel, while an embolus occurs when a thrombus breaks off and obstructs blood flow in a distal location. Aortic thromboembolism, also known as saddle thrombus, often causes acute neurologic dysfunction affecting the hindlimbs, most commonly in cats, in addition to clinical signs of poor peripheral perfusion, such as nail bed cyanosis. The disease can occasionally affect dogs and may present more chronically as lameness or exercise intolerance affecting the hindlimbs.

Etiology

Cats with systemic thromboembolic disease have a thrombus that obstructs the terminal aorta. The most frequent underlying disease in cats with thromboembolism is hypertrophic cardiomyopathy but also other unclassified cardiomyopathies. In dogs, the disease is more commonly associated with steroid use, hyperadrenocorticism, and neoplasia.

Pathophysiology

Aortic thromboembolism is also known as saddle thrombus. Thrombi form in the left atrium, and dilation of the left atrium is one of the greatest risk factors for aortic thromboembolism. The three conditions that favor thrombus formation include blood stasis, hypercoagulability, and endothelial damage (Virchow's triad). Once the thrombus forms, it usually follows a path of least resistance and eventually lodges at the aortic trifurcation. Restriction of blood flow by the embolus and release of vasoactive substances cause ischemic injury to the nerves and muscles of the hindlimbs.

Clinical Presentation

The median age of onset in dogs is 10 years, but it has been seen in dogs from the age of 2 upward. Acute onset of clinical signs is extremely common in cats but is only seen in approximately 15%–47% of affected dogs. Clinical signs consist of acute onset of an asymmetrical hindlimb paresis and/or paralysis. Abyssinian, Birman, Ragdoll, and male cats were overrepresented in one study. The femoral pulse is weak or absent. The limbs are cold, and the nail beds are cyanotic and fail to bleed when cut. The hindlimbs are stiff, and the muscles are hard and painful on palpation. Typically, there is loss of hindlimb nociception distally. Tachypnea and hypothermia are frequently seen. Congestive heart failure and arrhythmias can each be seen in over 40% of cats. The more common chronic presentation in dogs is less likely to be painful, may be asymmetric, and many dogs are ambulatory, with over 40% of dogs having detectable femoral pulses. The term "claudication" has been proposed to describe cases with intermittent painful lameness, especially during exercise, and this is caused by anomalies of the peripheral blood flow to one or both pelvic limbs.

Diagnosis

Aortic thromboembolism is suspected based on clinical signs. Common biochemical abnormalities in these cats include hyperglycemia, hyperkalemia, azotemia, and a markedly elevated CK concentration soon after the embolic episode. A decrease in blood glucose of 17%–34% compared to unaffected limbs can be observed in dogs with arterial thrombosis, and absolute glucose cutoffs of 30 mg/dL and 16 mg/dL, in cats and dogs, respectively, corresponds to 100% sensitivity for the disease. Evidence of cardiac disease is further supported by physical examination findings, thoracic radiographs, and echocardiography. Doppler ultrasonography and/or CT of the aorta and its trifurcation can sometimes identify thrombotic disease (Figure 14.31).

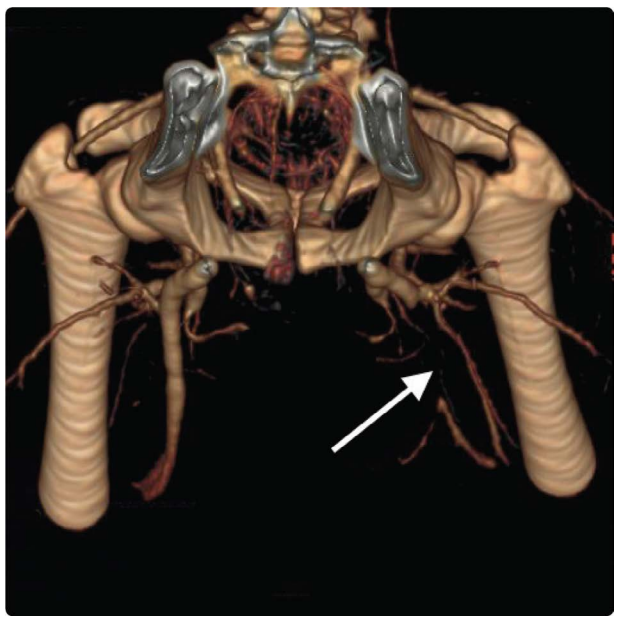


FIGURE 14.31 3D reconstructed CT scan of the pelvis and hindlimbs identifying a lack of vascular perfusion in the left femoral artery (arrow) secondary to an intravascular thrombus. (*Courtesy of Davies Veterinary Specialists.*)

Management

Initially, therapy involves management of the cardiac disease and supportive care.

Limiting the formation of further thrombi, controlling hypercoagulable states, and allowing normal thrombolysis to occur are the mainstay of current therapy for dogs and cats with aortic thrombosis or aortic thromboembolism. Medical management consists in treating the acute phase with:

1. Anticoagulants (e.g., unfractionated or low-molecular-weight heparins, warfarin, rivaroxaban, and apixaban). Rivaroxaban and apixaban are two of the newest group of anticoagulant medications, which include direct factor Xa inhibitors and direct thrombin inhibitors known as direct small molecule inhibitors.
2. Antithrombotics (e.g., clopidogrel, aspirin). Clopidogrel would be ideally recommended (2–4 mg/kg per day) due to evidence of improved platelet inhibition compared to aspirin, and clopidogrel administration has been associated with significantly reduced likelihood of recurrent arterial thromboembolism compared to aspirin with a longer median time to recurrence.
3. Thrombolysis (tissue plasminogen activator or TPA). Survival of TPA-treated cats was recently shown to be similar to those that just received pain medications and thromboprophylaxis. Complications are reportedly high in cats with administration of TPA, which include azotemia, cardiac arrhythmias, hyperkalemia, acidosis, and sudden death.
4. Heart failure therapy in cats when present.
5. Surgery can be considered to remove the thrombus if anesthesia can be administered.
6. Intense supportive and symptomatic therapy is warranted including pain relief.

The prognosis is guarded in dogs with 50%–60% survival to discharge and with 28% being alive at 100 days in one study. Ambulatory status and a chronic presentation are the only known positive predictors of outcome documented in dogs, with a median survival time of 293 days reported for dogs with a chronic progressive course. The prognosis for cats is typically poor, with 26%–66% of cats euthanized in the acute phase, a reported rate of survival to discharge of 0%–50%, and a 6-month recurrence rate of 45%–75%. Only 2% of 250 cats in one study survived over a year. Low rectal temperature, bradycardia, and multiple limb involvement have all been associated with decreased survival rate in cats.

TRAUMATIC DISEASES

FRACTURES AND LUXATIONS

Definition/Overview

Spinal fracture and luxation in dogs and cats are most commonly associated with severe external trauma, occurring in approximately 6% of cases as the cause of spinal cord dysfunction. The resulting clinical signs can vary from pain to paralysis with loss of nociception.

Etiology

Automobile-related injury is the most common cause of exogenous trauma to the spine.

Pathophysiology

The thoracolumbar junction is the most commonly injured site in dogs and cats. Fractures occur between T11 and L6 in 50%–60% of patients after blunt trauma. Fractures in the thoracic spine may have little displacement because of the protection provided by the ribs, ligamentous support, and epaxial musculature. Fractures and luxations of the thoracolumbar spine are often associated with other systemic injuries (e.g., pneumothorax, pulmonary contusions, orthopedic injuries, urogenital injuries, and diaphragmatic hernia). Approximately 20% of patients with thoracolumbar fractures have a second spinal column fracture. In the neck, the atlantoaxial junction is relatively unstable and, therefore, particularly at risk. The axis is the most commonly fractured cervical vertebra because it acts as a fulcrum between the caudal cervical spine and the so-called cervicocranium (the skull, atlas, dens, and body of the axis) (**Figure 14.32a–c**).

Primary mechanical injury to neural tissue can subsequently lead to secondary biochemical injury. The amount of neural tissue injury is related to the rapidity and severity of insult and the amount and duration of compression.

Clinical Presentation

The neurologic signs are determined by the level of any associated spinal cord damage. Schiff–Sherrington posture is a common finding associated with acute thoracolumbar injury but is not a prognostic indicator (**Figure 14.33**). Pain perception is carefully assessed in paraplegic animals to assist with determination of prognosis. Respiratory crises may be noted with acute cervical spinal cord injury.

Diagnosis

Results of the neurologic examination are used to determine neuroanatomic localization and severity of the spinal cord injury. It is important to perform the neurologic examination with care to prevent further injury and displacement of the spine. The neurologic examination findings are most important in establishing the prognosis, irrespective of radiographic findings. Plain radiography of the entire spine should be performed. Two views are used while minimizing patient movement by obtaining the ventrodorsal view using horizontal beam. Results of survey radiography are used to determine the precise lesion location(s) and extent, demonstrate multiple lesions, and guide appropriate management (**Figure 14.34**). Myelography or cross-sectional imaging is used when the radiographic findings do not



FIGURE 14.32 **(a)** Ventrodorsal radiograph of the cranial cervical spinal column. A fracture of the cranial aspect of the body of C2 (arrow) can be identified. **(b)** Sagittal CT scan of the cranial cervical spinal column of the same dog as in (a) showing the linear fracture (arrow). **(c)** Transverse reconstruction through the C2 vertebra showing displacement of the body fracture.



FIGURE 14.33 A 4-year-old mixed-breed dog exhibits Schiff–Sherrington posture secondary to an acute thoracolumbar spinal trauma.

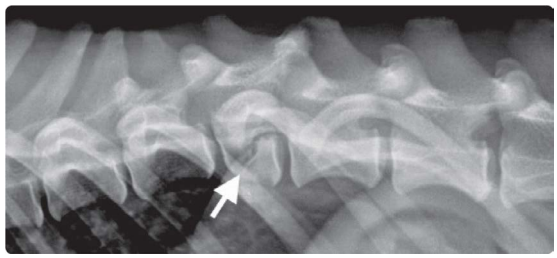


FIGURE 14.34 Lateral radiograph of a canine thoracic vertebral column, showing a T12 compressed body fracture (arrow).

correlate with the neurologic examination, to evaluate spinal cord swelling in concussive injuries and further assess severity of spinal cord compression. CT or MRI is useful for further evaluating bone and spinal cord tissues, respectively, and provide a 3D configuration of the fracture/luxation extent for assessment of spinal stability (Figure 14.35a–d).

Management

The critical factor in determining whether conservative or surgical management of spinal fracture and luxation is appropriate depends on the presence of instability. Spinal stability is assessed using a three-compartment theory (Figure 14.36). Priority is placed on treatment of extraneural injuries, beginning with management of shock and hemorrhage. Management of an animal with spinal trauma focuses on the prevention of secondary injury to the spinal cord parenchyma. Indications for nonsurgical management include minimal neurologic deficits, minimal vertebral displacement, and lack of myelographic evidence of spinal cord compression. Principles of conservative management are appropriate confinement for 6–8 weeks and use of external coaptation. The aim of external support is to provide immobilization of the vertebral segments cranial and caudal to the damaged area. It is important to follow principles of bandage care when using methods of external support. The patient will need to be turned regularly and kept clean and dry to prevent urine scalding.

Surgical management often provides a better chance for more rapid and complete neurologic recovery.

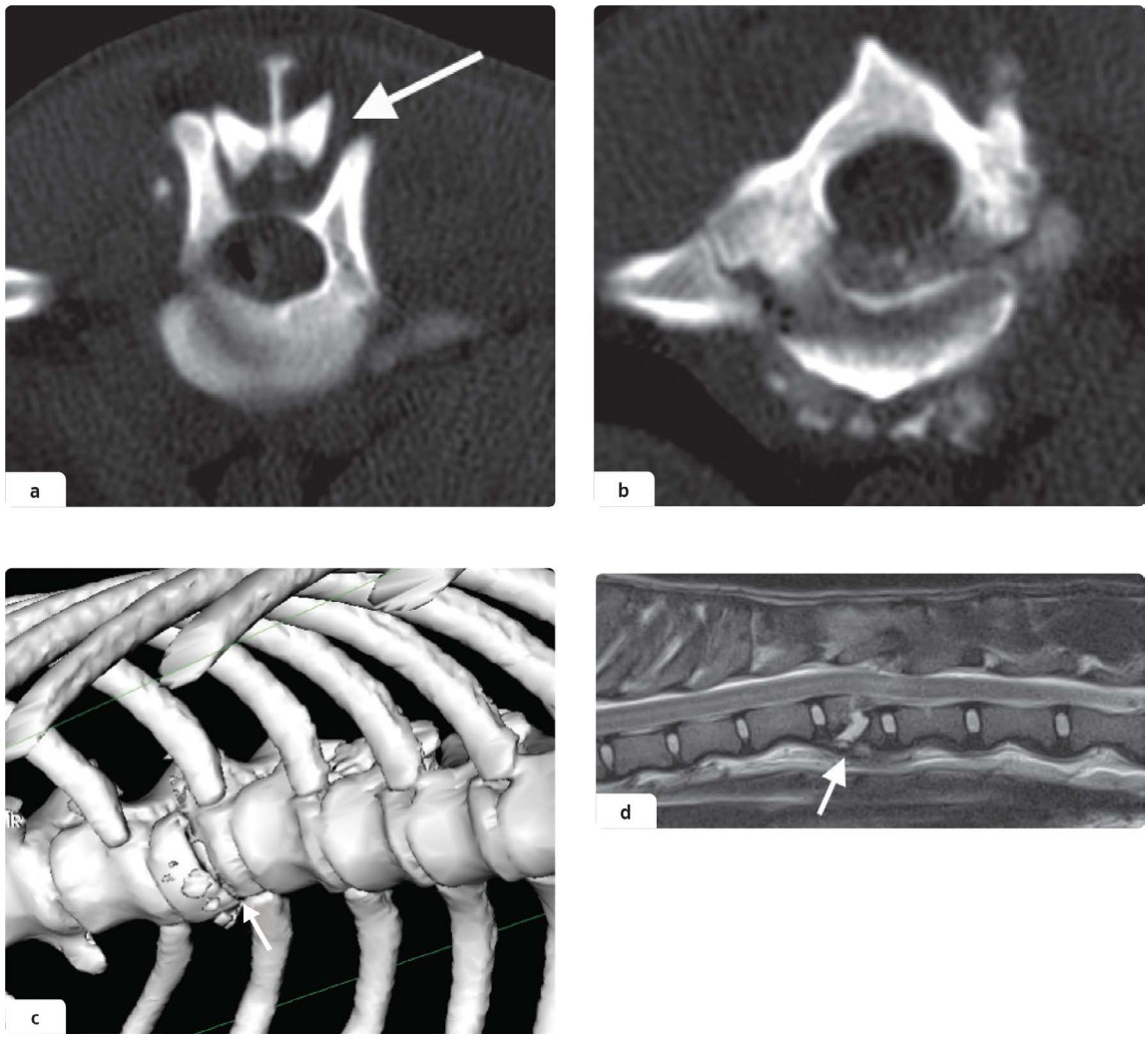


FIGURE 14.35 **(a)** Transverse T12 and T13 vertebral CT scan of the fracture depicted in **Figure 14.34**. Note the subluxation of the articular processes (arrow). **(b)** Transverse T12 vertebral body CT scan showing the fracture depicted in **Figure 14.34**. **(c)** 3D reconstructed CT scan of the thoracic vertebrae helps identify the ventral aspect of the T12 body fracture (arrow). **(d)** Sagittal T2-weighted MR image of the thoracic vertebrae is useful to visualize the effect of the T12 fracture (arrow) on the spinal cord.

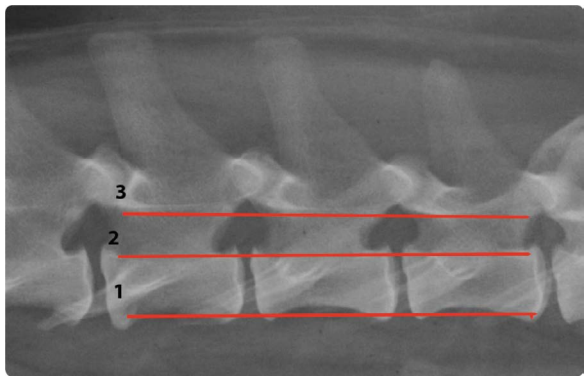


FIGURE 14.36 Three-compartment model of vertebral instability. Compartment one contains the ventral three-quarters of the vertebral body, the disc, and the ventral longitudinal ligament. The second compartment consists of the dorsal one-quarter of the vertebral body, the disc, and the dorsal longitudinal ligament. The third compartment includes the articular processes, lateral pedicles, dorsal laminae, interarcuate ligaments, and dorsal spinous processes.

However, the role of surgery for spinal trauma remains unclear. Indications include severe neurologic deficits and deteriorating neurologic status, imaging evidence of compression, and damage of two or more vertebral compartments. Timely surgical intervention is important to allow for maximal recovery. The objectives for surgical management of spinal trauma are decompression, realignment, and stabilization. The decompressive procedure should be conservative so as not to disrupt further the integrity of the vertebrae but large enough to allow for removal of compressive material. Successful outcome after surgical fixation depends on the type and strength of fixation, the surgeon's skill and knowledge of the spinal anatomy, and the accuracy of vertebral column alignment (**Figure 14.37**).

Careful attention to postoperative care is imperative for the wellbeing of the patient. Potential complications include urinary tract infections, decubital ulcers (**Figure 14.38a, b**), and implant failure. Physical rehabilitation is important in the recovery process.

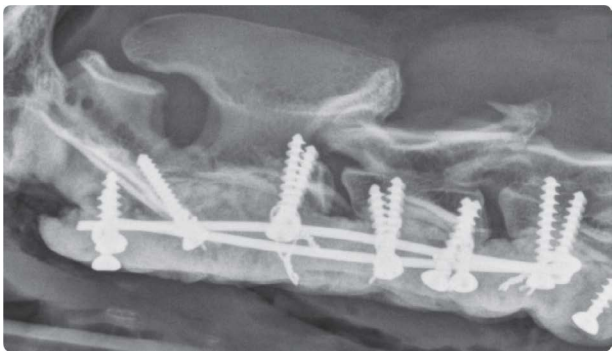


FIGURE 14.37 Lateral postspinal fixation radiograph of the dog with a C2 vertebral fracture illustrated in Figure 14.33.

Prognosis following vertebral fracture and luxation is largely dependent on the severity of neurological deficits. In the case of thoracolumbar spinal trauma, prognosis is considered poor in dogs presenting with paraplegia and absent deep pain perception. In one study, only 12% of dogs presenting with presenting with absent deep pain perception following thoracolumbar fracture/luxation recovered ambulation, and none regained deep pain perception regardless of surgical or medical management. As a result, careful consideration should be given to whether to go ahead with treatment in a dog or cat presenting with paraplegia absent deep pain perception following vertebral trauma. Referral or reassessment of deep pain perception after a short period (<24 hours) of supportive care and immobilization can be considered, at which point if deep pain perception is still absent, owners should be informed that functional recovery is unlikely to occur.

Although no prospective comparisons are available, outcome in dogs and cats with intact deep pain perception tends to be good with both surgical and medical management when the treatment option is selected according to individual patient factors. Retrospective studies suggest a 70%–95% recovery rate for medical management of vertebral fractures and luxation, suggesting a good outcome can be achieved in patients for which surgery is not deemed indicated.

While a similar functional recovery has been reported following cervical, thoracic, and lumbar vertebral fractures and luxation, surgical management of cervical fractures does appear to be associated with a higher risk of perioperative mortality, up to 36% in one study. This may reflect the need for ventilatory support in severely injured dogs with cervical fractures, particularly if the surgery is associated with further iatrogenic damage. Prompt identification and referral is recommended in cases of cervical vertebral trauma presenting with nonambulatory tetraparesis or tetraplegia.





FIGURE 14.38 (a) An early-stage decubital ulcer appearing over the ischium following a short period of recumbency in a paralyzed dog. (b) A later stage, open, and granulating decubital ulcer.

BRACHIAL PLEXUS AVULSION

Definition/Overview

Traumatic injuries causing avulsion of the nerve roots of the brachial plexus are the most common cause of acute forelimb monoparesis or monoplegia in small animals.

Etiology

These injuries are usually a result of abduction and simultaneous caudal displacement of the forelimbs caused by road traffic accidents or falls from a height.

Pathophysiology

The site of root avulsion is usually intradural where the nerve roots arise from the spinal cord. At this point, nerve roots lack a well-defined perineurium and constitute the weakest structure between the spinal cord and the peripheral nervous system. If the avulsion is severe enough, it may place traction over the spinal cord and damage spinal cord pathways, causing ipsilateral hindlimb neurologic deficits. Both dorsal and ventral nerve roots can be affected, but the motor roots appear to be more susceptible to this type of trauma.

Clinical Presentation

Signs are peracute in onset following the traumatic incident. Depending on which nerve roots are affected, avulsions are divided into three types:

- Cranial avulsions (C6–C7 nerve roots)
- Caudal avulsions (C8–T2 nerve roots)
- Complete avulsions (C6–T2 nerve roots)

Cranial avulsions are rare and result in few clinical signs. The elbow extensor muscles are not affected, so the animal can bear weight on the affected limb. There is loss of shoulder movement and elbow flexion, and atrophy of supraspinatus and infraspinatus muscles usually develops.

Caudal and complete avulsions are more common and cause more severe clinical signs. They both cause paralysis of the triceps brachii muscle, so the animal cannot extend the elbow or bear weight on the affected limb. Affected animals drag the limb knuckled over (Figure 14.39). Forelimb muscles are hypotonic, and severe neurogenic atrophy starts about 1 week after the injury. Spinal reflexes and postural reactions are reduced. If the elbow flexor muscles are spared (caudal avulsions), the animal can carry the limb flexed at this level, avoiding contact with the floor.

Sensory signs are also common. The pattern of decreased or absent sensation in the affected limb allows better determination of the type of avulsion. Cutaneous sensation should be checked in the entire limb, but particular attention should be paid to nociception in the medial (radial and musculocutaneous) and lateral (radial and ulnar) digits, since it is essential in determining a prognosis.



FIGURE 14.39 Forelimb monoplegia and moderate proximal limb muscle atrophy are evident in this dog with a right-sided brachial plexus avulsion following a traumatic insult.

A high percentage of patients with brachial plexus avulsions show partial Horner's syndrome and/or loss of cutaneous trunci reflex ipsilateral to the side of the avulsion. Avulsion of the T1 ventral nerve root causes injury to the preganglionic sympathetic nerve fibers to the eye, causing ipsilateral miosis (partial Horner's syndrome). Loss of the cutaneous trunci reflex is caused by damage to the C8–T1 ventral spinal nerve roots that form the lateral thoracic nerve and innervate the cutaneous trunci muscle. The contralateral reflex is usually present after ipsilateral stimulation.

Diagnosis

A history of forelimb monoparesis after a traumatic incident should raise a high suspicion of brachial plexus avulsion. Every animal unable to use one forelimb after trauma should be examined carefully to detect orthopedic as well as neurologic abnormalities. MRI of the affected plexus may provide information on the degree of nerve and associated soft tissue trauma. Electromyography allows detection of spontaneous electrical activity in the denervated muscles 7–10 days after the injury. Nerve conduction velocity studies of the radial and ulnar nerves allow determination of the degree of injury. Since the radial nerve is commonly injured in brachial plexus avulsions, serial electrodiagnostic evaluations of this nerve may provide useful diagnostic and prognostic information.

Management

Unfortunately, there is no routinely effective treatment for this type of injury. The degree of recovery depends only on the severity of the nerve lesion at the time of injury.

If nociception is present in the medial and lateral digits, prognosis for recovery is good, and aggressive physiotherapy should be recommended to the owner. If nociception is absent, prognosis will depend on the severity of the axonal injury, being good for neurapraxic lesions but guarded to poor for axonotmetic (nerve injury to axon while sparing the myelin) and neurotmetic (disruption of axon, myelin sheaths, and connective tissue) lesions. Pure axonotmesis occurs rarely, so the potential for recovery, although present, is low and prognosis poor.

When the proximal branches of the radial and musculocutaneous nerves are spared so that the elbow flexor and extensor muscles are not denervated, corrective surgery can be used to provide carpal extension and prevent the distal part of the limb from collapsing. Tendon transplantation or carpal arthrodesis procedures can be performed.

Animals with caudal and complete brachial plexus avulsions have a poor-to-guarded prognosis if neurotmesis has occurred. Only those with neurapraxic

(temporary loss of sensory and motor function due to nerve injury) injuries show improvement and recover completely. However, most animals do not improve but go on to show severe limb atrophy, eventually developing serious complications such as trophic ulcers, joint contractures or self-mutilations from paresthesia, or abnormal sensation in the affected areas produced by regeneration of sensory nerves. In these cases, amputation of the limb is necessary. The best predictor of complete recovery seems to be nociception. Preservation of nociception is an indicator of a milder type of injury and should prompt the clinician to recommend supportive therapy while waiting for motor function to recover. However, if no improvement is seen during the first 2 months, recovery is unlikely to occur.

DEGENERATIVE DISEASES

DEGENERATIVE MYELOPATHY

Definition/Overview

Degenerative myelopathy (DM) is a slowly progressive nonpainful paresis and ataxia usually affecting large-breed dogs (especially the German Shepherd Dog).

Etiology

For many years the etiology of DM remained unknown. A mutation in the superoxide dismutase 1 (SOD1) gene is now associated with this disease.

Pathophysiology

The uniformity of clinical signs, histopathology, age, and breed predilections suggested an inherited basis for DM. Segregation of DM in families has been reported in the Siberian Husky, Pembroke Welsh Corgi, and Chesapeake Bay Retriever. Dogs testing homozygous for the mutation are at risk for developing DM. Some dogs are homozygous for the mutation but remain free of clinical signs, which suggests age-related incomplete penetrance. A different SOD1 mutation has been discovered in the Bernese Mountain dog; therefore, currently available DNA tests cannot be used to rule out a diagnosis of DM. Other sequence variants in the same gene or in a different gene might produce a similar disease phenotype. A progressive degeneration of the spinal cord, predominantly in the T3–L3 region, is responsible for the clinical signs.

Clinical Presentation

Dogs with DM show an insidious, progressive ataxia and paresis of the hindlimbs, ultimately leading to paraplegia and euthanasia. If hindlimb hyporeflexia is observed, reflecting nerve root involvement, the disease is sometimes termed canine degenerative radiculomyelopathy. Although the German Shepherd Dog is the most commonly affected breed, DM has been reported in many other pure and mixed breeds. There is no sex predilection. In most breeds, the mean age of onset of neurologic signs is 9 years.

Progressive, asymmetric UMN paraparesis, hindlimb ataxia, and lack of paraspinal hyperesthesia are key clinical features of DM. The clinical course of DM can vary after the presumptive diagnosis. Pet owners usually elect euthanasia when dogs can no longer support weight in their hindlimbs and need walking assistance (Figure 14.40a, b). Smaller breed dogs can be cared for by the pet owner over a longer time. The median disease duration in the Pembroke Welsh Corgi is 19 months. As a result of a longer survival time, affected Pembroke Welsh Corgis often have signs of forelimb paresis at the time of euthanasia. The earliest clinical signs of DM are general proprioceptive ataxia



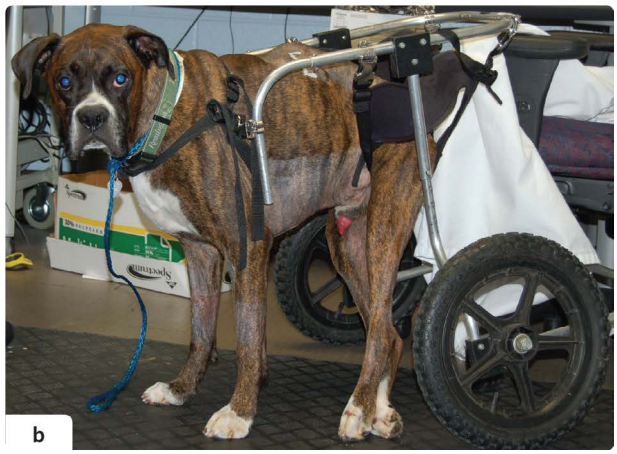


FIGURE 14.40 (a) A 9-year-old German Shepherd Dog with degenerative myelopathy demonstrates profound weakness of the hindlimbs. **(b)** Severe motor dysfunction of the hindlimbs can be assisted with the use of canine support carts, as shown in this photo.

and mild paresis in the hindlimbs. Worn nails and asymmetric hindlimb weakness are apparent on physical examination. Asymmetry of signs at disease onset is frequently reported. At disease onset, spinal reflex abnormalities are consistent with UMN paresis localized in the T3–L3 spinal cord segments. Patellar reflexes may be normal or exaggerated; however, hyporeflexia of the patellar reflex has also been described in dogs at a similar disease stage. Flexor reflexes may also be normal or show crossed extension (suggestive of chronic UMN dysfunction). Most large-breed dogs progress to nonambulatory paraparesis within 6–9 months from onset of clinical signs and are euthanized during this disease stage. If the dog is not euthanized early, clinical signs will progress to LMN paraplegia and ascend to affect the forelimbs. Flaccid tetraplegia ultimately occurs in dogs with advanced disease. The paresis becomes more symmetrical as the disease progresses. LMN signs emerge as hyporeflexia of the patellar and withdrawal reflexes, flaccid paralysis, and widespread muscle atrophy beginning in the hindlimbs as the dogs become nonambulatory. Widespread and severe loss of muscle mass occurs in the appendicular muscles in the late stage of DM.

Diagnosis

Tentative antemortem diagnosis is presently based on ruling out other diseases causing progressive myelopathy. Common differentials include intervertebral disc disease (IVDD), inflammatory disease, and spinal cord neoplasia. Hip dysplasia and degenerative lumbosacral stenosis often can be confused with the diagnosis of DM, although the neurologic findings are different if a careful examination is performed. It is not uncommon for DM affected dogs to have coexisting neurological and orthopedic diseases. Diagnostic testing is typically performed in the early disease stage. The lack of abnormal findings of electrodiagnostic testing and myelography or cross-sectional imaging (MRI, CT), along with characteristic disease pattern for progression of neurologic signs, support a presumptive diagnosis of DM. Definitive diagnosis of DM is determined postmortem by histopathologic examination of the spinal cord. A blood test is available to identify SOD1 mutations, but the results can only suggest the disease or help rule it out rather than confirm it.

Management

Treatment regimens have been empiric, with lack of evidence-based medicine approaches. Moreover, there exists no prophylactic or curative treatment for human DM. Aminocaproic acid, an antiprotease agent, has been advocated for long-term management of DM; however, there have been no published clinical data to support drug efficacy. While treatment of vitamin deficiencies can resolve neurologic disease in some animals, therapy with parenteral cyanocobalamin or oral alpha-tocopherol did not affect neurologic progression in a study of DM affected dogs. Physical rehabilitation regimens have been advocated for management of DM. Overall, long-term prognosis is considered poor.

HANSEN TYPE 1 INTERVERTEBRAL DISC DISEASE

See also Chapter 15, Musculoskeletal Disorders.

Definition/Overview

Herniation of degenerate nucleus pulposus can result in sudden onset of clinical signs, ranging from spinal pain to the loss of motor function and pain sensation. This is most common in the thoracolumbar spinal column but can affect the cervical spinal cord as well. While most reports in the veterinary literature relate to dogs, intervertebral disc extrusions are also reported in cats.

Etiology

Herniation of the nucleus pulposus through the annulus of the disc and extrusion of nuclear material into the spinal canal, resulting in concussion of the spinal cord and concurrent compression.

Pathophysiology

Hansen type 1 IVDD is herniation of the nucleus pulposus through the annular fibers and extrusion of nuclear material into the spinal canal. The condition is typically associated with chondroid disc degeneration. The disc extrudes through the dorsal annulus, causing ventral, ventrolateral, or circumferential compression of the spinal cord. Acute disc extrusion is characterized by the presence of soft disc material within the vertebral canal and extradural hemorrhage. Chronic disc extrusion is characterized by extradural fibrous adhesions around the herniated disc material, which has often become a hard mineralized mass. Hansen type 1 IVDD typically affects chondrodystrophic breeds and has an acute onset. However, large nonchondrodystrophic breeds of dog such as the Dobermann and Labrador Retriever may also be affected. The Dachshund has the highest incidence, but other frequently affected breeds include the French Bulldog, Pekingese, Welsh Corgi, Beagle, Lhasa Apso, and Miniature Poodle. In Dachshunds, severe disc degeneration denoted by presence of mineralization on spinal radiography is highly heritable. Genetic investigations have recently identified an FGF4 retrogene insertion on chromosome 12 associated with the development of Hansen type 1 intervertebral disc extrusions and chondrodystrophy across several dog breeds.

Hansen type 1 IVDD most commonly occurs within the thoracolumbar region of chondrodystrophic breeds. The thoracolumbar junction (T12–T13 to L1–L2) accounts for the highest incidence of all disc lesions. The incidence of thoracolumbar IVDD progressively decreases from T12–T13 caudally. The most common site for Hansen type 1 IVDD in large, nonchondrodystrophic breeds is the interspace between L1 and L2.



FIGURE 14.41 An arched back (kyphosis) is often indicative of thoracolumbar pain.

Clinical Presentation

Onset of neurologic signs may be peracute (<1 hour), acute (<24 hours), or gradual (>24 hours). Dogs presented with peracute or acute thoracolumbar disc extrusions may manifest clinical signs of spinal shock or Schiff–Sherrington postures. These indicate acute and severe spinal cord injury but do not determine prognosis. The degree of neurologic dysfunction is variable and affects prognosis. Clinical signs vary from spinal hyperesthesia only to paraplegia with or without nociception. Dogs with pain only are usually reluctant to walk and may show kyphosis (Figure 14.41); these dogs often have myelographic, CT, and MRI evidence of substantial spinal cord compression. Dogs with paraplegia and lack of nociception usually have undergone acute and severe disc extrusions (Figure 14.42).

Diagnosis

The initial diagnosis of IVDD is obtained from the signalment, history, and neurologic examination. Differential diagnoses to be considered include trauma, fibrocartilaginous embolism, discospondylitis, neoplasia, and meningomyelitis. Diagnosis of thoracolumbar



FIGURE 14.42 Typical posture adopted by dogs with paraplegia.

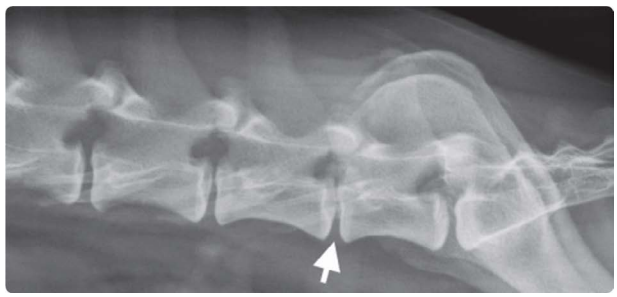


FIGURE 14.43 The radiographic characteristics of intervertebral disc disease are highlighted in this radiograph at L6–L7 (arrow).

disc extrusion and/or protrusion is confirmed by cross-sectional imaging and surgery.

Survey spinal radiography can help to determine the diagnosis and site of a thoracolumbar disc extrusion if radiographic signs are well defined and consistent with neuroanatomic localization. Radiographic findings signifying suspected IVD extrusion include the following (Figure 14.43):

- Narrowing of the IVD space
- Wedging of the disc space
- Narrowing of the intervertebral foramen
- Mineralized material in the spinal canal or superimposed over the intervertebral foramen

As survey radiographs identify the correct site of disc extrusion in only about 70% of cases, further imaging, such as myelography or cross-sectional imaging (CT, MRI), is strongly recommended prior to surgery.

CT or MRI is used alone or as an adjunct to myelography to delineate lateralization of extruded disc material and lesion extent. CT alone has been shown to be more accurate than myelography at identifying the major site of disc herniation and has the advantage of being a more rapid test with fewer side effects than myelography. Mineralized disc material and acute hemorrhage can be identified in the vertebral canal using noncontrast-enhanced CT (Figure 14.44). Acutely extruded disc material typically is recognized as a heterogeneous hyperattenuating extradural mass. The attenuation of the disc material increases with the degree of mineralization. Chronically extruded disc material has a more homogeneous hyperattenuating appearance.

MRI provides a more sensitive technique in recognition of spinal cord pathology (e.g., edema and hemorrhage) and 3D delineation of the spinal cord compression, allowing for an accurate surgical approach and determining the extent of surgical decompression required. MRI is considered the best method for early recognition of in situ disc degeneration and for determining localization and extent of extruded disc material within the epidural space (Figure 14.45). MRI may have diagnostic value in detecting myelomalacia. Findings from a recent study in dogs with IVD extrusion and lack of nociception suggested that an area of hyperintensity >7 times the length of L2 on T2-weighted

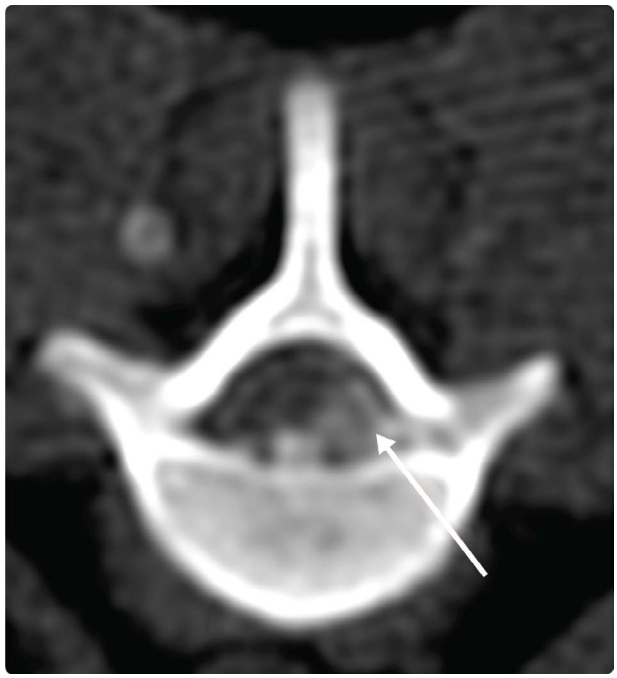


FIGURE 14.44 Transverse CT scan of the lumbar spinal column at the site of an acute mineralized intervertebral disc extrusion (arrow).

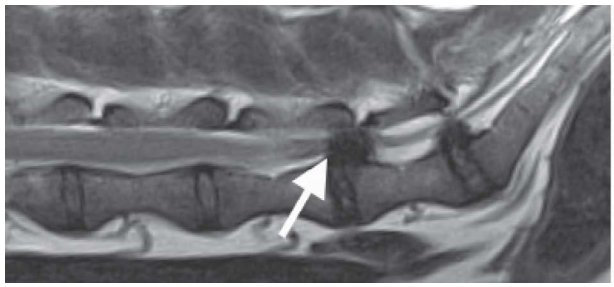


FIGURE 14.45 Sagittal T2-weighted MR image of the lumbar spine of the dog in **Figure 14.43**. An acute mineralized disc extrusion (arrow) is seen to compress neural tissue at L6/7.

sagittal images may allow for a presumptive diagnosis of myelomalacia.

Management

Indications for nonsurgical treatment of thoracolumbar IVDD include a first-time incident of spinal pain only, mild-to-moderate paraparesis, and the financial constraints of the client. The last is the only reason for nonsurgical treatment of a recumbent patient, which should always be considered a surgical candidate, if possible. Dogs can be managed with strict cage rest for 4–6 weeks combined with pain relief using anti-inflammatory drugs, opioids, and muscle relaxants. GI protectants also may be necessary with use of anti-inflammatory therapies. Never use NSAIDs in combination with corticosteroids, as gastric ulcers can result, and in some cases, these may lead to the death of the animal. Acupuncture also has been advocated as a treatment for pain management. Dogs should be monitored closely for deterioration of neurologic status. If pain persists or the neurologic status worsens, surgical management is recommended. Studies have shown that recovery rates in nonambulatory dogs are lower and recurrence rates higher following conservative rather than surgical treatment. Success rates for conservative management of ambulatory dogs with pain only or mild paresis range from 82% to 100%. More recent retrospective studies of conservatively managed dogs with thoracolumbar disc disease documented 30%–50% recurrence rates in dogs with minimally affected ambulatory status. Recurrence of spinal pain in dogs with thoracolumbar IVDD that are conservatively managed usually occurs within 6 months to 1 year from onset of the initial clinical signs. Methylprednisolone sodium succinate is not recommended for the treatment of this disease due to the lack of demonstrated efficacy and the side effects.

Indications for surgical management of thoracolumbar IVDD include spinal pain or paresis unresponsive to medical therapy, recurrence or progression of clinical signs, nonambulatory paraparesis or paraplegia with intact nociception, and paraplegia without nociception for <24–48 hours. Prolonged loss of nociception (>48 hours) carries a poor prognosis, and owners should be made aware of this prior to surgery. However, it is often difficult to know when nociception was lost; in addition, recovery has been observed in dogs that had surgery >5 days after the onset of paraplegia. There is currently no consensus regarding the impact of the duration of signs prior to treatment on outcome in dogs with thoracolumbar intervertebral disc extrusion, with variable findings among several studies. However, there is some recent evidence to suggest that an interval of >12 hours between onset of nonambulatory status and surgery might increase the risk of progressive myelomalacia in paraplegic dogs with absent deep pain perception. It has also been suggested that an overnight delay to performing decompressive surgery could increase the risk of clinically meaningful deterioration in nonambulatory dogs with thoracolumbar intervertebral disc extrusion. As a result, while even deep pain perception negative dogs can recover following a delay of >48 hours after losing ambulatory function, it is reasonable to suggest that prompt intervention should be sought in severely affected (nonambulatory) patients and that unnecessary delays should be avoided.

Surgery includes spinal cord decompression by removal of extruded disc material. Chronicity of disc extrusion at the time of surgery may influence the ease with which extruded disc material can be removed.

HYDRATED NUCLEUS PULPOSUS EXTRUSION (HNPE)

Definition/Overview

Included in the degenerative disease category due to the variable degree of degenerative change associated with the affected intervertebral disc, hydrated nucleus

pulposus extrusion (HNPE) is a relatively recent addition to the list of terms used to describe forms of intervertebral disc disease in dogs. To reflect the characteristic clinical and diagnostic imaging features of the condition, this condition is also sometimes referred to as "acute compressive HNPE."

Etiology

Acute compressive HNPE is associated with the presence of well-hydrated nucleus pulposus material in the vertebral canal, leading to a variable degree of spinal cord compression.

Pathophysiology

The underlying pathophysiology leading to the extrusion is not fully understood but differs from Hansen type 1 intervertebral disc extrusion in that the extruded material is typically only minimally to nondegenerated. It is possible that a small tear in the annulus fibrosus occurs acutely following sudden biomechanical changes, with a resulting extrusion of hydrated nuclear material into the vertebral canal ventral to the spinal cord. In contrast to acute noncompressive nucleus pulposus extrusion (ANNPE), the hydrated material then remains in the vertebral canal of sufficient volume to cause spinal cord compression.

Clinical Presentation

The vast majority of reported cases of HNPE occur in the cervical region (although it can also affect the thoracolumbar region), resulting in a characteristic clinical presentation of acute-onset tetraparesis or tetraplegia. The acute onset typically occurs spontaneously without an inciting traumatic event or exercise and is followed by a short period of progression over 24–48 hours in most cases. HNPE is most often associated with symmetrical neurological deficits, as opposed to the lateralization typically seen with ANNPE or ischemic myelopathies such as FCEM. In contrast to Hansen type 1 intervertebral disc extrusion, cervical HNPE typically presents without evidence spinal hyperesthesia but with more severe neurological deficits, leading to tetraplegia with reduced ventilation in some cases. HNPE is predominantly seen in middle-aged or older dogs without any specific breed predispositions, affecting both chondrodystrophic and nonchondrodystrophic breeds.

Diagnosis

The characteristic clinical presentation of an acute onset, symmetrical, nonpainful myelopathy localized to the cervical region (C1–C5 or C6–T2 spinal cord segments), with a short progressive phase, allows a high index of suspicion for a presumptive diagnosis of HNPE. However, advanced imaging is required to confirm the diagnosis and exclude differential diagnoses such as Hansen type 1 intervertebral disc extrusion, ANNPE, and fibrocartilaginous embolic myelopathy (FCEM). The diagnostic imaging modality of choice for diagnosing HNPE is MRI (Figure 14.46), with the following characteristic features reported:

- Ventral, midline extradural material overlying an intervertebral disc, with features of hydration (T2-weighted hyperintense, T1-weighted hypointense)
- A characteristic bilobed, or "seagull" shaped appearance to the extradural material
- Spinal cord compression at this level, with or without an adjacent focal intramedullary T2-weighted hyperintensity
- The affected intervertebral disc is narrowed with a reduced volume of T2-weighted hyperintense nucleus pulposus signal

Although a diagnosis of HNPE is typically made using these MRI features, a recent study has suggested

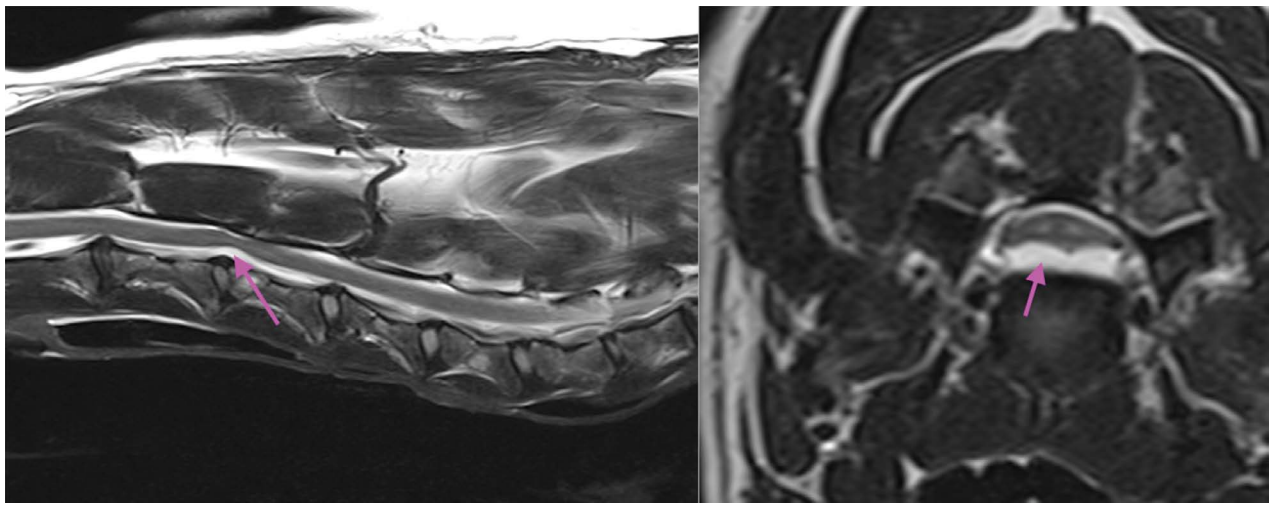


FIGURE 14.46 A T2W sagittal (left) and transverse (right) image of the cervical spinal cord of a dog with a peracute onset of tetraparesis. There is a ventral, midline extradural mass overlying the C3–C4 disc space with features of hydration (T2-weighted hyperintensity) which exhibits the characteristic bilobed, or "seagull" shaped appearance (arrow on right) of HNPE.

that contrast-enhanced CT is also a feasible means of reaching a diagnosis with a sensitivity of 91% and specificity of 100% reported. In that study, HNPE was characterized by the presence of compressive extradural hypodense material immediately dorsal to an intervertebral disc, with rim enhancement and narrowing of the affected disc.

Management

Both medical and surgical management options are described for HNPE in dogs. Recovery is typically rapid and complete regardless of treatment modality, with the majority of dogs returning to ambulatory function within 1 week. Unsuccessful outcomes are rare and typically involve complications in dogs presenting with tetraplegia and compromised ventilatory function. However, it should also be noted that recovery of ambulation has been reported even in these most severely affected dogs following surgery.

Medical management usually consists of restricted exercise in combination with appropriate nursing care, physical therapy, and rehabilitation according to the severity of neurological dysfunction. Dogs presenting with tetraplegia should be assessed for reduced respiratory function as they may require mechanical ventilation. Although typically a nonpainful condition, appropriate analgesia should be administered according to examination findings.

Surgical treatment typically involves performing a decompressive ventral slot procedure of the affected intervertebral disc. Although surgical management has often been recommended for cases with severe signs and obvious spinal cord compression, a recent retrospective study did not find a difference in outcome between dogs managed medically or surgically for cervical HNPE. However, since most unsuccessful outcomes or deaths following cervical HNPE have involved tetraplegic dogs with reduced respiratory function, it is possible that these most severely affected patients may benefit from surgical management.

ACUTE NONCOMPRESSIVE NUCLEUS PULPOSUS EXTRUSION

Definition/Overview

Various terms have been used to describe this type of intervertebral disc herniation, including high-velocity, low-volume disc extrusion; traumatic intervertebral disc extrusion; intervertebral disc explosion; missile discs; and Hansen type 3 intervertebral disc disease. Over time, most of these terms have fallen out of favor, and given that Hansen classification system did not describe a type 3, the use of Hansen type 3 in particular for this purpose has been discouraged. Most reports of this condition describe a peracute extrusion of nondegenerated (hydrated) nucleus pulposus that results in spinal cord contusion with minimal compression, typically occurring at exercise with or without external trauma. Based on these characteristics, the term acute noncompressive nucleus pulposus extrusion (ANNPE) has become widely adopted in the veterinary literature as the most appropriate and descriptive terminology for this condition in dogs and cats.

Etiology

A peracute extrusion of nondegenerated (hydrated) nucleus pulposus that results in spinal cord contusion with minimal compression, typically occurring at exercise with or without external trauma.

Pathophysiology

The normal (nondegenerated) intervertebral disc is comprised of a well-hydrated, gelatinous nucleus pulposus, surrounded by a dense, fibrous annulus fibrosus. As a result of the lamellar structure of the annulus fibrosus, the annulus fibrosus provides strength as well as mobility to the vertebral column. However, when the intervertebral disc is subjected to supraphysiological forces during moments of brief exertion (e.g., running, twisting, jumping to catch a ball) or external forces (e.g., blunt trauma), the annulus can suddenly rupture. In the nondegenerated disc, this can lead to a sudden extrusion of a relatively small volume of nuclear material at great force, which then impacts the spinal cord causing a primarily contusive injury. As a result of the well-hydrated nature of the extruded material, it can then dissipate and be resorbed, leaving minimal to no spinal cord compression. In some cases, the material can even penetrate the dura, recently referred to as an intradural/intramedullary intervertebral disc extrusion. Given the typically nonsurgical nature of the condition and good prognosis in most cases, histopathological descriptions of ANNPE are rare. However, postmortem findings in similar cases have historically revealed tears in the dorsal annulus fibrosus of affected dogs, with evidence of nondegenerated nucleus pulposus material present in the vertebral canal.

Clinical Presentation

In dogs, ANNPE typically presents with a very characteristic peracute onset myelopathy (ranging from ataxia and paresis to plegia of the limbs distal to the lesion) occurring during strenuous exercise or associated with external trauma (in which case it is sometimes referred to as traumatic intervertebral disc extrusion). Clinical signs are usually nonprogressive after the first 24 hours and often quite markedly lateralized, with asymmetrical deficits reported in up to 90% of dogs with ANNPE. Another characteristic feature associated with ANNPE is spontaneous vocalization at the onset of signs, which is often described in dogs, although clinical examination usually reveals only mild to no spinal hyperesthesia on palpation. The thoracolumbar junction is the most commonly affected region of the vertebral column, as seen with Hansen type 1 intervertebral disc extrusions,

although ANNPE can also occur in the cervical region. When ANNPE occurs in the thoracolumbar region, the peracute onset myelopathy may be associated with a Schiff–Sherrington posture, as well as signs of spinal shock in the affected limb(s). Although these signs do not have prognostic significance, they must be recognized on examination to ensure an accurate neuroanatomical localization. For example, reduced withdrawal reflex and limb tone in the affected limb(s), in the presence of an intact patella reflex, perineal reflex, and thoracolumbar cutaneous trunci cutoff, suggests a lesion affecting T3–L3 spinal cord segments with associated spinal shock. Based on this characteristic clinical presentation, important differential diagnoses for ANNPE in dogs and cats include other peracute lesions such as an ischemic myelopathy (e.g., fibrocartilaginous embolic myelopathy, FCEM) or vertebral fracture/luxation where there is a history of external trauma.

Although there are fewer descriptions of feline ANNPE in the literature, more cats have been reported to present with symmetrical clinical signs compared to dogs, and up to 75% of cats with ANNPE present following external trauma.

Diagnosis

Based on the particularly characteristic clinical presentation, a high index of clinical suspicion for ANNPE can typically be reached prior to performing diagnostic tests. The main differential diagnosis in dogs and cats with a peracute onset, nonprogressive, minimally painful (after initial onset), lateralized signs of spinal cord dysfunction is an ischemic myelopathy (typically caused by an FCE in dogs). If there is a history of trauma, vertebral fractures and luxations should be excluded as a priority. Plain spinal radiographs can be used as an initial step in such cases and may also reveal a narrowed intervertebral disc space, which can be seen with ANNPE. In cases where there remains a clinical index of suspicion for trauma despite unremarkable radiographs, advanced imaging such as CT should be considered to fully exclude fractures or luxations.

In order to make a more specific diagnosis, spinal MRI is typically required which can be used to differentiate between ANNPE and ischemic myelopathy using reported imaging criteria. The MRI features that can be used to make a diagnosis of ANNPE are outlined and demonstrated in Figure 14.47.

- Focal intramedullary T2-weighted hyperintensity of the spinal cord
- Spinal cord lesion located overlying an IVD
- Reduced volume of T2-weighted hyperintense nucleus pulposus signal in the affected IVD
- Mild narrowing of the affected IVD in midsagittal view
- Small volume extradural material (T2-weighted hyperintense, T1-weighted hypointense) dorsal to the IVD with minimal to no spinal cord compression

Management

As there is no significant spinal cord compression associated with ANNPE, treatment is focused on supportive medical management in order to aid functional recovery from the primarily contusive injury, and to minimize complications. Although there are currently no treatments with documented benefit in the management of secondary spinal cord injury in dogs, it is important to ensure that adequate systemic blood pressure and oxygenation are maintained to optimize spinal cord perfusion in cases with a concurrent history of trauma, for example. As around half of dogs with ANNPE present with spinal hyperesthesia on examination, nonsteroidal anti-inflammatory or opioid analgesia may be indicated. The mainstay of subsequent medical management involves supportive nursing care for recumbent patients (regular bladder expression if required, monitoring for skin abrasions and urine scald, nutritional support),

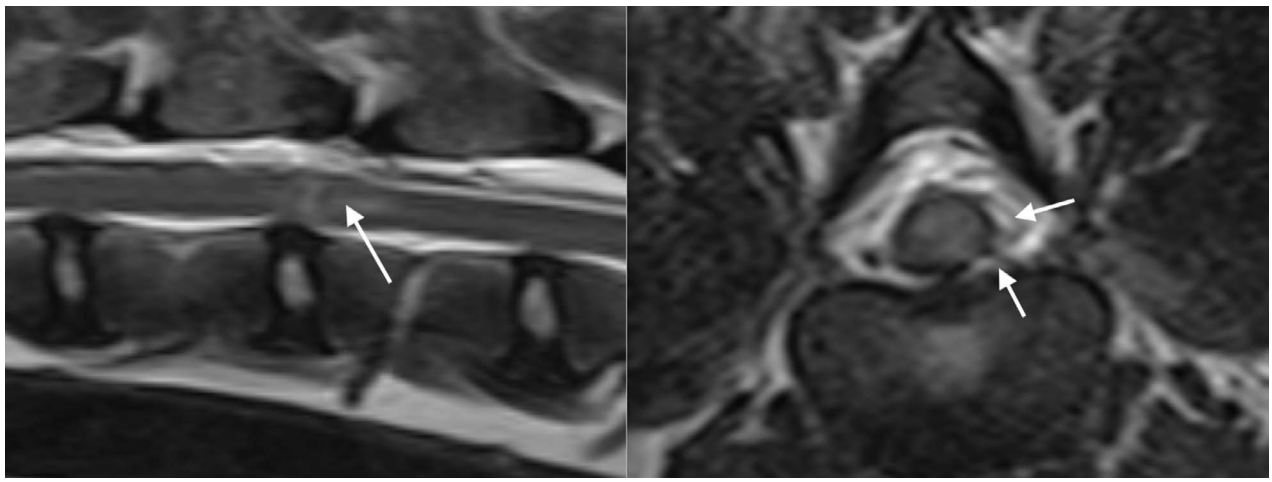


FIGURE 14.47 A T2W sagittal (left) and transverse (right) image of the thoracolumbar spinal cord of a dog with a peracute onset of paralysis due to an ANNPE. There is a focal intramedullary spinal cord T2-weighted hyperintensity overlying the L2–L3 disc space. The nucleus pulposus signal at this site has a reduced volume, and there is a small volume of extradural material around the cord (arrows on right) with minimal to no associated compression.

and physical therapy adapted according to the severity of associated neurological deficits.

As with other causes of acute spinal cord injury, outcome following ANNPE is largely dependent of the severity of neurological dysfunction on examination. While most dogs will return to ambulatory function, those presenting monoplegic, paraplegic, or tetraplegic will often retain gait abnormalities in the long term. Dogs that are paraplegic with absent deep pain perception due to ANNPE have a guarded prognosis, with few examples of recovery of ambulation in such dogs reported. Diagnostic imaging findings may also provide some prognostic information, with an increased intramedullary lesion size on MRI suggested to be associated with a poorer functional outcome. Variable degrees of urinary and fecal incontinence are also reported following thoracolumbar ANNPE, mainly in more severely affected dogs, with long-term urinary and fecal incontinence seen in 18% and 54% of paraplegic dogs with intact deep pain perception, respectively, in one study. Both severity of signs (paraplegia with or without deep pain perception) and MRI lesion size (>40% of spinal cord transverse cross-sectional area) were found to be associated with the subsequent development of long-term urinary and fecal incontinence.

Although there is limited number of cases in the literature on which to evaluate outcome following ANNPE in cats, a return to ambulatory function and continence was seen in most cases in a recent case series.

HANSEN TYPE 2 INTERVERTEBRAL DISC DISEASE

Definition/Overview

Herniation of the annulus fibrosus can result in slow, progressive clinical signs ranging from intermittent spinal pain through ataxia and paresis to the loss of motor function in the later stages. This is most common in the thoracolumbar spinal column but can affect the cervical and lumbosacral spinal cord as well, where it can be accompanied by degenerative changes of the vertebrae, creating a more dynamic/position-associated disease. (See Cervical Spondylomyelopathy and Degenerative Lumbosacral Syndrome.)

Etiology

Herniation of the annulus of the disc (protrusion) into the spinal canal resulting in spinal cord compression.

Pathophysiology

Hansen type 2 IVDD is annular protrusion caused by shifting of central nuclear material and is commonly associated with fibroid disc degeneration. The annulus fibrosus slowly protrudes into the spinal canal to cause spinal cord compression. The chronic compression can lead to focal ischemia and other microvascular derangements of the spinal cord. Type 2 IVDD usually occurs at the mobile points of the spinal column and is more common in older, nonchondrodystrophic breeds of dog. It is not uncommon to identify multiple affected disc spaces. Chronic spinal instability may be an underlying predisposition to type 2 IVDD.

Clinical Presentation

The clinical signs of Hansen type 2 IVDD include slowly progressive hindlimb ataxia, weakness, reluctance to rise or jump on furniture, and difficulty climbing stairs. Onset of clinical signs is considered chronic and progressive, although acute exacerbations of signs are not uncommon. Localization is focal with asymmetrical or symmetrical weakness. Paraspinal hyperesthesia may or may not be present.

Diagnosis

Diagnosis may be suspected on routine spinal radiographs that show the presence of degenerative changes in the spinal column, such as spondylosis. Myelography, CT myelography, or MRI is necessary to locate the spinal cord compression (Figure 14.48).

Management

Medical therapy is indicated in animals with early-onset type 2 IVDD and mild deficits. It also is indicated in those animals that are concurrently afflicted with suspected DM. Medical therapy involves administration of NSAIDs or corticosteroids. The use of a muscle relaxant such as diazepam or methocarbamol should be considered in patients with spinal hyperesthesia. Clinical signs do not always respond to medical therapy and often return after discontinuation of these therapies. Surgical decompression may offer a better long-term outcome.

The type of surgical decompression depends on the location of the lesion. A hemilaminectomy is performed for lesions in the thoracic spine and lumbar spine cranial to L5 (Figure 14.49a, b). A dorsal laminectomy is performed if the lesion is located in the lumbosacral area (Figure 14.50). Typically, type 2 disc protrusions require more spinal cord manipulation to relieve the compression from the annulus. The protrusion is usually excised; however, decompression by laminectomy alone may also be adequate in cases where the disc material is irretrievable. Lateral corpectomy is an alternative method for decompression of ventral and lateroventral

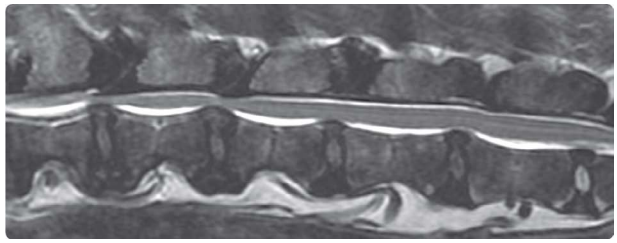


FIGURE 14.48 Sagittal T2-weighted MR image of the thoracolumbar spinal column in a dog with multiple type 2 intervertebral disc herniations.

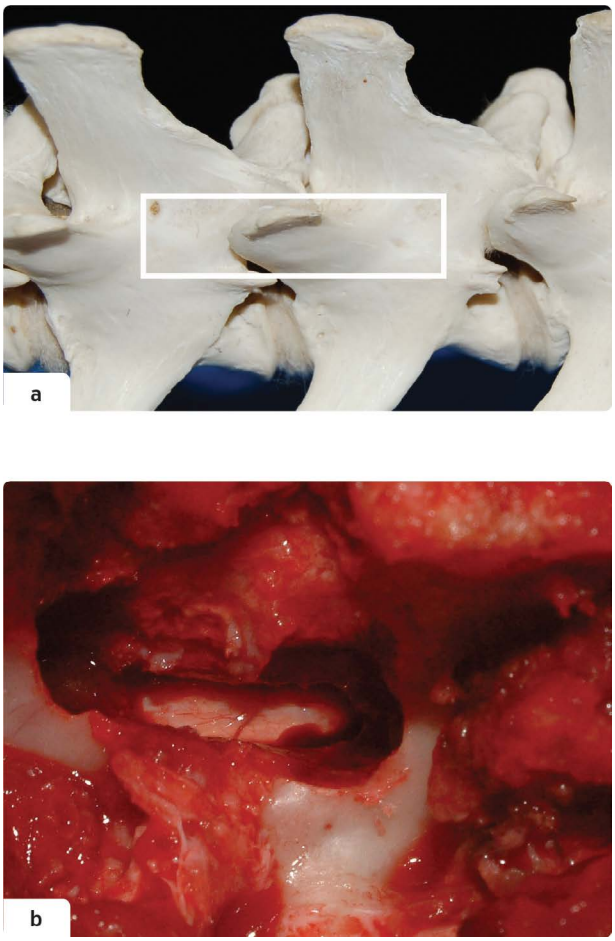


FIGURE 14.49 (a) The surgical "window" for a hemilaminectomy is illustrated on a spinal column model. (b) The spinal cord is visible through the hemilaminectomy window made in the vertebrae.

thoracolumbar disc disease. Often the neurologic status of the animal is worse after surgery, but this is usually temporary. Often dogs with chronic clinical signs have multiple IVDD herniations, which complicate surgical decision making.

If surgery is instituted early, prognosis is usually fair to good when patients are considered refractory to medical therapy. If the disease has coursed for several months and is associated with severe neurologic signs (i.e., paraplegia), the prognosis is considered guarded.

CERVICAL SPONDYLOMYELOPATHY (WOBBLER SYNDROME)

Definition/Overview

Cervical spondylomyelopathy describes a syndrome of compression of the cervical spinal cord as a result of degenerative and congenital changes in the cervical spine. There are many names for this syndrome, including wobbler syndrome, caudal cervical stenotic myelopathy, cervical malformation/malarticulation, and disc-associated wobbler syndrome (DAWS). Classically, this is thought of as a disease of large (e.g., Dobermann, Dalmatian) and giant breed (e.g., Great Dane, Mastiff breeds, Bernese Mountain dog) dogs, although identical changes also occur in toy and small breed dogs such as Chihuahuas and Yorkshire Terriers.

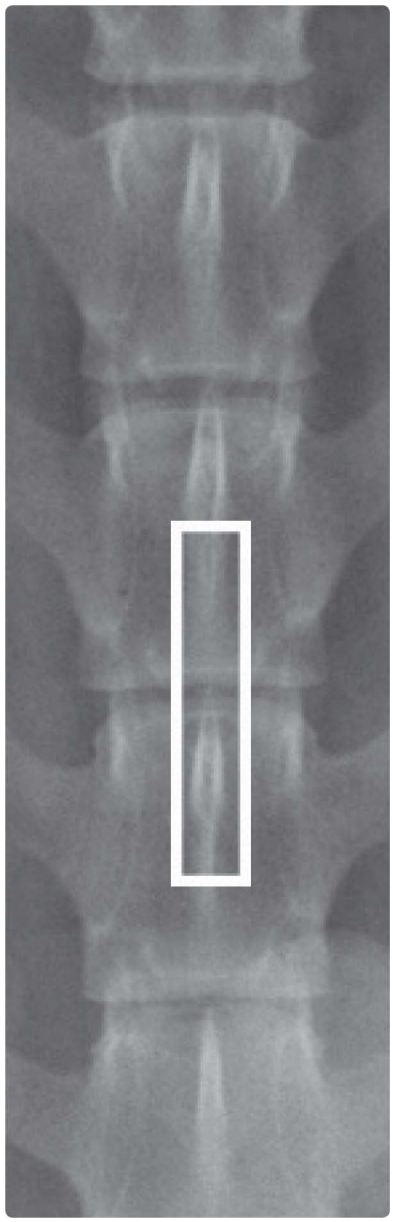


FIGURE 14.50 The surgical "window" for a dorsal laminectomy is illustrated in this lumbar vertebral radiograph.

Etiology

The etiology of these changes is most likely multifactorial. Genetic factors probably play a role, as the disease is seen in specific breeds of dog, although a pattern of inheritance has not been established in commonly affected breeds. Overnutrition and excess calcium supplementation in the first year of life has been implicated

in Great Danes, but correction of these feeding patterns has not prevented occurrence of the disease in this breed. It has also been postulated that conformation of the head and neck influences the development of lesions. However, a study on Dobermanns failed to find a correlation between various body dimensions and radiographic or neurologic signs. It is believed by many that the degenerative changes seen in this syndrome ultimately result from relative instability of the cervical spinal column.

Pathophysiology

Progressive spinal cord compression results from both congenital stenosis and degenerative changes in the vertebral column. The changes can be listed as:

- Hypertrophy and protrusion of the annulus fibrosus, often associated with "tipping" of vertebrae. This change is classically associated with DAWS in Dobermanns.
- Hypertrophy of the ligamentum flavum and dorsal longitudinal ligament. These changes are also common in DAWS.
- Hypertrophy of synovial membrane and formation of synovial cysts at the articular facets, occurring in giant breed stenotic myelopathy and associated with remodeling of the facets.
- Stenosis of the vertebral canal; historically, this has been described in giant breed stenotic myelopathy. However, there is evidence that Dobermanns also have a relative stenosis of their cervical vertebral canal.
- Degenerative joint disease and remodeling of the articular processes, commonly found in giant breed stenotic myelopathy.

Clinical Presentation

Clinical signs include progressive ataxia, tetraparesis, and, sometimes, neck pain (Figure 14.51). Signs in the hindlimbs are more severe than the forelimbs. Dogs with caudal cervical compression frequently have a short, stilted forelimb gait with a dysmetric, disconnected hindlimb gait. Nerve root entrapment can cause forelimb lameness and muscle atrophy; in particular, compression of the suprascapular nerve can produce marked atrophy of the supraspinatus and infraspinatus muscles, making the scapular spine easily palpable. Although this is typically a chronic progressive disease, acute onset of severe signs can occur.



FIGURE 14.51 An 8-year-old Dobermann with cervical vertebral spondylomyelopathy (Wobbler syndrome) presenting with neck pain.

Diagnosis

Survey radiographs of the cervical spine may show degenerative changes typical of this syndrome but cannot be used to identify sites of spinal cord compression. Stressed views should not be taken, as compression of the spinal cord can be exacerbated. Myelography combined with CT used to be the gold standard for diagnosis of cervical spondylomyelopathy and for surgical planning. Linear traction views of the myelogram are used to determine whether compression can be addressed by distraction and fusion of vertebrae (i.e., a dynamic lesion). However, MRI has largely replaced CT and myelography. The advantages of MRI include greater accuracy at detecting spinal cord compression and parenchymal disease in addition to decreased morbidity associated with this imaging modality (Figure 14.52a–d).

Management

Dogs with neurologic deficits should be treated surgically, as this is a chronic progressive disease. However, many owners cannot afford, or do not wish, to have surgery performed. Medical therapy can be considered in such cases and in dogs with mild deficits. Medical management includes treatment of pain with anti-inflammatory drugs and muscle relaxants and restriction of unmonitored activity combined with controlled exercise and physical therapy. Anti-inflammatory doses of corticosteroids have been used to reduce vasogenic edema but do not appear to influence the outcome. Acupuncture can be useful to control chronic pain in some dogs. Dogs managed in this way should be monitored weekly to biweekly to allow early recognition of deterioration and recommendation for surgical intervention.

The aims of surgery are to decompress and/or stabilize the cervical spine. Surgical strategies include the ventral slot (to remove disc material from the canal), distraction/stabilization techniques (to treat lesions responsive to traction) (Figure 14.53), and dorsal laminectomy (to remove dorsal compression or address multiple disc protrusions). Postoperative rehabilitation of patients is critical to their recovery, and owners need to be fully informed about the implications of rehabilitating a nonambulatory large or giant breed dog. Rehabilitation includes passive range-of-motion exercises and massage in the recumbent dog, hydrotherapy, and controlled exercise. Recovery of these dogs can be prolonged (6–12 weeks or more) due to the chronic nature of the disease.

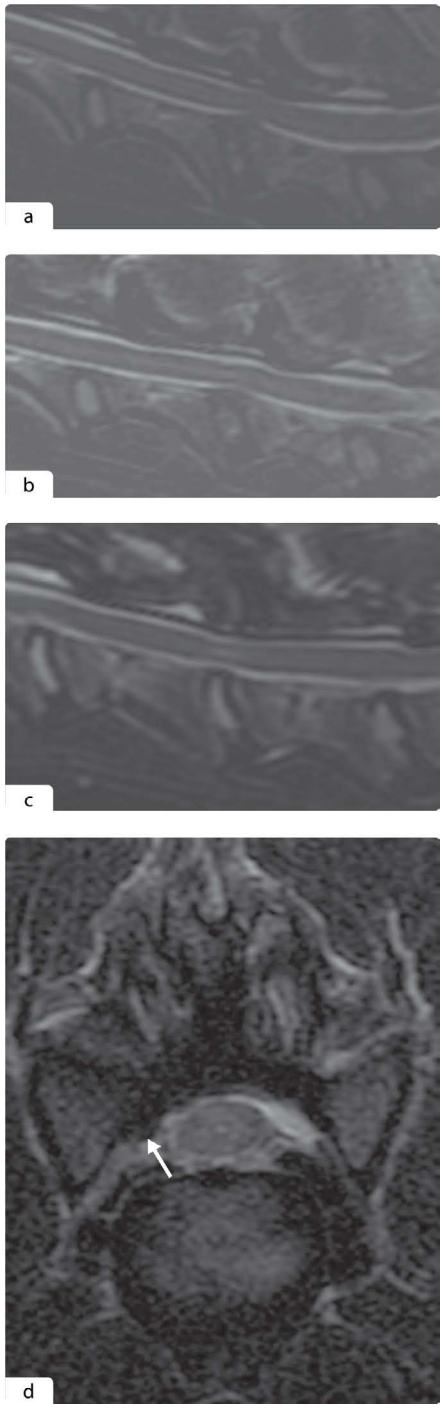


FIGURE 14.52 (a) T2-weighted sagittal caudal cervical MR image of the Dobermann in **Figure 14.51**. A ventrally compressive lesion is seen over the disc space of C6–C7. **(b)** Following mild traction applied to the neck, the MRI is repeated and shows a concurrent mild reduction in the degree of ventral compression, indicating a traction-responsive lesion. **(c)** T2-weighted sagittal caudal cervical MR image of a 1-year-old Great Dane with chronic, progressive tetraparesis. Mild compression of the cord can be seen, as can central cord hyperintensity related to the chronic compression. **(d)** T2-weighted transverse MR image at the level of the compression seen in (c), confirming that the compression is due to articular process malformation (arrow) and concurrent stenosis of the spinal canal.



FIGURE 14.53 Lateral postoperative radiograph of the cervical spine of the dog with the traction-responsive compression in **Figure 14.52**. A distraction fusion surgery has been performed using cancellous screws and polymethylmethacrylate cement.

DEGENERATIVE LUMBOSACRAL STENOSIS

Definition/Overview

Lumbosacral stenosis (cauda equina syndrome, lumbosacral malarticulation and malformation, lumbosacral instability, lumbosacral spondylopathy) is common in middle- to old-aged, large-breed dogs and represents a plethora of orthopedic abnormalities associated with the lumbosacral anatomy. Degenerative lumbosacral stenosis is also being recognized with increasing frequency in the cat.

Etiology

Neurologic abnormalities occur coincident with tissue (joint capsule, interarcuate ligament, disc, bone, fibrous adhesions) impingement on the cauda equina, the nerve roots at the level of the foramina, or the vascular supply. Transitional vertebrae have been identified as a predisposing cause of cauda equina syndrome in German Shepherd Dogs and other breeds.

Pathophysiology

The pathologic process begins with Hansen type 2 IVD degeneration followed by osteophyte formation of the L7–S1 endplates and articular processes. The syndrome is characterized by stenosis of the spinal canal from vertebral subluxation and/or stenotic intervertebral foramina. Concurrent with compressive disease, underlying instability may further accentuate the clinical signs, especially in active dogs.

Clinical Presentation

Neuroanatomic localization to the lumbosacral region is determined by the neurologic examination based on signs related to sensory, motor, and autonomic dysfunction. Nonspecific observations include reluctance to rise and hindlimb lameness. Neurologic signs commonly include pain and motor dysfunction as a result of LMN weakness (sciatic, pudendal, caudal nerves). Pain is the most consistent clinical sign and reflective of



FIGURE 14.54 A Labrador Retriever with degenerative lumbosacral disease exhibiting reduced tail tone, hindlimb muscle atrophy, and a weak stance.

compressive or inflammatory processes affecting pain-sensitive structures (nerve root, meninges, periosteum, and joints). It is the opinion of the author that the pain primarily originates from nerve root (radicular pain) compression (particularly L7). The affected patient often stands with the hindlimbs tucked under the caudal abdomen to flex the spine and lessen the nerve root compression (Figure 14.54). Motor dysfunction varies in severity. The patient may have mild-to-severe gait and postural reaction deficits. The gait is frequently short-strided or shuffled. Postural reaction deficits are often asymmetrical, depending on the degree of cauda equina involvement. Reflex dysfunction of the limbs commonly involves those muscles innervated by the sciatic nerve (L6–S1 nerve roots, but L7 and S1 provide the major contribution), particularly the flexor and extensor muscles of the hock. The patellar reflex may appear hyperreflexic due to loss of antagonism from the flexor muscles (pseudo-hyperreflexia). The cranial tibial and gastrocnemius reflexes may be hyporeflexic. The withdrawal reflexes are reduced in the stifle and hock joints. Less commonly, the pudendal and caudal nerves may be involved. The pudendal nerve (S1, S2, and S3) innervates the perineal region, including the external anal and urethral sphincters. The caudal nerves innervate the tail. Decreased tail tone is assessed on palpation and inability to wag. Other less common clinical signs include fecal and urinary incontinence. If micturition dysfunction is suspected, it is important to closely evaluate sensory perception of the perineal region and the anal reflex.

Diagnosis

A diagnosis of lumbosacral syndrome is suspected from the neurologic examination. Definitive diagnosis of degenerative lumbosacral stenosis is difficult because no one test has 100% specificity and sensitivity, leading to false-positive and false-negative results. Dynamic imaging is important to investigate mobility of the joint and concurrent changes in nervous tissue compression. Diagnostic procedures to test for degenerative lumbosacral stenosis include electrophysiology, survey and contrast radiography, CT, and MRI. Survey radiography is useful to rule out other causes of cauda equina syndrome. Abnormal findings associated with degenerative lumbosacral stenosis include osteochondrosis of the sacral endplate, transitional vertebrae, spondylosis, subluxation, sclerosis of the endplates, and bony proliferation of the articular processes.

Stress radiography (extension and flexion views) has been used to identify underlying "instability" of the lumbosacral junction; however, normal dogs might also have evidence of such "instability". MRI is superior to radiography for demonstrating dynamic compression of the neural tissues.

CT has the advantage of better soft tissue and bone resolution. Cross-sectional, dorsal, and sagittal images allow determination of lesion extent. The articular processes, IVDs, and foramina can be evaluated. CT imaging studies should be performed prior to injecting contrast medium into the vertebral canal or subarachnoid space. Abnormalities detected by CT include loss of epidural fat, increased soft tissue opacity in the intervertebral foramen, bulging of the IVD, thecal sac displacement, spondylosis, narrowed vertebral canal, thickened articular processes, and osteophyte formation on the articular processes in the intervertebral foramen.

MRI is superior to CT with regard to soft tissue definition (Figure 14.55). The spinal cord, CSF, IVDs, ligaments, and nerve roots can be directly visualized. MRI may allow early recognition of IVD degeneration and a more accurate assessment of epidural fat displacement, although this is open to overinterpretation.

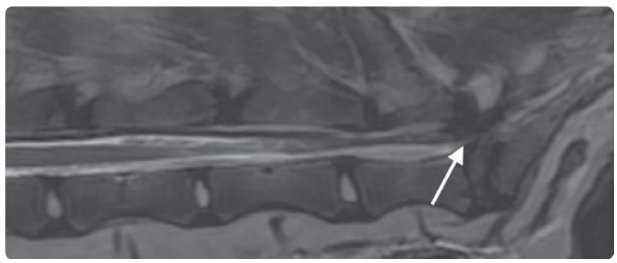


FIGURE 14.55 Sagittal T2-weighted caudal lumbar spinal MR image of the dog in Figure 14.54 confirming marked neural tissue compression at the L7–S1 intervertebral disc space (arrow).

Parasagittal and transverse views can provide evidence of stenosis within the L7–S1 intervertebral foramina. As with radiography, extension and flexion views of the lumbosacral spine can provide evidence of dynamic disease. Importantly, CT and MRI imaging findings may not correlate with the severity of the clinical signs and thus should not be used to predict surgical outcomes or determine the prognosis.

Management

Indications for medical management include the first episode of clinical signs or intermittent pain. Management consists of strict confinement for 8–14 weeks, anti-inflammatory medication using low-dose prednisolone or NSAIDs, and weight loss. The recovery rate with medical management is between 24% and 50%. A recent report described the use of methylprednisolone sodium acetate (40 mg/mL) injections into the lumbosacral epidural space at a dose of 1 mg/kg. The treatment resulted in clinical improvement in 79% and complete resolution of clinical signs in 53% of dogs mildly affected by degenerative lumbosacral stenosis. The protocol included injections at 0, 2, and 6 weeks, with additional injections as needed.

Indications for surgical management include failure of medical management, severe pain, and moderate-to-severe neurologic deficits (in particular incontinence). Surgical techniques include decompression and excision of the proliferative tissue and fixation and fusion of the lumbosacral junction. Surgical decompression is the most common treatment, although distraction–fusion techniques may also be used if indicated. The most crucial aspect of postoperative care is strict cage confinement for 8–12 weeks and a gradual return to fitness. It is important to institute-controlled exercise as part of the physical rehabilitation program. In addition, bladder management involves proper monitoring of bladder emptying to avoid urinary tract infections. If the clinical signs resolve with surgery, then the prognosis is fair to good. Dogs with severe neurologic deficits and urinary and fecal incontinence for more than a few weeks prior to surgery have a guarded to poor prognosis. Rates of postoperative improvement range from 41% to 95%.

SPONDYLOSIS DEFORMANS

Definition/Overview

Degenerative change associated with the vertebrae, most often the vertebral bodies, easily seen on radiographs but rarely a cause of clinical disease.

Etiology

Degenerative, often age-related change.

Pathophysiology

Spondylosis deformans is characterized by formation of bony growths and bridges at the intervertebral spaces.



FIGURE 14.56 Lateral radiograph of the lumbar vertebrae demonstrating ventral bridging spondylosis.

The condition is a common radiographic finding in older dogs along the thoracic and lumbar spine. Most likely spondylosis is associated with degeneration of the annulus fibrosus of the IVD. Presence of spondylosis deformans has been associated with type 2 IVDD and degenerative lumbosacral stenosis; however, these diagnoses are often made independent of the presence of spondylosis.

Clinical Presentation

Spondylosis rarely causes neurologic signs but is occasionally associated with back pain.

Diagnosis

The lesion is radiographically identifiable (Figure 14.56). The osteophyte formation usually does not compress the neural tissue or encroach within the vertebral canal.

Management

NSAIDs or steroids have been reported to lessen spinal discomfort in animals with severe ankylosing spondylosis. Spondylosis deformans is usually an incidental finding and is rarely associated with clinical signs; therefore, the prognosis is good.

SPINAL SYNOVIAL CYSTS

Definition/Overview

Spinal synovial cysts occur in the cervical spine of young large-breed dogs but more commonly involve the thoracolumbar region in older large-breed dogs.

Etiology

Cysts originate from synovial joint lining of vertebral joints.

Pathophysiology

Spinal extradural synovial cysts and ganglion cysts arise from the articular facets. Some authors have referred to both structures as intraspinal cysts due to the confusion of tissue origination. Pathogenesis of synovial cysts has been associated with degenerative disease and trauma. Increased mechanical stress and joint motion may predispose the thoracolumbar junction to osteoarthritis and synovial cyst formation. Histopathology of the cyst reveals fibrous connective tissue with a synovial cell lining.

Clinical Presentation

Clinical signs are consistent with a progressive myelopathy and include paraspinal hyperesthesia.

Diagnosis

Radiographic findings include degenerative changes and remodeling of the articular processes. Myelography demonstrates spinal cord compression, especially on the ventrodorsal view, with attenuation of the contrast column medial to the articular processes. Attenuation of the ventral and dorsal columns (giving an hourglass appearance) is also present on lateral projections. The lesion is better defined using CT myelography and MRI. Cysts will appear as hyperintense lesions on both T2-weighted and short tau inversion recovery (STIR) images (Figure 14.57). Albuminocytologic dissociation is a consistent finding on lumbar CSF analysis.

Management

The treatment often involves surgical decompression and excision of the cyst. Surgical intervention is indicated with severe neurologic deficits and refractory pain. A hemilaminectomy is often performed if one side is affected. The cyst and any protruding disc material are removed. Marked improvements in gait and neurologic deficits occur post surgery.

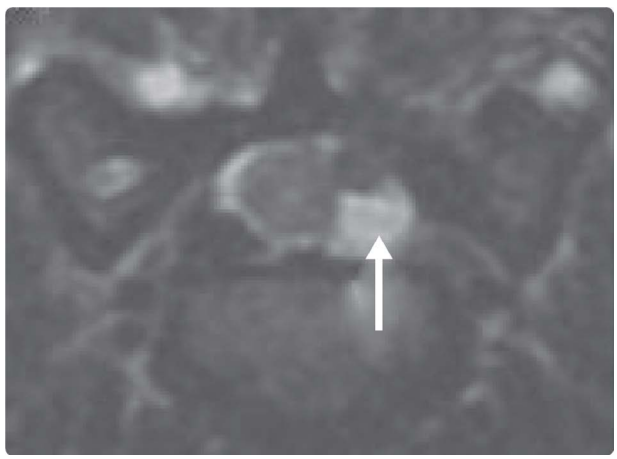


FIGURE 14.57 T2-weighted transverse spinal MR image showing compression of the spinal cord by a laterally situated fluid-filled synovial cyst (arrow).

ANOMALOUS DISEASES

CHIARI-LIKE MALFORMATION SYNDROME AND SYRINGOMYELIA (SEE ALSO BRAIN DISEASE SECTION)

Overview/Definition

Chiari-like malformation syndrome (CLMS), also known as caudal occipital malformation syndrome, and syringomyelia (SM) often occur together, although both may occur independently of the other. SM is a condition characterized by the presence of a fluid-filled cavity (syrinx) or cavities within the parenchyma of the spinal cord. CLMS and SM are most common in toy and small breed dogs, best described in the CKCS and the Brussels Griffon. Less consistently affected breeds are French Bulldogs, Boston Terriers, and Pug dogs. Perhaps surprising, many toy breeds with extreme facial foreshortening, such as the Pekinese, Japanese Chin, and Shi Tzu, are not as predisposed, perhaps reflecting a different skull shape, brain size, and genetic heritage. Brachycephalic cats, especially the Persian, can have CM, but associated SM is not reported.

Etiology

In Cavalier King Charles Spaniels (CKCSs), CLMS/SM is a hereditary condition, possibly autosomal recessive with incomplete penetrance. CLMS is caused by congenital hypoplasia of the supraoccipital bone resulting in overcrowding of the structures within the caudal fossa; this finding is in line with human studies.

A consistent feature is neuroparenchyma disproportion with the "box" (skull and cranial cervical vertebrae) being too "short" for the contents (brain and cranial cervical spinal cord). The reduction in craniofacial bony tissue results in forebrain crowding—the rostral forebrain has a flattened appearance with reduced ventrally displaced olfactory bulbs. The caudal cranial fossa is reduced rostrally by the displaced forebrain and caudally by a short, straight supraoccipital bone (also known as caudal occipital malformation syndrome). Some predisposed breeds such as the CKCS have comparatively big brains. The cerebellum is flattened against the supraoccipital bone, resulting in vermal indentation and herniation of the vermis into or though the foramen magnum. Craniocervical junction overcrowding is compounded by craniocervical junction deformation, including change in angulation of the dens (cervical flexure) and increased proximity of the atlas to the skull and loss of the cerebellomedullary cistern (sometimes referred to as atlanto-occipital overlapping). Overcrowding of the

craniocervical junction results in kinking or elevation of the medulla. In some miniature toy breeds such as the Chihuahua and Pomeranian, cerebellar deformation is not as a prominent feature, especially if they have occipital dysplasia—failure of ossification of the membranous supraoccipital bone thought to be secondary to pressure of the cerebellum against the developing bone. In these breeds, the craniocervical junction abnormalities seem more important to development of clinical signs.

SM is secondary to abnormal CSF flow and is usually associated with CLMS, although it may be associated with other trauma, inflammation, and neoplasia. SM associated with CLMS is predisposed by two morphological phenotypes (or combination of), the first by more extreme brachycephaly and the second by more extreme craniocervical junction deformation. Other factors likely important in the development of SM are reduced CSF absorption through nasal lymphatics, reduced venous drainage, altered neuroparenchymal compliance and conformation of the spinal canal and cord. The pathogenesis of spinal cord fluid cavitation secondary to CSF channel obstruction is debated. The most accepted theory is that CSF in the subarachnoid space fluid enters the spinal perivascular space and then the spinal cord parenchyma because of a mismatch in timing between the arterial pulse peak pressure and CSF pulse peak pressure.

Pathophysiology

Pain in CLMS is thought to relate to failure to equilibrate intracranial pressure due to obstruction of CSF pathways. Intracranial pressure is affected by the systolic pulse, venous drainage, the balance between CSF production and absorption, and microgravitational effects; for example, when being lifted rapidly or with head position. Pain can be exacerbated by Valsalva, a brief increase in intrathoracic pressure, for example when coughing or with abdominal straining.

The pathogenesis of SM appears to be multifactorial (see Etiology), as its dorsoventral size and sagittal extent do not correlate well with a single morphologic abnormality. The location of the syrinx within the dorsal aspect of the spinal cord affecting the dorsal horn is thought to be one mechanism behind the development of pain, specifically neuropathic pain and scratching behavior. Neuropathic pain is secondary to disordered processing of sensory information within the nervous system and results in spontaneous pain, paresthesia, dysesthesia, allodynia, or hyperpathia.

Clinical Presentation

Onset of signs may be acute or chronic in dogs ranging from 6 months to 10 years of age, but no sex predisposition has been identified; most dogs with clinically relevant disease will show signs of CLMS or SM before 4 years of age.

Clinical signs can be seen in dogs with CLMS alone and are usually related to neuropathic pain syndromes. These include vocalization on posture change or on lifting, spinal pain, head and ear rubbing or scratching, aversion to touch, refusal or difficulty jumping or climbing stairs, exercise intolerance/reduced activity, sleep disruption, and behavioral change.

In the presence of SM, neuropathic pain syndromes and neurologic deficits related to spinal cord destruction can present variably. The most common sign of CLMS/SM is pain, predominately isolated to the cervical region, occurring in 35% of affected dogs. "Phantom scratching," where the dogs will attempt to scratch often without making contact with their skin, is the most notable manifestation of these neuropathic pain abnormalities and has been described in affected dogs, ranging from an infrequent to a near constant problem.

Other clinical signs include scoliosis and neurologic deficits relating to cervical spinal cord dysfunction. Tetraparesis, sensory ataxia, and abnormal proprioceptive positioning in all limbs have been noted in dogs with CLMS/SM. Intracranial signs, such as facial paresis and vestibular dysfunction, have also been reported. However, dogs may be completely asymptomatic for CLMS and/or SM.

Diagnosis

These structural abnormalities are best diagnosed with MRI, but they may be clinically silent; therefore, their significance must be carefully considered when such abnormalities are discovered. SM is seen as hyperintensity on T2-weighted MR images and as hypointensity on T1-weighted images; a prominent or dilated central canal can be seen in some dogs. The extent of SM is very variable, with some cases exhibiting a focal cyst-like structure most commonly in the dorsal cervical cord (predominantly gray matter) and others exhibiting multifocal, multiloculated lesions throughout the entire spinal cord (holocord syringomyelia) (Figure 14.58). Suggestive of a "presyrinx" is a local area of T2-weighted FLAIR hyperintensity associated with the central canal. It is important to rule out other concurrent diseases as being the cause of clinical signs, which can be difficult, but performing CSF analysis is important. As CLMS/SM occurs in toy breed and small dogs, it is essential to consider a CSF tap to investigate the possibility of an inflammatory disease and imaging to rule out disc disease. Evaluating the clinical significance of CLMS or SM MRI findings is difficult. In addition to the 2D measurements of skull and cerebellar sizes, it

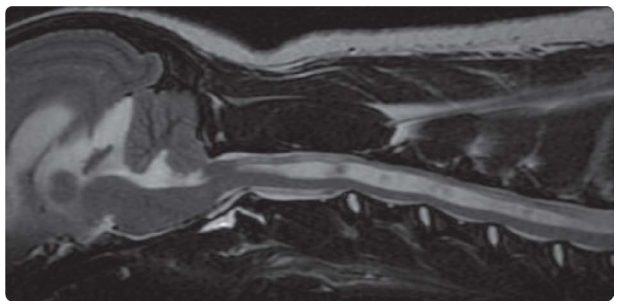


FIGURE 14.58 T2-weighted sagittal cervical spinal MR image. A large, centrally located, fluid-filled cavity can be seen within the spinal cord, representing syringomyelia.

has become apparent that volumetric ratios of the caudal fossa size can be useful in supporting an association with clinical signs.

Management

Treatment may not be necessary in asymptomatic dogs or dogs with mild nonprogressive signs. Dogs exhibiting pain, more severe neurologic deficits, or progressive signs can be treated either medically or surgically. Typically, medical therapy is pursued initially, involving the use of analgesics and drugs that reduce CSF formation. There is poor evidence that pain associated with CLMS will improve with prescription of carprofen alone. There is some evidence of improvement with combination of carprofen and gabapentin and good evidence of improvement with pregabalin.

Furosemide (1–2 mg/kg p.o. q.12 h.) and prednisone (0.5–1.0 mg/kg p.o. q.24 h., tapering dose) are frequently used together in an attempt to decrease CSF production. There is less evidence to support the clinical use of acetazolamide and omeprazole for this purpose, but these drugs are also options.

Clinical signs will progress in approximately 75% of dogs, and approximately 15% will be euthanized. However, despite progressive signs, many dogs with signs of pain and phantom scratching respond to medical management and are considered by their owners to have an acceptable quality of life. Although syrinx width increases over time, the rate of increase is not constant. Many syrinxes appear to rapidly expand within months (or even days) and then can remain remarkably unchanged over years, having achieved a hydrodynamic equilibrium. Dogs that are presented with SM before 3 years of age have a poorer prognosis and are more likely to develop severe weakness which is more difficult to manage. Cervicotorticollis can improve slowly despite persistence of the syrinx.

If medical therapy does not alleviate the clinical signs, surgical decompression of the foramen magnum has been suggested (suboccipital craniectomy) and is the treatment of choice in people. Foramen magnum decompression has been performed in dogs, with success rates reported at about 80%; however, recurrence is common in nearly half of cases in the long term, and neuropathic pain and the accompanying signs of scratching may persist, requiring continued medical therapy. Additionally, multiple surgeries may be necessary if scar tissue develops at the surgical site, obstructing CSF flow, although cranioplasty may reduce the likelihood of this complication. Improvement may not result in the reduction of syrinx size, which usually persists.

SUBARACHNOID DIVERTICULA (SAD) (SUBARACHNOID CYSTS)

Definition/Overview

Subarachnoid diverticula (SAD; also known as subarachnoid cysts, meningeal cysts, intra-arachnoid cysts, and leptomeningeal cysts) can cause compression of the cervical or thoracolumbar spinal cord.

Etiology

Congenital, inflammatory, traumatic.

Pathophysiology

Arachnoid diverticula occur in the intradural–extramedullary space. Although SADs can occur over the entire length of the vertebral column, they occur most commonly in the cranial cervical or thoracolumbar region. Cervical SADs have most commonly a C2–C3 localization and thoracolumbar SADs most commonly a T13–L1 localization. Large-breed dogs are most commonly affected by cervical and small breed dogs most commonly by thoracolumbar SADs. In Pugs, SADs are, however, also regularly seen in the cervical region, and one report described cervical SADs in seven related young Pugs. Most SADs are single lesions with a midline dorsal localization. They can also be multiple, multilobulated, or have ventral or lateralized localizations. Reports have indicated that Rottweilers are predisposed for SAD. Pugs and French Bulldogs are also significantly overrepresented. SAD have occasionally been reported in cats. So far, all reported feline SADs are considered to be acquired and secondary to other causes

Clinical Presentation

The nature of clinical signs is reflected by the location of the SAD. The clinical presentation is predominantly a slowly progressive, general proprioceptive ataxia and hypermetria. Obvious paresis is noted in <5% of affected cases. Although unusual for lesions located in the thoracolumbar region, approximately 20% of dogs with thoracolumbar SAD have urinary or fecal incontinence. It has been suggested that this upper motor neuron incontinence is related to the midline dorsal location of most SADs interfering with the sensory pathways for conscious urination and defecation. Spinal hyperesthesia is not common and occurs in approximately 20% of cases. Dogs with cervical SAD can demonstrate a stiff and floating gait of the thoracic limbs. Because of the multifactorial etiology of SAD, there is a wide variation in the age of onset of clinical signs. Dogue de Bordeaux with SAD are younger, while Pugs develop clinical signs later in life compared to other breeds with SAD

Diagnosis

Myelography is useful for detecting the diverticula within the intradural space. On MRI, the diverticula appear as focal, well-circumscribed lesions that are isointense to CSF on both T1-weighted and T2-weighted images (**Figure 14.59**). MRI is more sensitive than CT in detecting associated intramedullary lesions such as SM.

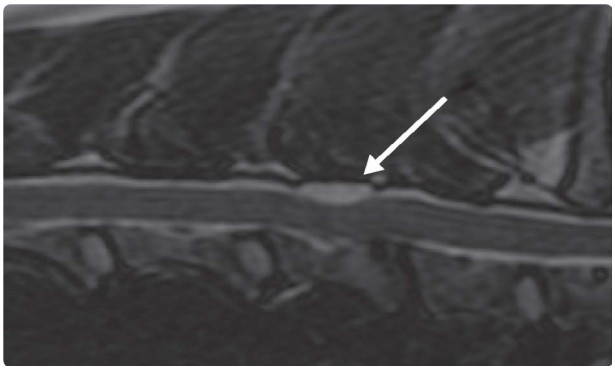


FIGURE 14.59 T2-weighted caudal cervical spinal MR image depicting a dorsal fluid-filled lesion (arrow) associated with the spinal cord and subarachnoid space. This is often referred to as a subarachnoid cyst or diverticulum.

Management

Medical and surgical treatment options have been reported for SAD. Medical treatment typically consists of administration of anti-inflammatory doses of prednisolone (0.5 mg/kg s.i.d. p.o.). The rationale for administering prednisolone is to ameliorate vasogenic edema and decrease the rate of CSF production. Several surgical techniques have been described, which include a durotomy, durectomy, or marsupialization with subsequent removal of present arachnoid adhesions. There is no clear evidence of superiority of one surgical technique over the others. Although transient early postoperative neurological deterioration is common, most dogs will experience long-term improvement. There is some evidence that surgery is associated with a better long-term outcome compared to medical management. The prognosis is good for young dogs if treated soon after development of clinical signs. Dogs older than 3 years of age and those with clinical signs for a duration of >4 months have a poor long-term outcome when treated with only fenestration of the cyst.

One study reported that 82% of dogs treated surgically experienced a long-term neurological improvement, while 3% remained stable and 16% deteriorated. After medical management, 30% experienced a long-term neurological improvement, while 30% remained stable and 40% deteriorated.

Although rare, late-onset recurrence of clinical signs is possible. The median time to recurrence of neurological signs is 20.5 months after surgery, and the reasons for these relapses include regrowth of the SAD, herniation of the spinal cord through the laminectomy membrane, and laminectomy membrane formation.

Although surgery has been associated with good outcomes in most dogs, it has been suggested that Pugs have a poor long-term prognosis after surgery for thoracolumbar SAD. One study demonstrated that although 80% of Pugs experienced a good short-term outcome after surgery, 85% of these dogs experienced late-onset recurrence of neurological signs. Although it is currently unclear why Pugs have a more unfavorable prognosis, it is possible that thoracolumbar SAD formation in this breed is associated with a multifactorial etiology and variety of pathological mechanisms.

VERTEBRAL COLUMN MALFORMATIONS

ATLANTOAXIAL INSTABILITY

Definition/Overview

Subluxation of the atlantoaxial junction is a relatively common problem in toy breed dogs and causes acute to chronic tetraparesis, ataxia, and pain.

Etiology

Trauma, congenital malformation.

Pathophysiology

The atlas (first cervical vertebra) and axis (second cervical vertebra) are held together by ligaments that run from the dens of the axis to the atlas and the skull, over the dens binding it to the floor of the atlas (the transverse ligament), and between the dorsal lamina of the atlas and the dorsal spinous process of the axis. The dens is a bony projection from the cranial aspect of the body of the axis and develops from a separate growth plate. The atlantoaxial and atlanto-occipital region is prone to congenital defects, which can predispose to this luxation:

- Aplasia, hypoplasia, or dorsal angulation of the dens (toy and small breeds of dog are predisposed to this condition)
- Congenital absence of the transverse ligament
- Incomplete ossification of the atlas

Clinical Presentation

Onset of signs in dogs with the congenital form of the disease usually occurs in young dogs (<2 years of age), although problems can develop at any age. Signs can develop acutely or gradually, and waxing and waning of signs is often reported, presumably a reflection of instability at the atlantoaxial junction causing repeated injury to the spinal cord. Signs include neck pain (variably present), ataxia, tetraparesis, and postural reaction and conscious proprioceptive deficits with normal-to-increased muscle tone and myotatic reflexes in all four legs. In severe cases, animals can present with tetraplegia and difficulty breathing, and they may die acutely as a result of respiratory failure. Some animals present with seizure-like episodes that involve sudden onset of opisthotonos and vocalization, presumably reflecting intermittent compression of the spinal cord and nerve roots, causing severe but transient pain and paresis.

Diagnosis

Atlantoaxial subluxation can be diagnosed from survey radiographs of the cervical spine, although extreme care must be taken when restraining and moving dogs in which this disease is suspected. If the animal is sedated or anesthetized, the head and neck should be supported in slight extension to avoid further spinal cord injury. On lateral radiographs, an increased space can be seen between the dorsal lamina of the atlas and the dorsal spinous process of the axis. In severe cases, malalignment of the bodies of the atlas and axis is clearly visible. The presence and size of the dens can be evaluated most accurately on ventrodorsal views. If there is no evidence of subluxation on the lateral views, the neck can be carefully flexed to see if there is instability (the space between the dorsal lamina of the atlas and the dorsal spinous process of the axis should be evaluated). It is preferable to do this with fluoroscopy so that the movement can be monitored to prevent accidental iatrogenic subluxation. Advanced imaging is commonly performed to aid in decision-making for surgery. CT allows clear identification of the bony components of the atlantoaxial region, facilitating surgical planning for implant placement. MRI highlights the spinal cord and brainstem parenchyma, allowing diagnosis of concurrent abnormalities such as CLMS or hydrocephalus, which might complicate recovery from surgery (Figure 14.60a, b).

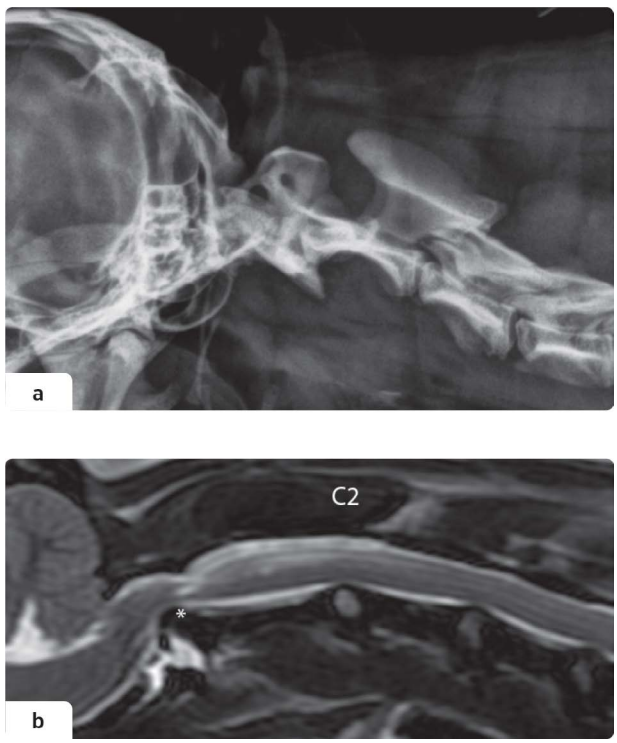


FIGURE 14.60 **(a)** Lateral radiograph of a Yorkshire Terrier with acute-onset neck pain. There is a notable space present between the dorsum of C1 and the dorsal arch of C2 compatible with atlantoaxial subluxation. **(b)** Sagittal T2-weighted MR image of the cranial cervical spine of the dog shown in (a). Marked cord compression can be seen associated with a subluxation of the dens (asterisk).

Management

Dogs with mild signs can be treated conservatively by placing an external splint for at least 6 weeks. The splint must immobilize the atlantoaxial junction and so must come over the head cranial to the ears and go back to the level of the chest. The aim is to stabilize the junction while the ligamentous structures heal. The dog and the splint should be checked daily by the owner for signs of decubital ulcers and checked weekly by the veterinarian, with regular bandage changes if necessary (Figure 14.61). Splint placement addresses instability and can produce an immediate improvement, although severe displacement of the atlantoaxial junction may not be adequately addressed. In one study, 6 of 16 dogs failed to improve following splint placement and were euthanized, while the remaining 10 dogs responded well and maintained a good outcome 1 year after splint removal. Surgery is recommended in dogs with neurologic deficits, although it can be associated with high perioperative morbidity and mortality (Figure 14.62). Dorsal and ventral approaches to the atlantoaxial junction have been described, but dorsal approaches, although requiring less dissection and retraction of important soft tissue structures such as the esophagus, pharynx, and larynx, are associated with a greater risk of causing spinal cord injury during surgery and a higher incidence of implant failure. A neck splint may be placed postoperatively while fusion occurs if transarticular screws alone are used. This is a problematic area to repair surgically. Bone quality is often poor, the bones are small, movement of the vertebrae may cause additional injury to the spinal cord, and the pharynx and larynx can be damaged during retraction. There is a risk of respiratory arrest and death in the perioperative period as a result of additional spinal cord injury or inflammation of the upper airways secondary to retraction. While this is a serious disease, dogs treated surgically have an excellent prognosis if they survive the 48-hour perioperative period. Although reported surgical success rates range from 50% to 90%, the majority report a mortality rate in the region of 20%, with the majority of deaths occurring either during or



FIGURE 14.61 External stabilization of the neck requires a ventral splint and bandaging, which needs to extend from the mandible to the midthorax.



FIGURE 14.62 Lateral postoperative radiograph of the dog in **Figure 14.60**. A ventral fixation approach using transarticular pins, screws, and polymethylmethacrylate cement has been used.

immediately after surgery. As with all spinal cord diseases, prognosis is worse in animals with severe and chronic neurologic deficits. It has also been shown that prognosis is better in young dogs (<24 months).

VERTEBRAL ANOMALIES

Definition/Overview

Vertebral anomalies (e.g., hemivertebra, butterfly vertebra, block vertebra, spina bifida, and caudal articular dysplasia) involve defects in formation of the vertebra and segmentation defects. Congenital anomalies of the vertebral column may be associated also with anomalies of the spinal cord (dysraphism) and/or other organ systems (e.g., cardiovascular and urogenital). Spina bifida is considered a form of spinal dysraphism and is characterized by failure of the vertebral arches to fuse, with or without protrusion of the spinal cord and meninges. Caudal articular process dysplasia (CAD) is characterized by a complete (aplasia) or partial (hypoplasia) absence of one or more caudal articular processes. Although every breed can be affected, this condition has been heavily associated with the Pug breed. The caudal articular processes of the caudal thoracic vertebrae, between T10 and T13, are most often affected in animals with neurological signs.

Etiology

Congenital.

Pathophysiology

Vertebral anomalies are common in the brachycephalic and "screw-tailed" breeds of dog such as Bulldogs and Boston Terriers and the "tailless" cat, the Manx. If they are associated with clinical signs, it can be due to associated osseous compression, disc disease, or associated soft tissue abnormalities (subarachnoid diverticula).

It has been proposed that CAD can lead to low-grade and repetitive vertebral instability, which can lead to a condition termed "constrictive myelopathy" or "meningeal fibrosis." This is characterized by the formation of a dense, circumferential band of fibrotic tissue causing intradural adhesions between the arachnoid and pia mater and constriction of the spinal cord. Although meningeal fibrosis has traditionally been associated with caudal articular process dysplasia, this condition has also been reported in Pugs without concurrent vertebral anomalies. The causative relationship between meningeal fibrosis and caudal articular process dysplasia is, therefore, unclear. Meningeal fibrosis in Pugs could potentially represent a multifactorial neurological syndrome or a disease entity in itself. Pathological and histopathological findings in Pugs with meningeal fibrosis include circumferential fibrosis with concomitant focal gliosis, syringomyelia, or hydromyelia. Lymphohistiocytic inflammation is also commonly present. Meningeal fibrosis has also been associated with spinal arachnoid diverticulum (see mentioned in the text earlier) formation in Pugs.

Clinical Presentation

Vertebral anomalies are often an incidental finding and usually cause no clinical signs. Malformations involving the spinal cord are more likely to cause neurologic deficits, the nature of which is determined by the location of the abnormality.

Caudal articular process dysplasia and meningeal fibrosis can cause a chronic onset of slowly progressive paraparesis and ataxia of the pelvic limbs. Urinary and especially fecal incontinence is common. Spinal hyperesthesia is typically not present. Clinical signs are not caused by the vertebral anomaly in itself but by the constrictive meningeal fibrosis. Affected animals develop clinical signs later in life, with one study reporting a median age around 7.5 years. This vertebral malformation occurs, however, commonly in neurologically normal small brachycephalic dogs. A study evaluating CT studies of dogs without spinal disease revealed that 70.4% of French Bulldogs, 84.1% of English Bulldogs, and 97% of Pugs showed evidence of caudal articular process dysplasia. Compared to the other two breeds, Pugs demonstrated a significantly higher prevalence of caudal articular process dysplasia with a higher prevalence of aplasia, a lower prevalence of hypoplasia, more affected vertebrae per dog, and more vertebrae with bilateral caudal articular process dysplasia. Pugs also demonstrated most often caudal articular process dysplasia between the vertebral levels of T10 and T13, while in French and English Bulldogs, this occurred most often in the more cranial thoracic vertebrae.

Diagnosis

Diagnosis is suspected based on clinical signs, signalment, and survey radiographic findings. Myelography and cross-sectional imaging are useful for determining the extent of compression, stenosis or other possible spinal cord and spinal column deformities. MRI is more sensitive for determining spinal cord involvement and associated defects of altered CSF flow (cyst, syrinx, edema).

Caudal articular process dysplasia can be readily visualized on survey radiographs and especially CT. Because this vertebral anomaly can occur in clinically normal dogs and occurs in the vast majority of neurologically normal Pugs, it is not sufficient to merely observe hypoplastic or aplastic caudal articular processes on diagnostic imaging studies. The imaging modality of choice to diagnose meningeal fibrosis is MRI. The MRI abnormalities associated with meningeal fibrosis include an irregular subarachnoid space, multiple linear hypointense bands that transverse from the arachnoid to the pia across the arachnoid space, spinal cord distortion and compression, cerebrospinal fluid to accumulation in multiple pockets, and bilateral V-shaped ventrolateral extradural lesion. An intraparenchymal hyperintensity is usually present at the site of spinal cord compression. An additional advantage of MRI is the possibility to detect concurrent spinal conditions such as intervertebral disc disease, spinal arachnoid diverticula, and syringomyelia. It is not uncommon for multiple spinal conditions to be present at the site of caudal articular process dysplasia. One study demonstrated compressive intervertebral disc protrusion in 56% and spinal arachnoid diverticula in 22% of Pugs with caudal articular process dysplasia at the same site. Although a causal relationship has been hypothesized, the relationship between caudal articular process dysplasia and other spinal conditions is currently unclear.

Management

If clinical signs are nonprogressive, conservative management is recommended. Decompressive surgery is recommended with clinical signs of compressive myelopathy. Likewise, spinal instability and malalignment require vertebral stabilization techniques. The prognosis is good for most vertebral anomalies because the majority of cases do not produce clinical signs. The prognosis is considered guarded if signs of spinal cord dysfunction are present. Multiple anomalies may exist concurrently.

Little is known about the natural progression or results of medical management associated with constrictive myelopathy and caudal articular process dysplasia. Surgical treatment consisting of decompressive surgery in combination with dissection of the pia–arachnoid adhesions has been associated with a poor outcome. Surgical treatment consisting of vertebral stabilization with or without additional decompression has been associated with neurological improvement in the majority of cases. Concurrent urinary or fecal incontinence is, however, expected to resolve in less than half of affected cases. Another study reported favorable outcomes after subarachnoid–subarachnoid shunt placement to bridge the site of cerebrospinal fluid flow obstruction in dogs with pia–arachnoid fibrosis. Objective comparison of outcome data is, however, challenging because of the variety of imaging findings, pathological abnormalities, and the substantial proportion of dogs with concurrent spinal disorders, such as intervertebral disc protrusion and spinal arachnoid diverticula.

SPINAL STENOSIS

Definition/Overview

Spinal stenosis indicates a malformation of the spine present at birth and occurs as a primary lesion or in association with other anomalies that predispose to stenosis.

Etiology

Congenital.

Pathophysiology

Relative stenosis refers to canal narrowing that does not cause compression of neural tissue, whereas absolute stenosis refers to a stenosis causing spinal cord compression. Dobermanns have a relative stenosis that most commonly involves the cranial thoracic vertebrae (T3–T6). There have also been reports of thoracic vertebral stenosis in Bull Mastiffs, Great Danes, Basset Hounds, Dogues de Bordeaux, and English Bulldogs.

Clinical Presentation

Neurologic signs reflect the neuroanatomic localization of the stenosis. Onset is usually insidious and progressive.

Diagnosis

Diagnosis is based on survey radiography that defines associated vertebral anomalies but requires myelography and/or cross-sectional imaging to determine the presence of stenosis. MRI of the spinal cord is recommended to further delineate associated neural tissue anomalies or abnormalities.

Management

Surgical decompression may relieve the compression; however, associated vertebral and spinal cord anomalies need to be considered. The prognosis is considered guarded due to chronicity and presence of other anomalies. The lack of information available with regard to surgical follow-up makes it difficult to give an accurate prognosis.

NEOPLASTIC DISEASES

SPINAL MENINGIOMAS

Definition/Overview

Tumors affecting the spinal cord are described based on their location as extradural, intradural–extramedullary, or intramedullary. Intradural–extramedullary tumors include meningioma and nerve sheath tumors. Meningiomas affecting the spinal cord are most common in the neck.

Etiology

Unknown.

Pathophysiology

Spinal meningiomas are the most common primary spinal cord tumor in cats older than 8 years of age. The mean age for spinal meningiomas in dogs is 9 years. Spinal meningiomas in dogs are most common in the cervical spinal cord but can occur in any region of the spinal cord.

Clinical Presentation

Meningiomas of the spinal cord in dogs and cats tend to present with a progressive paraparesis. The clinical signs represent the spinal cord region involved. Paraspinal pain may or may not be present.

Diagnosis

Myelography typically shows an intradural–extramedullary compressive lesion. With MRI, these tumors are isointense to hypointense on T1-weighted images, hyperintense on T2-weighted images, and demonstrate strong, uniform contrast enhancement (Figure 14.63).

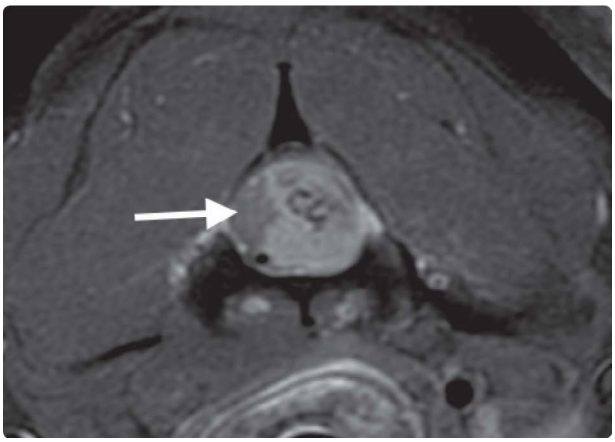


FIGURE 14.63 Transverse postcontrast T1-weighted MR image at the level of C2 showing a strongly enhancing lesion markedly compressing the cord (arrow) to a fraction of its normal size. Surgical resection of the lesion was performed and confirmed a meningioma.

Management

These lesions should be surgically explored because many meningiomas can be completely or partially removed and, therefore, may be associated with prolonged survival after surgery. Postoperative radiation therapy may be used adjunctively to prolong survival in dogs and cats with incompletely excised tumors. Treatment with surgery and radiation therapy can result in an improved outcome and prevent recurrence. Surgical results are guarded when meningiomas are associated with an intumescence, a ventral location, and invasion of the neural parenchyma.

NERVE SHEATH TUMORS

Definition/Overview

Peripheral nerve sheath tumors (PNSTs) are neoplasms that arise from cells surrounding the axons in peripheral nerves or nerve roots, and they are divided into benign and malignant variants. Most PNSTs in dogs are anaplastic, have a high mitotic index, and an aggressive biological behavior, so they are designated as malignant PNSTs. Malignant nerve sheath tumors are common in dogs but rare in cats. No sex or breed predilection has been demonstrated for PNSTs in dogs. Most affected animals are adults over 7 years of age, but younger animals may also be affected.

Etiology

Unknown.

Pathophysiology

Malignant PNSTs in dogs most commonly affect the caudal cervical (C6–C8) and the cranial thoracic (T1–T2) nerve roots, although nerve sheath tumors have also been described affecting the sciatic nerve and femoral nerve. These tumors may have their origin in the nerve roots or the brachial or lumbosacral plexi, or they may arise from more peripheral locations in the nerves. Usually, the tumor spreads slowly, both distally and proximally, and may invade the vertebral canal, causing spinal cord compression and associated neurologic deficits. As the tumors grow proximally, they spread to neighboring nerves in the plexus bundle, with a high percentage of dogs showing evidence of multiple nerve involvement at the time of diagnosis. PNSTs are highly invasive locally, but they rarely metastasize, although pulmonary metastasis in advanced cases has been described.

Clinical Presentation

Malignant PNSTs typically affect older dogs and have been described occasionally in cats. Slowly progressive forelimb lameness or paresis and muscle atrophy are the predominant clinical signs of malignant PNSTs (Figure 14.64). In addition, pain on palpation of the limb or



FIGURE 14.64 A Yorkshire Terrier demonstrating left forelimb root signature associated with a peripheral nerve sheath tumor.

axillary region may be encountered. A palpable axillary mass may be present in some cases, but it is not common. Enlargement of the affected limb has been described in one case. Clinical signs progress slowly, and orthopedic disease is often suspected before a definitive diagnosis is made. As the PNST spreads proximally and compresses the spinal cord, neurologic deficits may develop in the ipsilateral hindlimb, progressing to all four limbs. If the dorsal cervical nerve roots are affected, animals may also show cervical pain.

Unilateral, partial, or complete Horner's syndrome may appear if the cranial thoracic nerve roots are affected by the tumor itself or if there is cord compression at this point (Figure 14.65). Similarly, the ipsilateral cutaneous trunci reflex may be absent due to invasion of the C8–T1 ventral nerve roots or compression of these spinal cord segments.



FIGURE 14.65 Left-sided Horner's syndrome comprising ptosis, miosis, and third eyelid protrusion is seen in this adult cat.

Diagnosis

Orthopedic disease must be excluded by careful orthopedic examination and radiographs of the appropriate joints. Complete blood work (CBC, serum biochemistry panel), thoracic radiographs, and abdominal ultrasonography should be performed in any dog suspected of having a malignant PNST in order to rule out metastatic disease and assess general health status. Survey radiographs of the spine are often normal. Oblique views may reveal enlargement of the affected intervertebral foramen due to pressure atrophy, caused by the thickened nerve root. Occasionally, lysis of the affected vertebral bodies may be observed. CT imaging allows visualization of some malignant PNSTs, and masses as small as 1.0 cm can be identified on contrast-enhanced CT scans. Enhancement of the mass with iodinated contrast medium provides excellent views, helps differentiate vascular structures, and allows subtle differences in soft tissue opacity created by tumor vasculature to be seen. MRI evaluation of the brachial plexus or peripheral nerves provides excellent diagnostic images, but again, not all PNSTs can be detected using this imaging modality early in the course of the disease (Figure 14.66).

Ultrasound examination of the affected limb may allow visualization of large, hypoechogenic tubular masses that displace vessels and destroy normal architecture, and ultrasound-guided fine-needle aspirates of the masses may be useful to reach a final diagnosis in some cases. Electromyography reveals abnormal, spontaneous electrical activity in the affected limb muscles and is of great assistance in differentiating neurologic from orthopedic disease.

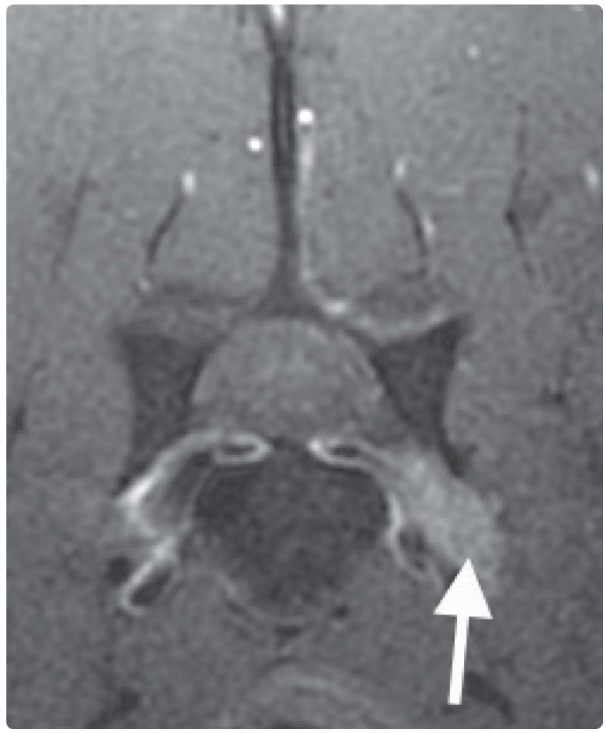


FIGURE 14.66 Nerve root enhancement (arrow) associated with a nerve sheath tumor is depicted on this transverse postcontrast T1-weighted MR image at the level of C7.

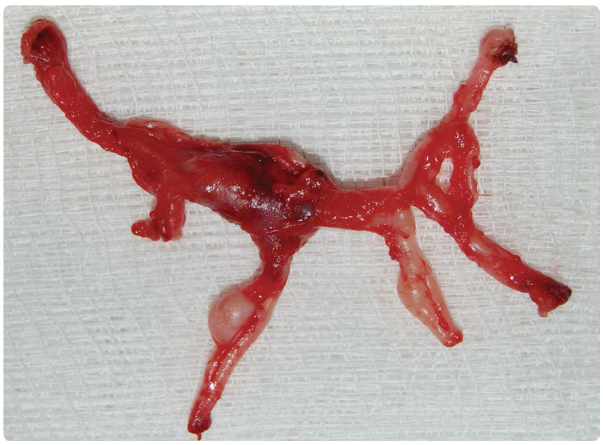


FIGURE 14.67 The lumbar plexus of a dog affected with an extensive malignant peripheral nerve sheath tumor.

Management

Unfortunately, there is usually no curative treatment for PNSTs. Complete surgical resection may be difficult due to the invasive behavior of these tumors and the late detection of the disease in most cases. Tumors within the brachial plexus or peripheral nerves are treated with local excision or amputation of the affected limb. Repeated surgeries may be needed as recurrences are common. In many instances, amputation of the limb is the only option. Early diagnosis and aggressive surgical intervention are recommended to maximize the possibility of complete tumor resection. Aggressive surgical resection at an early stage, if the tumor is peripheral, can be curative (Figure 14.67). Amputation is only advisable when the tumor is distal, and there is no invasion of the spinal canal. In addition, amputation is performed in some cases just to prevent or avoid self-mutilation and injuries to the limb in cases of loss of sensation or paresthesias. Surgery can be followed by a course of radiation therapy, but it is unclear whether this positively affects the prognosis, since these tumors are poorly responsive to radiation. Despite aggressive management, the overall prognosis is poor for most cases of malignant PNSTs. Recurrence rate after surgery is high. There is a tendency for dogs with more proximally located tumors to respond less favorably to surgery and to relapse earlier (1 month for nerve root tumors and 7.5 months for plexus tumors) than those with peripherally located tumors (>9 months after surgery). Incomplete resection is common, indicating that grossly visible margins at the time of surgery are frequently inaccurate indicators of tumor excision.

VERTEBRAL BODY TUMORS

Definition/Overview

Tumors affecting the spinal cord are described based on their location as extradural, intradural–extramedullary, or intramedullary. Extramedullary tumors are the most frequent and most commonly are primary vertebral tumors.

Etiology

Unknown.

Pathophysiology

Vertebral body tumors are primary or metastatic tumors most frequently reported in large and giant breed dogs. Commonly described tumors in dogs include osteosarcoma, fibrosarcoma, chondrosarcoma, hemangiosarcoma, plasma cell tumor, carcinoma, lymphoma, and liposarcoma. Small breed dogs have a higher rate of vertebral metastasis than large breed dogs. In cats, the most commonly described vertebral body tumor is osteosarcoma. Primary vertebral body tumors will cause a secondary myelopathy by compression or direct spinal cord invasion.

Clinical Presentation

Clinical signs may be focal or multifocal depending on the extension of the tumor. Signs include pain and paraparesis or paralysis. Pathologic fractures of the vertebral body result in an acute onset of neurologic deficits.

Diagnosis

Diagnosis is often based on survey radiographic findings, such as lysis and pathologic fractures secondary to tumor destruction of the bone. Other supportive diagnostic techniques, such as CT, MRI, and myelography, are used to determine lesion extent (Figure 14.68). MRI and scintigraphy can be used to detect multiple metastases. Fluoroscopic-guided needle aspiration or surgical biopsy can be used to obtain a definitive diagnosis.

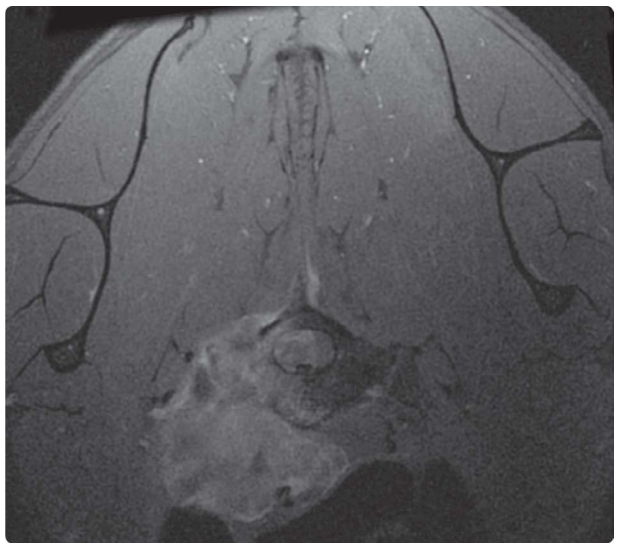


FIGURE 14.68 Transverse postcontrast T1-weighted MR image at the level of the T2 vertebra clearly demonstrating a large irregular lesion associated with the vertebral body and compressing the spinal cord. The lesion was confirmed to be a chondrosarcoma.

Management

Palliative treatment options include surgery, radiation therapy, chemotherapy, or various combinations of the three. A vertebrectomy with a bone allograft fusion has been used for the treatment of a primary vertebral neoplasm in a dog. Decompression or stabilization techniques are used in patients that are rapidly deteriorating. The overall prognosis is considered guarded for dogs and cats with vertebral neoplasia. Survival is not impacted greatly by various treatments but is often determined by the neurologic deficits at the time of diagnosis.

THORACOLUMBAR SPINAL TUMOR OF YOUNG DOGS (SPINAL NEPHROBLASTOMA)

Definition/Overview

Canine nephroblastoma is an intradural–extramedullary neoplasm in young dogs located between T10 and L2 in the spinal cord. Occasionally, this tumor is extradural or intramedullary.

Etiology

The origin of the tumor is unknown, but descriptions have included medulloepithelioma, embryonal nephroma, nephroblastoma, and Wilms tumor (Figure 14.69).

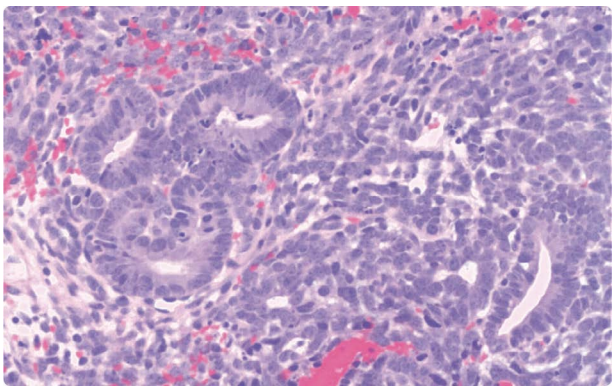


FIGURE 14.69 Histopathologic section of a nephroblastoma stained with hematoxylin and eosin.

Pathophysiology

Primary spinal nephroblastoma is thought to arise from embryonic tissue trapped within the dura during fetal development. Histologic appearance may vary. Usually, neuroepithelioma involves one kidney or the spinal cord but not both. Rarely, renal neuroepithelioma will secondarily metastasize to the spinal cord, bone marrow, and spinal canal.

Clinical Presentation

Clinical signs of spinal nephroblastoma are dependent on tumor location. The most common neurologic findings include progressive paraparesis and ataxia. Clinical signs of spinal neuroepitheliomas consist of a progressive asymmetrical T3–L3 myelopathy.

Diagnosis

Survey radiography of the spine shows no abnormalities. Myelography is useful for determining location and lesion extent. CT or MRI of the spine can better assess vertebral and spinal cord involvement (Figure 14.70a, b). Abdominal radiography and ultrasonography can assess for primary renal involvement if present. Immunohistochemistry is used to identify the mesenchymal or epithelial components of neuroepithelioma. Staining with Wilms tumor 1 (WT-1) antibody can support a diagnosis of nephroblastoma.

Management

If detected early, surgical excision can lead to long-term survival with limited morbidity. Adjunct irradiation is considered when total surgical resection is not possible and may provide a good functional outcome. Overall prognosis is uncertain because of the limited number of cases reported. Prognosis is considered guarded to poor because spinal cord involvement is often extensive by the time of diagnosis. Long-term prognosis is poor because of tumor recurrence.

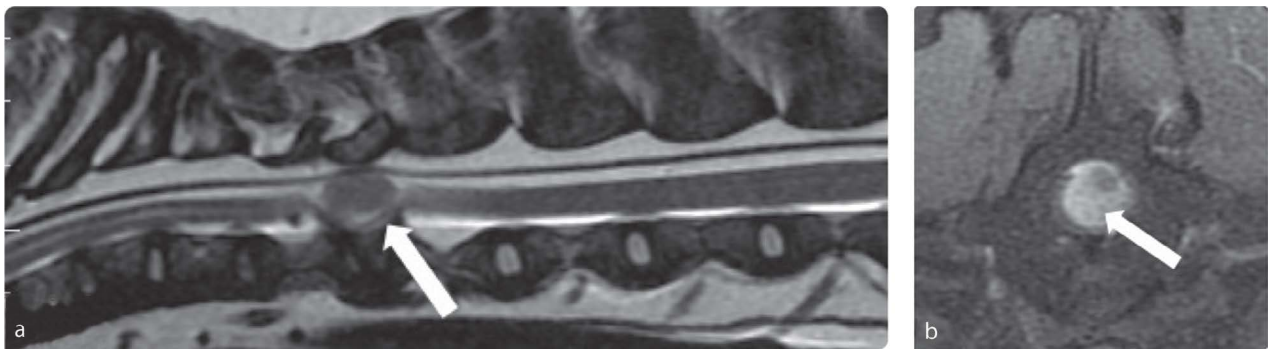


FIGURE 14.70 **(a)** Sagittal T2-weighted and **(b)** transverse postcontrast T1-weighted MR images of a nephroblastoma (arrows) compressing the spinal cord in the thoracic spine.

SPINAL LYMPHOMA

Definition/Overview

Extradural lymphoma is the most common tumor to induce spinal cord dysfunction in cats and occurs less commonly in dogs.

Etiology

Unknown.

Pathophysiology

Feline leukemia virus has been implicated and is an important factor associated with lymphoma in young cats. Feline spinal lymphoma has a predilection for the thoracic and lumbar spinal cord. Most affected cats are <2 years of age, but older animals may also be affected. Lymphoma in cats commonly is found in extraneural sites. Renal lymphoma is likely to relapse in the CNS. Lymphoma is the most commonly diagnosed malignant tumor in dogs, but involvement of the nervous system is relatively unusual. Involvement of the CNS is more common than the peripheral nervous system in both dogs and cats.

Clinical Presentation

Neurologic signs are related to the location of the lymphoma and are often insidious, but there can be an acute exacerbation with rapid deterioration. Often, cats with lymphoma have multifocal signs reflective of multiple lesions in the CNS. The most common initial clinical sign in cats is paraparesis, with pain and other nonspecific abnormalities such as anorexia, lethargy, weight loss, and respiratory tract infection.

Diagnosis

The safest and most reliable method of obtaining a diagnosis of lymphoma in the CNS may be by confirming the presence of lymphoma in other organ systems. The abdominal organs and bone marrow are commonly aspirated but may not be affected. CSF analysis may detect the presence of malignant lymphocytes, but lack of this finding cannot rule out CNS involvement (Figure 14.71). Survey spinal radiography may detect bone involvement. Myelography is useful for determining lesion extent and determining extradural, intradural–extramedullary, or intramedullary involvement. Spinal lymphoma is detected most commonly as an extradural lesion. MRI may detect intramedullary lesions (Figure 14.72). A definitive diagnosis can be determined from cytologic examination of the contents of fluoroscopic-guided fine-needle aspirations or a surgical biopsy.

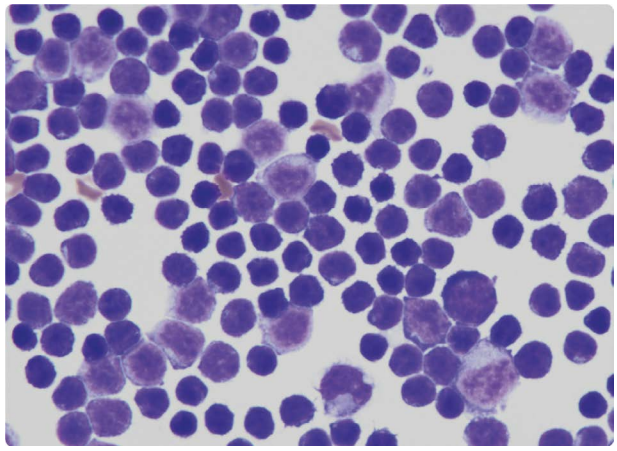


FIGURE 14.71 Cytologic analysis of CSF from a dog with a CNS lymphoma.

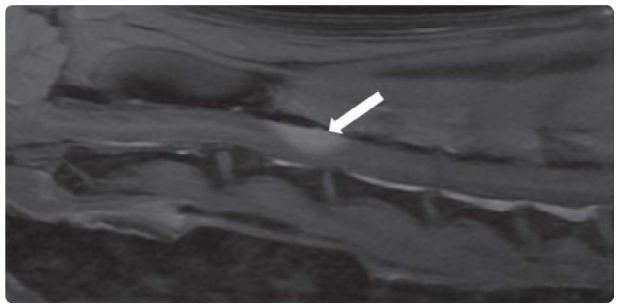


FIGURE 14.72 Sagittal postcontrast T1-weighted cervical spinal cord MR image of a dog with a spinal cord lymphoma (arrow).

Management

Therapies used in combination or alone include surgical resection, focal irradiation, and systemic chemotherapy (e.g., cytarabine or methotrexate and corticosteroids). A laminectomy procedure provides an accurate histologic diagnosis and adequate decompression. Surgical treatment is necessary for cats that fail to respond rapidly to chemotherapy. Duration and remission times vary among studies. Intramedullary lymphoma is difficult to treat because of poor penetration across the blood–brain barrier of some chemotherapeutic agents. Effectiveness of chemotherapy for lymphoma with neural involvement still remains to be determined. In general, the prognosis for hindlimb paresis or paralysis in cats is guarded to poor. The median duration of complete or partial remission in six cats with spinal lymphoma and severe neurologic deficits, treated with vincristine sulfate, cyclophosphamide, and prednisolone, has been reported as 14 weeks (range 5–28 weeks) and 6 weeks (range 4–10 weeks), respectively.

INFLAMMATORY DISEASES

DISCOSPONDYLITIS/OSTEOMYELITIS

Definition/Overview

Discospondylitis is due to infection of the intervertebral disc and adjacent vertebral endplates. If the infection is confined to the vertebral body, it is called vertebral

osteomyelitis or spondylitis. The sites most commonly affected are L7–S1, caudal cervical, midthoracic, and thoracolumbar spine. The infection is usually slowly progressive but can result in acute signs due to secondary pathologic vertebral fractures and IVDD. Its most common clinical sign is that of spinal pain, but neurologic signs are seen and related to the localization. An association with empyema has been documented in several dogs, which may represent an extension of the disease and should be considered when considering diagnostic tests and/or when dealing with a refractory case.

Etiology

Coagulase-positive *Staphylococcus* spp. (*S. intermedius* or *S. aureus*) are the most common etiologic agents associated with canine discospondylitis. Other less commonly identified organisms include *Streptococcus* spp., *E. coli*, *Actinomyces* spp., and *Brucella canis*, as well as *Aspergillus* spp. Young German Shepherd Dog bitches and Hungarian Vizslas seem to be predisposed to aspergillosis, whereas young American Basset Hounds contract discospondylitis due to systemic tuberculosis.

Pathophysiology

Hematogenous spread from distant foci of infection (urogenital tract, skin, dental disease), penetrating wounds, surgery, or plant material migration can cause direct infection of the disc space or vertebrae, the latter of which is usually seen at the level of L2–L4 at the insertion of the diaphragmatic crus. Immunosuppression due to factors such as hyperadrenocorticism is considered a predisposing cause. Infection causes osseous lysis, proliferation, and soft tissue reaction, which can cause neural compression.

Canine brucellosis (*Brucella canis*) accounts for a high percentage of discospondylitis cases in countries where it is endemic. It is also increasingly recognized in nonendemic countries where street dogs are imported from endemic countries for rehoming. *Brucella suis* is a notifiable disease that has recently emerged in dogs in New South Wales. Most cases occurred in dogs that participated in feral pig hunting (or were exposed to those dogs) or were fed raw feral pig meat. Other signs include orchitis, sacroiliitis, epididymitis, pyrexia, and lameness. Testing should be performed in countries in which brucellosis is not yet eradicated, especially if the dog is fed raw pig meat, is used for hunting, or kept on a farm. In Western Europe, Brucella testing should be performed in any dog presenting with spinal pain that was "rescued" and imported from countries with a large stray population, especially if from Eastern or Southern Europe. Canine brucellosis (*B. canis*) is not notifiable to WHO or EU, whereas *B. abortus*, *B. suis*, and *B. melitensis* are, even though it is an accepted zoonotic disease. In the United States, there is mandatory reporting of brucellosis in dogs to state health authorities and mandatory communication with veterinarians and dog owners to alert them of the zoonotic risk. One aspect of reducing the zoonotic potential is educating owners about options for managing *B. canis*–positive dogs, such as sterilization, antimicrobial drug therapy, and repeat testing, or euthanasia if those measures cannot be applied. Anyone who has contact with an infected dog should maintain good hygiene standards when handling its urine, feces, or reproductive products.

Clinical Presentation

Spinal pain is the most common initial clinical sign in this disease, which is most frequently seen in large intact male young to middle-aged dogs. With proliferation of inflammatory tissue, compression of neural tissue can lead to ataxia, paresis, and occasionally paralysis dependent on where the lesion is located. Although it can occur in any animal, the condition is less common in toy and chondrodystrophoid breeds of dog and rare in cats. Purebred dogs seem more commonly affected than mixed breeds. Approximately 30% of dogs have signs of systemic illness such as fever and weight loss.

Diagnosis

Hematological changes are usually not present unless there are concurrent conditions such as endocarditis. Serum C-reactive protein is elevated in cases of discospondylitis and may be clinically more useful to screen dogs with back pain than pyrexia or leukocytosis alone. Urine cytology may reveal bacterial or fungal agents. Blood and urine cultures should be performed in all suspected cases and are positive in up to 75% and 50% of cases, respectively. Ideally, these should be performed prior to initiating antibiotic therapy. Serology for brucellosis should also be performed, especially in view of its zoonotic potential; this has been reported to be positive in up to 10% of cases. The standard test for *B. canis* is culture. Commonly collected samples include blood, vaginal discharge, and semen. Of these, blood is the most commonly collected; however, because bacteremia can be intermittent, positive animals may be missed. The best time for culturing *Brucella* is 2–4 weeks after infection, after demonstration of reproductive failure, when bacteremia is the highest. Culture requires up to 9 days, increasing the risk for exposure of laboratory personnel if the cultures are not handled appropriately.

Definitive diagnosis is usually made with spinal radiographs, although radiographic change may not be evident in the first 2–4 weeks of infection (**Figure 14.73a–c**). The most commonly affected site is L7–S1, but other frequently affected sites include the caudal cervical/cranial thoracic vertebrae and the thoracolumbar junction. As this can be a multifocal disease, the entire spine should be radiographed. Radiographic evidence of disease includes narrowing of the disc space, accompanied by subtle irregularity of both endplates, through to gross lysis and osseous proliferation of the adjacent vertebral bone, and even pathological fractures. The radiographic appearance of discospondylitis can differ in dogs <6 months of age compared with adults. On initial radiographs in young dogs, there may

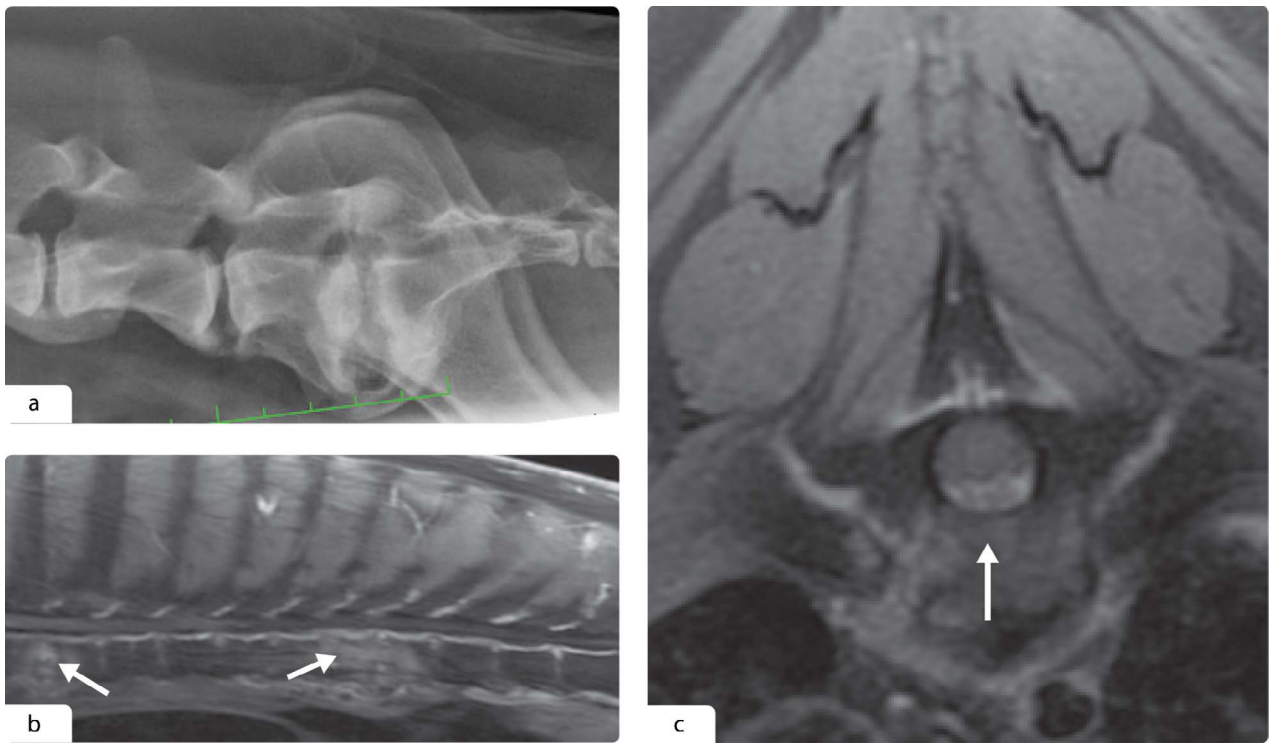


FIGURE 14.73 **(a)** Lateral radiograph of the lumbosacral joint of a dog with discospondylitis. Note the endplate sclerosis and lysis. **(b)** Sagittal and **(c)** transverse postcontrast T1-weighted MR images of the thoracic spinal column of a dog with multifocal discospondylitis illustrating the marked vertebral body uptake of contrast (arrows).

be intervertebral disc space narrowing without evidence of vertebral endplate osteolysis. Subtle osteolysis of the adjacent vertebral endplates can be seen on follow-up radiographs if performed. Over time, the majority of these dogs develop osteolysis of the vertebral metaphyses with an appearance similar to discospondylitis in adult dogs, and in one study, many with discospondylitis of the thoracolumbar vertebral column had a subluxation at the site on follow-up radiographs. Radiography can also be used to monitor the response to treatment or the progression of the disease, although clinical progression is equally important, as radiographic change can lag behind clinical improvement.

CT can identify subtle endplate erosion and paravertebral soft tissue swelling more readily than radiography. Postmyelogram CT clearly defines compression of the neural tissues by infected tissues, as does MRI. Discospondylitis appears to have increased signal intensity on T2-weighted images and decreased signal intensity on T1-weighted images, changes also seen in the paravertebral tissues in all cases. MRI can also highlight the inflammation in the surrounding muscles (Figure 14.73b, c).

If urine and blood culture and brucellosis serology have not identified an etiologic agent in cases of discospondylitis, percutaneous needle aspiration of the disc space can be a safe procedure to obtain tissue for bacterial and fungal cultures and cytology. However, this procedure requires general anesthesia, sterile surgical preparation, and fluoroscopic or CT guidance of the needle and is usually only performed in patients unresponsive to initial broad-spectrum antibiotics. The procedure has been documented to be up to 75% sensitive. Open biopsy of the vertebrae may be considered if needle aspiration is unrewarding. This has yielded positive cultures in approximately 80% of patients. In all cases, diagnostic investigation of potential systemic infectious foci should be considered. This should include abdominal ultrasonography for prostatic or renal disease, thoracic radiographs for pulmonary disease, and cardiac ultrasonography for endocardial disease.

Management

Once radiographic evidence of discospondylitis is present, treatment for the common potential pathogen *S. intermedius* infection may be started. Initial treatment of discospondylitis consists of antibiotics (potentiated amoxicillin or cephalexin), cage rest, and analgesics. Results of cultures may require alteration of this choice.

IV antibiotics should be considered if severe neurologic compromise or signs of sepsis are present; otherwise, oral antibiotics are acceptable. However quickly the patient improves, continuation of the antibiotics for 8–16 weeks is recommended. Resolution of clinical signs, such as pain and fever, should be expected within 5 days of initiating therapy; however, complete neurologic resolution may take 2–3 months. Residual deficits may remain, but persistent pain indicates an active disease, and these patients should be treated with an additional antibiotic and considered for further diagnostics, as they may have a potential fungal infection or surgical lesion.

Discospondylitis associated with *Aspergillus* spp. has been treated with itraconazole (5 mg/kg of body weight p.o. q.24 h.), although long-term reports of success are lacking, with the belief being that chronic recurrence and progression are likely. Treatment of *B. canis* and *B. suis* discospondylitis is controversial because infection is considered lifelong, and the dog will continue to shed bacteria intermittently. Transmission of *B. canis* from dogs to humans is possible; immunocompromised individuals are at greater risk. A 6-week course of a combination of doxycycline and rifampicin combined with surgical resection of infected tissues (castration after 2 weeks of preoperative antibiotics), taking into account zoonotic and recurrence risk, seems to be effective in dogs infected with *B. suis*. Rifampicin is hepatotoxic, and serum biochemistry should be monitored. No antibiotic therapy appears to eliminate *B. canis* completely from affected dogs.

Surgical decompression is rarely needed and should only be considered in refractory cases or those with severe neurologic deficits that show no sign of improvement within 3–5 days. Although internal fixation can be acceptable even at the site of an infection, it may be more appropriate to consider external skeletal fixation, as has been successfully described in dogs with lumbosacral discospondylitis.

The prognosis for this disease is generally very good unless the etiology is fungal or *B. canis*, there are multiple lesions, vertebral fracture or subluxation occurs, or there is endocarditis. The potential for recurrence should be considered, especially if brucellosis has been diagnosed or an underlying immunosuppressive condition is present. Residual neurologic deficits are possible, and in those cases that have severe neurologic deficits associated with the infection, the prognosis should initially be guarded.

STEROID-RESPONSIVE MENINGITIS–ARTERITIS

Definition/Overview

Steroid-responsive meningitis–arteritis (SRMA), also termed necrotizing vasculitis, juvenile polyarteritis syndrome, corticosteroid-responsive meningitis/meningomyelitis, aseptic suppurative meningitis, panarteritis, and pain syndrome, is a noninfectious inflammatory condition reported in Beagles, Bernese Mountain dogs, Border Collies, Boxers, German Short-haired Pointers, Nova Scotia Duck Tolling Retrievers, Golden Retrievers, Weimaraners, and Whippets but is noted and probably occurs in other medium-to-large dog breeds.

Etiology

An immunologic cause of this disease is suspected, resulting in a vasculitis. The etiopathogenesis is unknown, but an infectious cause has been suggested, although none as yet identified.

Pathophysiology

Notably, increased levels of CSF and serum IgA, increased CSF and blood B-cell/T-cell ratios, and CSF IL-8 levels are all thought to be compatible with immune system stimulation. High CD11a expression on polymorphonuclear cells appears to be an important factor in the pathogenesis of SRMA and may be involved in the enhanced passage of neutrophils into the subarachnoid space leading to meningitis and clinical signs. Matrix metalloproteinase-2 seems to also be involved in the neutrophilic invasion into the subarachnoid space. Involvement of such molecular markers provides a potential therapeutic target. Subsequent to neutrophilic invasion of the subarachnoid space, there is development of a fibrinoid arteritis and leptomeningeal inflammation in the spinal cord and, to a lesser degree, the brain. With chronic progression of the lesions, rupture and hemorrhage of the weakened vasculature may be present, accompanied by thickened leptomeninges with less severe inflammation.

The arteritis is systemic, and there may be other clinical or subclinical organ involvement, in particular the heart, glomerulonephritis, paraspinal muscle, and joints. Rarely, severe motor dysfunction may result from spontaneous bleeding into the subarachnoid space, spinal cord hematoma/hematomyelia, or subconjunctival hemorrhages. Some dogs with immune-mediated polyarthritis (up to 46% and especially Bernese Mountain dogs, Boxers, and Akitas) may show similar clinical signs to dogs with SRMA because of articular process involvement or concurrent meningitis.

Clinical Presentation

Affected dogs are often young adults (8–18 months old) but may be of any age and are usually febrile and hyperesthetic with cervical rigidity and anorexia (Figure 14.74). Neurologic deficits can be seen in the chronic form of

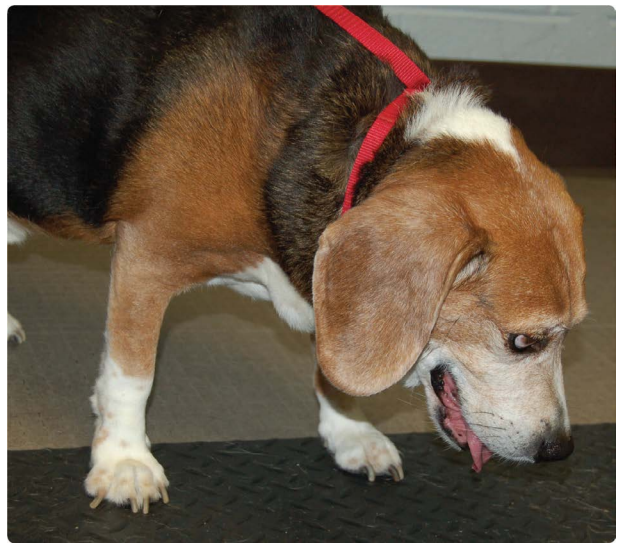


FIGURE 14.74 A Beagle with severe neck pain associated with its sterile meningitis.

this disease, and, rarely, severe motor dysfunction may result from spontaneous bleeding into the subarachnoid space. Some dogs (up to 46%) with immune-mediated polyarthritis, especially Bernese Mountain dogs, Boxers, and Akitas, may show similar clinical signs to dogs with SRMA and have concurrent meningitis. Some dogs may have concurrent glomerulonephritis.

Diagnosis

A marked peripheral neutrophilia with a left shift may be seen at the time of the clinical signs. C-reactive protein (CRP) is reported to be significantly higher in dogs with SRMA compared with dogs with other neurological diseases. However, this is a nonspecific test, as elevation can also occur in sepsis and other CNS inflammatory disease. CRP can also be used to monitor response to treatment. Serum CRP and other acute-phase proteins respond immediately to both the onset and resolution of inflammation and are consistently elevated in patients exhibiting signs suggesting SRMA relapse but with normal CSF and leukograms. CSF often reveals a marked neutrophilic pleocytosis and protein elevation; cell counts of >100 cells/μL are common. Neutrophils are nondegenerative, unlike bacterial meningitis. In the majority of dogs with either acute or chronic disease, there are elevations of IgA levels in the CSF and the serum, although this is not specific for this disease. IgA CSF concentrations are significantly higher in dogs with SRMA compared with other disease categories, with the exception of inflammatory CNS disease, and so are considered nonspecific.

Diagnostic imaging is not required for diagnosis of SRMA but is useful to eliminate other causes of cervical pain. In particular, spinal radiographs to rule out discospondylitis, an important differential for spinal pain and pyrexia in a juvenile dog. MRI of the cervical vertebral column is often normal but may reveal meningeal paramagnetic contrast enhancement, signal changes in the cervical paraspinal musculature (T2 or STIR hyperintensity or contrast enhancement) and multifocal ill-defined, T2-hyperintense lesions within the cervical spinal cord with variable contrast enhancement. MRI may also reveal changes consistent with hemorrhage within the subarachnoid space or spinal cord.

Arthrocentesis is indicated if joint pain is identified and is recommended if signalment is suggestive of SRMA, but CSF analysis is normal, as immune-mediated polyarthritis involving the articular processes can mimic SRMA.

Management

The prognosis can be good if dogs are treated early and aggressively with immunosuppressive doses of corticosteroids, with up to 80% of cases going into long-term remission. Infectious diseases should be ruled out before this treatment is initiated. The treatment is long term and has been reported to be required for over 2 years in some dogs; however, after this time, serum and CSF IgA levels were still elevated in some dogs, so are not considered valuable for disease monitoring. Monitoring of CSF cell count in dogs with this condition is a sensitive indicator of success of treatment. Serum CRP is more useful than CSF cell counts or serum and CSF IgA to guide tapering of therapy. However, normal serum CRP does not exclude future relapse.

In refractory cases or in patients with steroid-related adverse effects, alternative immunomodulation therapy such as mycophenolate, leflunomide, azathioprine, cyclosporin, or cytarabine should be considered. To reduce the adverse effects and reduction in quality of life associated with long-term, high-dose corticosteroids, a combination of mycophenolate and corticosteroids can be used in all cases of SRMA from the onset of the disease, adding leflunomide in refractory cases. This allows a reduction in the daily dose of corticosteroids. CRP, hematology, and ALT should be monitored every 1–2 months, and the mycophenolate is typically continued for 6 months. Successful treatment of SMRA with cytosine arabinoside and corticosteroids in a small cases series is reported. However, there was a high incidence of adverse events that required additional management. Successful treatment of SMRA with azathioprine and corticosteroids is also reported, with a reasonably low relapse rate found.

SPINAL EMPYEMA

Definition/Overview

Spinal empyema is defined as an extensive accumulation of purulent material in the epidural space of the vertebral canal. This is an uncommon condition.

Etiology

Direct extension of osteomyelitis or discospondylitis is the main cause of the infection in veterinary medicine. Infection could also be subsequent to surgery, foreign bodies, and trauma.

Pathophysiology

Extension or introduction of an infectious agent into the spinal canal can cause a purulent accumulation, which can result in compression of the spinal cord and systemic signs of an infectious disease.

Clinical Presentation

Characteristic clinical signs are a high fever, acute progressive spinal hyperesthesia, and progressive myelopathy.

Diagnosis

Hematology reveals an inflammatory leukogram. Blood cultures can be positive. *Staphylococcus* and *Streptococcus* spp. are commonly isolated. Radiography may reveal vertebral physitis or discospondylitis. Diagnosis is aided by myelography, CT, or MRI with



FIGURE 14.75 Epidural soft tissue material compressing the cord (arrow) and confirmed to be empyema can be seen on this sagittal postcontrast T1-weighted MR image of the caudal cervical spine.

identification of extradural compression that extends over multiple spinal cord segments. MRI is most sensitive for assessment of severity and extent of changes associated with infection of the paraspinal muscle and other soft tissue structures (Figure 14.75). Cross-sectional imaging can further help guide surgical therapy.

Management

Effective treatment is rapid institution of an appropriate antibiotic therapy and surgical drainage of the epidural fluid. Surgery is the treatment of choice because it allows for spinal cord decompression, drainage of the infected material, and direct culture of the organism. Dogs with spinal empyema have a good outcome when treated with surgery and the appropriate long-term antibiotic therapy based on culture and sensitivity.

CANINE DISTEMPER VIRAL MYELITIS

Definition/Overview

CDV is a *Morbillivirus* within the family Paramyxoviridae that can cause focal or diffuse lesions in both the gray and white matter of the CNS. Focal or diffuse demyelination can occur in the white matter of the spinal cord. Neurologic forms often occur as the only clinical manifestation in dogs with intermediate levels of viral immunity.

Etiology

CDV.

Pathophysiology

The type of lesion produced in the CNS depends on host immunity and the age and duration of infection. The type of lesion ranges from acute polioencephalomyelopathy with glial and neuronal necrosis in immature or immunodeficient dogs to more chronic leukoencephalomyelopathy with demyelination in older or immunosuppressed dogs. Demyelination is, therefore, a more prominent feature in the chronic stages of disease.

Clinical Presentation

Respiratory, enteric, neurologic, and ocular manifestations have been described in naturally occurring disease. Respiratory and enteric forms of the disease are more common in puppies or severely immunosuppressed adult dogs. Neurologic signs, whether acute or chronic, are usually progressive. Neurologic signs vary with the area of the CNS infected, but spinal cord signs can predominate. Clinical signs of CDV myelitis are focal or diffuse, with the T3–L3 spinal region more frequently involved. Paraspinal hyperesthesia can occur as a result of meningeal inflammation. Myoclonus (involuntary twitching of muscles) can present without other neurologic signs, but as the spinal cord disease progresses, there may be UMN signs in the affected limbs.

Diagnosis

Diagnosis of CDV infection is based on history and clinical signs. A definitive antemortem diagnosis of CDV is difficult to obtain. MRI may provide evidence of white matter involvement in the brain and spinal cord. Clinical laboratory findings and CSF analysis are often nonspecific. Immunofluorescent techniques for CDV antigen on conjunctival tissue, CSF, urine, skin, or blood can facilitate diagnosis but lack sensitivity. Multiple methods of detection increase diagnostic suspicion of CDV. PCR and analysis of CSF-specific IgG levels and determining the CSF-to-serum ratio can be used to detect chronic CDV infections.

Management

The treatment of CDV myelitis is often unsuccessful. Corticosteroid therapy of short duration may provide some remedy. Clinical signs typically wax and wane over time followed by a more rapid progression. The prognosis is considered poor for recovery.

FELINE INFECTIOUS PERITONITIS, MYELITIS, AND MENINGITIS

Definition/Overview

Feline infectious peritonitis (FIP) is a common viral disease in cats caused by the ubiquitous feline enteric coronavirus. FIP is an immune complex forming disease involving virus, antibodies, and complement, which results in multifocal inflammatory lesions affecting the nervous system. A T3–L3 myelopathy is one of three distinct clinical syndromes identified in cats with neurological FIP, which also includes central vestibular syndrome and multifocal CNS disease.

Etiology

Mutated feline coronavirus.

Pathophysiology

Histologic findings include granulomatous inflammation of the meninges, ependymal cells, and choroid plexus. FIP occurs in two forms: Noneffusive (dry) and effusive (wet). CNS involvement is seen most commonly with the dry form.

Clinical Presentation

Most cats infected are <2 years of age, but cats of any age can be infected. Clinical signs are often insidious and present with focal, diffuse, or multifocal distribution. Signs often are vague and reflect multiple organ system involvement. Keratic precipitates can be present on the corneas (see **Figure 14.14**). Systemic signs include pyrexia, weight loss, dullness, and anorexia. Commonly recognized spinal signs are hindlimb or generalized ataxia and paraspinal hyperesthesia. When the virus affects the spinal cord, the resulting pathology includes hydromyelia and myelitis. Other areas of the CNS such as the spinal cord can be involved but not as commonly as intracranial signs.

Diagnosis

Confirmation of FIP antemortem is very difficult. Biopsy confirmation of infected tissue is the only method to definitively diagnose FIP. CSF analysis is abnormal with an elevated total nucleated cell count and protein levels. The white blood cell differential often reflects a neutrophilic pleocytosis, but cellular distribution can be variable. CSF protein concentration can be extremely elevated (1,000–2,000 mg/dL). Results of serologic testing are difficult to interpret reliably. The most useful antemortem indicators of disease are a positive anti-coronavirus titer in CSF (>1:640), a high serum total protein concentration, and compatible findings on imaging. Magnetic resonance imaging abnormalities of cats with FIP myelopathy include meningeal contrast enhancement, ependymal contrast enhancement, and syringomyelia.

Management

FIP is an incurable disease, and clinical management involves supportive and palliative care. Use of corticosteroids and other immunosuppressive drugs may slow the progression of the disease. Various other drugs such as antiviral and immunomodulating (interferon) drugs have been used, but none have been shown to be effective. The prognosis for cats with FIP is poor, with median survival times of 14 days reported when the cats have CNS disease, although recent success has been achieved with the use of nucleoside analogues in cats with neurological FIP.

PROTOZOAL MYELITIS

Definition/Overview

Protozoal infection can cause a focal or disseminated myelopathy in dogs and cats, respectively. Meningoencephalomyelitis and myositis are common lesions associated with *Neospora caninum* infection. Rapid ascending myelitis is more common with *N. caninum* infection. Many previously reported cases of *Toxoplasma gondii* are now thought to be due to *N. caninum*.

Etiology

N. caninum and *T. gondii*.

Pathophysiology

Infection can occur in utero, by ingestion of oocysts (due to fecal contamination), or by ingestion of bradyzoites (in muscle). Although subclinical infection is common, clinically significant protozoal infections tend to occur in immunocompromised or young animals and can affect muscle, peripheral nerves, and the CNS.

Clinical Presentation

The neurologic signs of protozoal infection reflect disseminated or progressive multifocal disease. Dogs as young as 4 weeks of age may develop a progressive asymmetrical or symmetrical paraparesis from *T. gondii* or *N. caninum* infection. The organism infects the lumbosacral nerve roots and muscles and often causes a myelitis and/or meningitis. These dogs may have a "bunny-hopping" gait or present with severe rigid extension of the hindlimbs (**Figure 14.76**). The limbs are rigid because of muscle fibrosis and tendon contracture. The patellar and withdrawal reflexes are lost, and severe muscle atrophy often ensues. Rarely, the disease progresses rapidly to tetraparesis and respiratory paralysis.

Diagnosis

Diagnosis is suspected based on history and clinical signs. Electromyography shows diffuse fibrillation



FIGURE 14.76 A Labrador Retriever puppy exhibiting hindlimb hyperextension associated with a *Toxoplasma* infection of the local nerves and muscles.

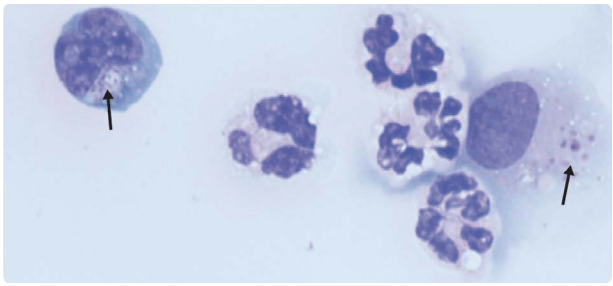


FIGURE 14.77 Cytologic analysis of CSF from a dog with *Toxoplasma gondii* infection revealed intracytoplasmic organisms in many cells (arrows).

potentials and sharp waves in the lumbar paravertebral and hindlimb musculature. CSF analysis shows a mixed cell or mononuclear pleocytosis and an elevated protein concentration, occasionally positive for organisms (Figure 14.77). Histology of the muscle and identification of the organism confirms the diagnosis. Serology for *T. gondii* and *N. caninum* is often positive, and PCR analysis of the CSF can confirm the diagnosis.

Management

Early treatment for 2–4 weeks with combinations of trimethoprim–sulfadiazine or ormetoprim sulfadimethoxine and clindamycin may improve clinical signs. Pyrimethamine may be added to the regimen but can cause bone marrow suppression in young animals. Early antibiotic treatment may improve clinical signs, but recovery is often incomplete. Poor prognostic indicators for resolution of clinical signs include rapidly progressive disease, signs of multifocal CNS disease, hindlimb hyperextension, and a long time interval between onset of clinical disease and treatment.

NEUROMUSCULAR DISORDERS

Clinical Signs

The classical clinical sign of neuromuscular disease is weakness. A paretic gait is usually manifested as a stilted stride that becomes progressively shorter with accompanying ventroflexion of the neck, reluctance to walk or run, lying down, and collapse. If ataxia is present, this suggests a UMN disorder or a sensory neuropathy. Following rest, muscle strength may greatly improve, but such a finding is not consistent. In between episodes, animals may be completely normal or clinical signs of weakness may persist.

Lesion Localization

A thorough history and physical and neurologic examination are essential to determine if weakness is a result of a neuromuscular disease or other systemic disorder. Metabolic and systemic diseases, cardiorespiratory disease, orthopedic, and central neurologic causes of weakness should be ruled out. It is important to approach the patient in a thorough and logical manner, excluding diseases by utilizing the least complex and least invasive tests first.

It is best to perform a standardized clinical examination so that a full physical and neurologic examination is consistently performed. A practical format used for the general examination includes inspection and palpation of muscles and nerves, passive motion of joints, percussion of muscles and tendons, sensory testing, and gait analysis.

Muscle atrophy or hypertrophy can be readily observed at rest, as can spontaneous muscle activity such as fasciculations or tremors. Weakness can often be observed at rest; however, it is easier to detect with moderate walking activity. Weakness of the paraspinal muscles can result in abnormal postures, including thoracic kyphosis and scoliosis. Extraocular, laryngeal, and pharyngeal muscles should also be examined at this time, particularly if the history is suggestive of dyspnea or dysphagia. A complete neurologic examination should be performed in all patients with a history of weakness, exercise intolerance, or collapse.

Gait disturbances can require close observation. An abnormal gait will result from weakness of any of the principal flexor or extensor muscles of the limbs, in addition to any structural abnormalities of the articular surfaces, joint capsules, or ligaments. A normal gait also requires coordination by the CNS, which stimulates or inhibits flexors, extensors, adductors, and abductors for counteracting gravity. In general, gait abnormalities result from (1) pain, (2) muscle weakness, (3) reduced range of joint motion, (4) weakness of UMN or LMN origin, (5) spasticity, (6) dystonia, (7) rigidity, and (8) ataxia. The gait should be observed from both sides as well as from front and back, with ample ambulating space. There are four phases of the gait that should be inspected: Palmar or plantar strike (as the foot meets the floor), midstance, push off, and midswing. The examiner should note the rhythm, symmetry, and strength of strides; the base width of the gait; and the duration of the phases. The base width is the distance between the feet during the strides. Assessment is subjective, but a base width larger than the width of the trunk can suggest sensory deficits causing the ataxia.

Exercise testing in muscle disorders provides the means to assess exercise capacity quantitatively, reproduce exercise-induced symptoms, and investigate the pathophysiology of exercise limitations. Exercise is a powerful tool for evaluating the integrity of the metabolic pathways that power muscular work and assessing the physiologic responses that are linked to the state of muscle energy metabolism. Thus, exercise testing is particularly useful in the investigation of disorders of muscle energy metabolism. In addition, exercise can be utilized to assess objectively the effectiveness of treatment in metabolic myopathies.

Neurodiagnostic Investigation

The diagnostic plan is dependent on the localization of signs, as well as their suspected underlying mechanism.

As some of these problems are episodic, their frequency must be taken into account, and it should be recognized that many of the tests will need to be performed at the time of an "episode." Most neuromuscular disorders, however, will result in continual signs, which may vary in severity based on the level of activity.

The following tests should be considered for all cases with weakness or collapse, particularly if a neuromuscular disorder is suspected.

Video Footage

If the episodes are so infrequent that they are not observed by the clinician, the owners should attempt to capture the event on videotape. Observation of the event is critical to the diagnosis. Without observation, the nature of the event must be surmised by listening to the "eyewitness" description offered by the owner.

Minimum Database

Comprehensive hematology, serum biochemistry (including CK, lactate, and electrolytes), urine analysis, a fecal examination, and a resting electrocardiogram, as well as thoracic and abdominal radiographs, should be considered the minimum essential database. A thyroid panel and an adrenocorticotropic hormone (ACTH) stimulation test should also be considered, as neuromuscular disease may be the first and only manifestation of endocrine disorders. Resting blood pressure assessments should also be performed if there is any concern about a cardiorespiratory disease, and peripheral vascular pulses should always be palpated to evaluate the potential of peripheral vascular compromise.

Serum Creatine Kinase

CK is a specific enzyme marker of myofiber damage and the one most frequently used in the diagnosis of muscle diseases. CK is often increased in necrotizing, inflammatory, and dystrophic myopathies and is usually normal in muscle diseases in which necrosis is not a feature (e.g., myotonia). The enzyme is very labile and so is nonspecific. As the half-life is only about 2 hours, the magnitude and persistence of increased CK activity is an indication of severity and activity of an underlying muscle disease. However, this enzyme can be elevated following IM injections, surgery, prolonged recumbency, and even anorexia in cats. Conversely, muscle disease should never be ruled out based on a normal CK level.

Cardiac Troponin I

Troponin is located in myofibrils and is the regulatory protein of contractile skeletal and cardiac muscle. Cardiac muscle can be affected by generalized myopathies, including muscular dystrophy, mitochondrial myopathies, and necrotizing myopathies. Although cardiac troponin concentrations are not affected by nonspecific types of skeletal muscle damage, a generalized disease of muscle affecting the myocardium could elevate this enzyme. This could be potentially helpful in the future as a prognostic marker based on extent of disease.

Myoglobin

Myoglobin present in the urine (myoglobinuria) usually indicates severe muscle damage, frequently rhabdomyolysis following trauma, toxins, infections, and malignant hyperthermia. However, a correlation does not exist between serum CK and myoglobinuria, and so it is considered an insensitive test. Recurrent myoglobinuria may be detected in inherited metabolic myopathies and in muscular dystrophy. Myoglobin is toxic to the renal tubules and can cause acute kidney injury.

Serology and PCR

Investigations of infectious diseases may require extensive serologic tests, and their interpretation may be difficult, but depending on the potential for exposure, serology should be performed on all possible infectious candidates (particularly *Toxoplasma gondii*, *Neospora caninum*, *Hepatozoon* spp. and *Leishmania* spp.) depending on geographic locale and travel history. Serology for autoimmune conditions such as rheumatoid arthritis, systemic lupus, and myasthenia gravis may be warranted if suspected. Antibodies against the acetylcholine receptor (AChR) should be measured in all dogs with acquired megaesophagus and dysphagia. Anti-GM2 ganglioside Abs have a diagnostic sensitivity of 60% and a specificity of 97% for acute canine polyradiculoneuritis and should be considered for patients with an acute onset of peripheral nerve disease.

Electrophysiology

Extensive electrophysiologic testing may be required to confirm the precise lesion localization of the disease if a neuromuscular abnormality is suspected. An abbreviated needle electromyography (EMG) test may be worthwhile in the initial investigations, as it can quickly aid identification of an axonal or muscular disease. This is particularly helpful in cases with obvious muscle hypertrophy or atrophy. Repetitive nerve stimulation and single-fiber EMG should be considered for neuromuscular junction assessment (**Figure 14.78**).

Advanced Imaging

Unless a CNS abnormality is suspected, it may not be necessary to consider spinal radiographs, CT, or MRI studies. Thoracic radiographs can assist with the diagnosis of megaesophagus and associated aspiration pneumonia. Fluoroscopy or contrast-enhanced radiography may be helpful to evaluate the function of the esophagus if enlargement is not obvious on plain survey radiographs and swallowing if dysphagia is present. Cardiac ultrasonography may be required if a cardiorespiratory condition is suspected.

MRI and CT scans have recently been utilized to document the presence of muscle pathology, particularly



FIGURE 14.78 Electrophysiologic assessment of the nerves in the forelimb. Stimulating needles are placed proximally in close association to a specific nerve, and recording electrodes are placed distally in the interosseous muscles to detect the resultant action potentials.

on postcontrast images. The location of the contrast uptake within the muscles detected on MRI or CT can assist with choosing suitable areas for a more high-yield biopsy, which is important in early-onset, localized, or patchy myopathies.

Cerebrospinal Fluid Analysis

A CSF tap may help to rule out CNS diseases as well as diffuse inflammatory conditions of the nerve roots, but rarely is it a specific test, and rarely will it be helpful in cases of neuromuscular collapse. Evaluation for infectious diseases can be achieved with serologic techniques or with PCR analysis of the CSF.

Muscle and Nerve Biopsy

If a neuromuscular disease is suspected, a muscle or nerve biopsy can provide a specific diagnosis of the underlying cause (Figure 14.79). Since a peripheral nerve can react in only a limited number of ways to a variety of insults, the biopsy in most instances just confirms the presence of axonal degeneration, demyelination, abnormalities of supporting structures, inflammation, or infiltrative neoplasia. However, a nerve biopsy can provide information on regeneration, remyelination, and degree of fiber depletion and fibrosis, which are important for prognosis. The muscle biopsy is of utmost importance in the diagnosis of most muscle diseases, particularly the inherited diseases.

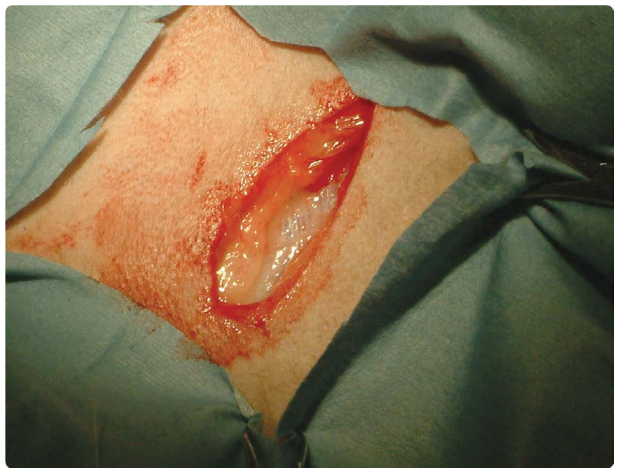


FIGURE 14.79 A linear skin incision exposes subcutaneous fat and shiny underlying muscle fascia. The fascia needs to be incised, which will allow a small piece of muscle to be sampled for histopathologic assessment.

NEUROPATHIES

BREED-RELATED NEUROPATHY

Definition/Overview

Inherited and breed-related neuropathies are rare diseases that usually affect young animals and can produce generalized motor, mixed motor and sensory, pure sensory, and/or autonomic deficits.

Etiology

Unknown, suspected genetic in many breeds.

Pathophysiology

Progressive, usually chronic degeneration of the myelin and/or the axons of sensory and/or motor fibers.

Clinical Presentation

Typically, progressive LMN paresis develops, often affecting the hindlimbs first but eventually involving the forelimbs. The concurrent development of laryngeal paralysis and megaesophagus is recognized as a syndrome called laryngeal paralysis polyneuropathy complex. This syndrome has been reported in young Rottweilers, Dalmatians, Leonbergers, white-coated German Shepherd Dogs, Miniature Schnauzers, Alaskan Malamutes, Black Russian Terriers, and Pyrenean Mountain Dogs among others. It is now recognized that older dogs with idiopathic laryngeal paralysis, in particular Labrador Retrievers, also suffer from a more generalized neuropathy that is likely hereditary. Sometimes referred to as geriatric-onset laryngeal paralysis and generalized polyneuropathy (GOLPP), late-onset laryngeal paralysis (LoLP), or idiopathic acquired laryngeal paralysis, it appears that the laryngeal paralysis is, in fact, part of a progressive generalized neuropathy. GOLPP is a common clinical condition affecting geriatric, large and giant-breed dogs, most commonly Labrador Retrievers, in which the laryngeal innervation degenerates over time. Owners of Labrador Retrievers with LoLP perceive it to be a life-limiting disease that negatively impacts their dog's quality of life. GOLPP

typically develops by 10–11 years of age. The condition appears to be a peripheral neuropathy, with degenerative changes present in peripheral nerves. It remains unknown whether the disease also affects the central nervous system. The underlying pathogenesis of GOLPP is not understood. It is currently unclear whether it is due to a single pathological mechanism or is a common clinical phenotype resulting from a variety of underlying pathologies.

Several different breeds of cat are also reported to have hereditary neuropathies, including the Siberian cat, the Snow-Show, the Bengal, and Birman. There are some general similarities between the reports in these breeds, giving rise to the idea that the breeds may be predisposed to the same disease rather than the disease truly being breed specific. Heterogenous motor polyneuropathies should be considered in young cats of any breed and sex that are presented with relapsing or progressive generalized neuromuscular disease. There is a suggestion that some of these breed-related and often self-limiting peripheral neuropathies may have an inflammatory component.

Familial sensory neuropathies are particularly unusual but have been reported in English Pointers, English Springer Spaniels, French Spaniels, Longhaired Dachshunds, Jack Russell Terriers, Border Collies, Miniature Pinschers, Fox Terriers, and German Shorthaired Pointers. The Border Collie breed is affected with a progressive proprioceptive ataxia with self-mutilation with an age of onset between 2 and 7 months. The neuropathy in this breed is classified as a sensory and autonomic neuropathy, and an inversion disrupting the FAM134B gene has been identified through whole genome sequencing. Dachshunds present with nociceptive deficits, mild ataxia, and loss of conscious proprioception. These dogs have been reported to self-mutilate their penis and dribble urine. The disease in English Pointers and French and English Spaniels is more severe and more specific to nociception. They lose nociception in their distal limbs around 3–8 months of age and as a result lick, chew, and even autoamputate their digits. These dogs do not have conscious proprioceptive deficits.

Diagnosis

Diagnosis is by recognition of typical breed, age of onset, presentation, and ruling out other disorders by electrophysiologic evaluation of nerve function and nerve biopsy. All dogs with laryngeal weakness should undergo investigation for a more extensive polyneuropathy with at least a neurological examination. Thyroid function and myasthenia gravis testing is encouraged. Esophageal function tests, including a swallowing study using barium contrast radiography or fluoroscopy, thoracic radiographs, or evaluation of swallowing reflexes/responses, should be considered in these dogs. In one study, all dogs (age range 7–15 years) with laryngeal paresis had abnormal esophageal function tests at the time of diagnosis, but only a third had clinical signs.

Management

Therapy is limited to symptomatic management of signs in most diseases. For cases with laryngeal paresis, treatment usually includes a unilateral surgical arytenoid lateralization, which is generally very successful and associated with an improved quality of life. The most common postoperative risk is aspiration pneumonia. Other surgical treatments include bilateral arytenoid lateralization, partial laryngectomy, and tracheostomy; however, these procedures are associated with a higher complication rate than unilateral arytenoid lateralization. There is no specific treatment for the progressive generalized polyneuropathy. Physical therapy is advised in many cases to maintain range of motion and muscle mass. It is important to recognize problems and diagnose the cause of signs in animals used for breeding.

ENDOCRINE NEUROPATHY

Definition/Overview

Endocrine diseases that are known or suspected to cause a peripheral neuropathy include diabetes mellitus, hypoglycemia (most commonly as a result of insulinoma in dogs), hypothyroidism, and hyperadrenocorticism. These diseases are associated with chronic progressive diffuse weakness with or without systemic signs of the specific endocrine disease.

Etiology

Diabetes mellitus, hypoglycemia (most commonly as a result of insulinoma in dogs), hypothyroidism, and hyperadrenocorticism.

Pathophysiology

Poorly controlled diabetes mellitus causes distal axonal degeneration, with the longest peripheral nerves affected first.

Clinical Presentation

The most common manifestation of diabetes mellitus is a sciatic neuropathy in cats causing a plantigrade stance in the hindlimbs at rest and when walking. Affected cats retain the ability to ambulate, but hock flexion is absent when the withdrawal reflex is tested. As the signs progress, they also develop a palmigrade stance. Although pathologic changes and sporadic cases of neuropathy have been detected in diabetic dogs, it is usually a subclinical problem in this species. However, when it does occur, it resembles a degenerative myelopathy, which will reverse with improved diabetic regulation. Hypothyroidism has been reported to be a cause of weakness in dogs as a result of a generalized peripheral neuropathy. In addition, idiopathic neuropathies such as facial or laryngeal paralysis, peripheral vestibular syndrome, and megaesophagus have been linked to hypothyroidism.

Diagnosis

Diagnosis of diabetic neuropathy is strongly suspected in animals with poorly controlled diabetes and classic neurologic findings. Definitive diagnosis is made by electrophysiologic studies and nerve biopsy. Although axonal degeneration can be present in severely affected animals, the most common findings are abnormalities in Schwann cells and myelin. Diagnosis of hypothyroidism is made by measurement of serum total and free T4 and thyroid-stimulating hormone levels.

Management

Prognosis for full recovery of peripheral nerve function associated with diabetes mellitus is good in most cases. Restoring normoglycemia prevents progression and, in most cases, may result in complete resolution of neurologic signs. Supplementation with thyroxine may reverse the signs of generalized peripheral neuropathy associated with hypothyroidism over 2–3 months, but laryngeal and esophageal abnormalities usually persist.

INSULINOMA

Definition/Overview

Chronic, severe hypoglycemia (<3 mmol/L [54 mg/dL]) is almost invariably associated with insulinomas in dogs and can result in a generalized neuropathy.

Etiology

Pancreatic beta cell tumor.

Clinical Presentation

The most common neurologic signs result from the effects of hypoglycemia on the CNS (seizures, weakness, exercise intolerance, and collapse). However, persistent hypoglycemia may also cause a distal peripheral neuropathy that manifests initially as a stiff gait, particularly in the hindlimbs, but progresses to more obvious signs of a generalized peripheral neuropathy with prominent sciatic deficits.

Diagnosis

Diagnosis is based on documentation of hypoglycemia with concurrent inappropriate hyperinsulinemia in the presence of the clinical signs and associated with a pancreatic mass, documented with ultrasound or MRI or surgical exploration (Figure 14.80) and histopathology following resection.

Management

Treatment of the insulinoma may improve the gait depending on the extent of the underlying disease.

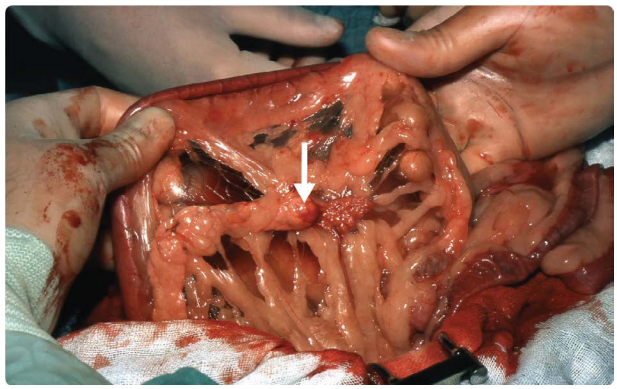


FIGURE 14.80 Insulinoma (arrow) as viewed at surgery in a dog. (*Courtesy of M. Schaer.*)

INFLAMMATORY DISEASES

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Definition/Overview

Chronic inflammatory demyelinating polyneuropathy (CIDP) causes slowly progressive LMN tetraparesis in adult dogs and cats with no gender or breed bias.

Etiology

CIDP is an immune-mediated disease in which the inflammatory reaction is focused on peripheral nerve myelin sheaths. The etiology of the disease is unknown, but it appears to be similar to chronic inflammatory demyelinating polyneuropathy in humans, which is believed to be an immune-mediated disorder driven by cell-mediated and humoral responses against peripheral nerve antigens. CIDP in humans has been associated with many systemic disorders such as diabetes, hypoproteinemia, thyroid dysfunction, and neoplasia.

Pathophysiology

CIDP is an apparently immune-mediated disease in which the inflammatory reaction is focused on peripheral nerve myelin. The chronic presentation in dogs normally is manifested by demyelination and remyelination with onion bulb formation associated with prominent mononuclear inflammation. Some aspects of this lesion are manifested in other canine radiculoneuropathies, usually in association with wider involvement of peripheral nerves

Clinical Presentation

Signs can relapse intermittently and can progress from paraparesis to tetraplegia. Shifting lameness, a plantigrade stance, and ventroflexion of the neck have been described in cats, along with megaesophagus and regurgitation. Leg tremors and laryngeal and facial paralysis have been noted in dogs.

Diagnosis

Anti-GM2 ganglioside antibody titer evaluation should also be considered in these cases, although other antibodies directed against molecules of the nodal and paranodal organization may be involved. MRI may frequently not be considered for a polyneuropathy, but hypertrophy of the cervicothoracic nerve roots in a dog with CIDP has been reported. Notably, nerve roots not always are bilaterally or symmetrically affected. Definitive diagnosis is reached by a combination of electrophysiologic studies and nerve biopsy. Typically, motor nerve conduction velocity is reduced. There is multifocal paranodal demyelination in teased nerve fiber preparations, and thinly myelinated fibers are visible on semithin sections. Electron microscopy reveals macrophages stripping myelin and the presence of demyelinated and remyelinated fibers. There is also a mononuclear infiltrate.

Management

Treatment consists of immunosuppression with prednisone (initial dose of 2 mg/kg p.o. divided q.12 h. for 1–2 weeks followed by gradual tapering over a period of weeks). Most cases respond favorably to this regimen, although some eventually relapse and become steroid resistant.

ACUTE POLYRADICULONEURITIS

Definition/Overview

Acute polyradiculoneuritis (APN) (inflammation of peripheral nerves and nerve roots) is probably the most common peripheral neuropathy of dogs and young purebred cats.

Etiology

The disease can be subclassified according to cause as Coonhound paralysis, (seen in North America, with onset of signs 7–10 days after raccoon bites), idiopathic polyradiculoneuritis, and postvaccinal polyradiculoneuritis (extremely rare). Risk factors suspected (apart from inoculation of racoon saliva and vaccination), include upper respiratory and gastrointestinal infections. Jack Russell Terriers and West Highland White Terriers have a significantly greater odds of developing APN. An important association in man is concurrent infection with a specific serotype of *Campylobacter jejuni*. A similar relationship has been documented in dogs, with the most common *Campylobacter* species identified being *Campylobacter upsaliensis*. This is possibly associated with consumption of raw chicken found in dogs' diets. APN dogs also have significantly lower serum 25-hydroxyvitamin D3 concentration when compared to control dogs. However, the cause and clinical significance of the altered vitamin D status in dogs with acute polyradiculoneuritis is not yet clear. It has also been shown that dogs with idiopathic acute polyradiculoneuritis are more likely to have positive titers for *T. gondii* than control dogs.

Pathophysiology

Signs are caused by an inflammatory reaction to axons and myelin sheaths that is most intense at the level of the ventral nerve root, with minimal dorsal root involvement. Electrophysiological findings in dogs suggest that it is primarily a motor axonopathy. A recent study in dogs has demonstrated the presence of anti-GM2 ganglioside antibodies in sera from a high percentage of dogs with APN. Gangliosides are found in high concentrations in membranes of neural tissue. When antiganglioside antibodies bind to gangliosides, the complement cascade is activated, resulting in an attack to membrane complexes, pathologic changes, and dysfunction of the structures targeted.

Clinical Presentation

Affected dogs suffer from an acute ascending paralysis that progresses over 2–4 days to LMN tetraparesis or plegia. Spinal hyperesthesia has been noted in some dogs, and CNs can become involved, leading to dysphonia and facial weakness. Severe cases may suffer respiratory failure. Affected cats develop a rapidly ascending flaccid tetraparesis with severely decreased to absent spinal reflexes within 72 hours from the onset of clinical signs. Some cats develop respiratory paralysis leading to apnea and eventual euthanasia, whereas others can recover uneventfully in 4–6 weeks.

Diagnosis

The number of diseases that cause acute onset of LMN tetraparesis/tetraplegia is limited, and polyradiculoneuritis should always be suspected when this clinical picture occurs. Other diseases to consider include botulism and, in the United States and Australia, tick paralysis. Fecal culture and PCR from fecal samples can help to identify *Campylobacter* species. Anti-GM2 ganglioside antibodies were detected in 14 out of 25 APN dogs, and anti-GA1 antibodies in one further dog, providing a diagnostic sensitivity of 60% and a specificity of 97%.

EMG reveals spontaneous electrical activity consistent with denervation (fibrillation potentials and positive sharp waves). Nerve conduction velocities are dispersed and reduced, with nerve roots more severely affected than the distal nerve. Definitive diagnosis is established with a nerve biopsy.

Management

Treatment is focused on supportive care and rehabilitation. Corticosteroid administration is not beneficial. The pulmonary function of recumbent animals must be monitored closely. If hypoventilation is suspected, a blood gas analysis should be performed to document progressive increases in PCO_2 (>65 mmHg; reference value 35–45 mmHg) to determine whether mechanical ventilation is necessary. Animals should be turned,

and passive range-of-motion exercises and massage of limbs should be performed at least four times a day. If pulmonary function is unaffected, with adequate supportive care most animals will recover over a period of 3–6 weeks. However, the need for mechanical ventilation, the presence of aspiration pneumonia, and severe muscle atrophy with development of contractures all worsen the outcome. The median time to ambulation (>3 steps without support) from onset of the clinical signs is 50.7 days (range 10–110 days). The median time to reach a plateau (best clinical improvement) is 95 days (range 13–300 days). Prolonged courses (up to 3–4 months) and incomplete recoveries are possible in some dogs. Usually, the more severe the clinical signs are, the longer the recovery time is.

PROTOZOAL NEURITIS

Definition/Overview

Infection with the protozoal organisms *Toxoplasma gondii* and *Neospora caninum* can cause an intense polyradiculoneuritis in dogs, accompanied by a myositis.

Etiology

Protozoal infection.

Pathophysiology

Clinically significant protozoal infections affect young or immunocompromised dogs. Dogs are both definitive and intermediate hosts for *Neospora* spp., with cattle, sheep, goats, and other mammals also acting as intermediate hosts. Cats are the definitive host for *Toxoplasma* spp., with most mammals serving as intermediate hosts. Infection can occur transplacentally (common for *N. caninum*), by ingestion of protozoal cysts from infected secondary hosts, and by ingestion of oocysts shed in feces (common for toxoplasmosis).

Clinical Presentation

Clinical signs can be extremely variable as a result of infection of muscle, peripheral nerve, and the CNS. Typically, the hindlimbs are affected first, and the combination of myositis and neuritis causes rigid extension of the limbs, with severe muscle atrophy and contractures developing quickly. However, multifocal CNS signs can be present, and a cerebellar syndrome has also been reported.

Diagnosis

Definitive diagnosis can be made by identification of the organisms in muscle or nerve biopsies, combined with serology. Serology alone can be confusing with a high rate of false-positive titers, particularly in the case of toxoplasmosis. PCR analysis of CSF may provide a more specific diagnosis, but the sensitivity of this test is unknown.

Management

Treatment of protozoal infections can be attempted using clindamycin. However, a combination of trimethoprim/sulfadiazine and pyrimethamine is more effective at actually killing the organisms and penetrates the CNS well. Animals on this protocol can be supplemented with folic acid. Azithromycin can be added as it is effective at killing intracellular organisms. Prognosis depends on the severity of clinical signs and muscle contractures. Recovery of normal function is unlikely, although institution of treatment can prevent progression of signs. If treatment is initiated while signs are still mild, the prognosis is better, but relapses can occur.

TOXIN-ASSOCIATED DISEASES

BOTULISM

Definition/Overview

Botulism intoxication can result in an acute onset of rapidly progressive diffuse neuromuscular signs. Multiple dogs can be involved at the same time depending on the source and accessibility of the toxin.

Etiology

There are several forms of the botulinum toxin produced by *Clostridium botulinum*, but botulinum C is the only form associated with canine disease. Rare cases have been described in association with types B and D.

Pathophysiology

Botulism is caused by absorption of the botulinum toxin following ingestion of spoiled carrion or raw meat. The spores formed by bacteria, which are highly resistant to severe environmental conditions, will germinate in anaerobic conditions such as those provided by rotten carcasses of dead animals. Following cell or spore lysis, the toxin is released and binds with other protein complexes to form progenitor toxins. These progenitor toxins are extremely stable, particularly at low pH, and pass through the stomach into the small intestine where the toxin is released and absorbed. The toxin is absorbed from the small intestine by endocytosis and enters the lymphatic system and from there the bloodstream. The botulism toxin heavy chain then binds rapidly and with extremely high affinity to presynaptic peripheral nerve terminals, affecting the limb, trunk, and head muscles.

The botulinum toxin produced by *C. botulinum* is taken up at the neuromuscular junction and prevents synaptic release of acetylcholine at the neuromuscular junction of cholinergic nerves. Botulinum toxins, like tetanospasmin, are zinc endopeptidases, and botulinum C binds to the presynaptic protein SNAP 25.

Clinical Presentation

Botulism causes LMN tetraparesis that starts in the hindlimbs as mild weakness but progresses to tetraplegia in severe cases. CNs are often involved, producing facial paresis, dysphonia, megaesophagus, and regurgitation. Autonomic signs such as mydriasis and dry eye are variably present. Onset of signs usually occurs over 2–4 days and is often preceded by a history of dietary indiscretion (usually consuming spoiled meat) and vomiting or diarrhea. Botulism is extremely rare in cats.

Diagnosis

History and clinical signs are indicative of the disease. Electrophysiologic studies may be supportive of the diagnosis. Reduced motor nerve conduction velocity has been reported, suggesting that there is a concurrent neuropathy. Definitive diagnosis is difficult to establish. The presence of botulinum toxin in the serum, feces, or vomitus may be detected using a specific antitoxin to perform a neutralization test in mice, and use of an ELISA has been reported, demonstrating an increase in serum titers to botulinum neurotoxin type C, 3 weeks after onset of signs. Typically, the toxin is no longer detectable by the time neurologic signs are evident.

Management

Treatment is supportive and recovery occurs over a period of approximately 3 weeks. Recumbent dogs should be turned regularly, kept clean and dry, and their bladder expressed if necessary. Megaesophagus and regurgitation should be managed by intermittent suction of the esophagus by means of a nasoesophageal tube, antacids (e.g., famotidine) to decrease acidity of stomach contents (decreases esophagitis and effects of aspiration), and antibiotics for aspiration pneumonia if necessary. Ampicillin, aminoglycosides, erythromycin, ciprofloxacin, and imipenem interfere with neuromuscular conduction and should be avoided. If megaesophagus is present, the dog should be fed while held or propped with the head up and that position maintained for approximately 30 minutes after feeding. Arterial blood gas analysis should be performed to check for hypoventilation in tetraplegic animals and in animals that may have aspirated. Passive range-of-motion exercises and massage should be performed every 6 hours while the animal is recumbent. If pulmonary function is not adversely affected, dogs have a good prognosis with adequate nursing. If aspiration pneumonia or hypoventilation develops, the prognosis is grave, but recovery can occur if appropriate ventilatory support can be provided.

TETANUS

Definition/Overview

Tetanus is a toxicoinfectious disease resulting from bacterial infection by *Clostridium tetani*. The infection can spread from its origin to the CNS and cause local or generalized muscular rigidity before potentially spreading to the brain. Without intensive supportive care, many cases can be fatal.

Etiology

Tetanus is caused by absorption of tetanus toxin (tetanospasmin) produced by the anaerobic motile, Gram-positive, nonencapsulated, spore-forming, rod-shaped bacterium *Clostridium tetani*. The organism's resistant spores are ubiquitous, with a natural habitat in moist, fertile soil; however, they can survive indefinitely in dusty indoor environments. The source of the bacterium is usually a penetrating wound providing both contamination with *Clostridium* and the conditions suitable for its growth. Infection can follow teething, dental fractures, nailbed infections, parturition, or surgeries such as ovariohysterectomy.

Pathophysiology

The exotoxin tetanospasmin is absorbed into the bloodstream and from there is taken up by the nerves. In a similar fashion to botulinum toxin, tetanospasmin has zinc metalloproteinase activity and binds to and cleaves synaptobrevin (a SNARE protein that mediates fusion of synaptic vesicles with the presynaptic membrane), preventing the release of neurotransmitter and causing failure of synaptic transmission. However, in tetanus, the toxin is transported retrogradely up the motor neurons and from there to inhibitor interneurons (the Renshaw cells) where it blocks release of the inhibitory neurotransmitters glycine and gamma-aminobutyric acid (GABA).

Clinical Presentation

Tetanus most commonly affects young large-breed dogs and is rare in cats. Clinical signs can take up to 3 weeks to become apparent from the onset of infection, although most cases exhibit symptoms within 5–12 days. Owners most frequently report changes in the face and eyes as the first clinical signs that they notice.

A characteristic facial expression (risus sardonicus) is often seen as a result of increased facial muscle tone. The palpebral fissure is wider than usual, the pupils are miotic, the ears are rigid, the lips are drawn back, and the forehead is wrinkled. The third eyelid may be protruded, and there is often profuse salivation because the animal has difficulty swallowing. Involvement of the head can lead to spasms of the masticatory and pharyngeal muscles, causing trismus (lockjaw) and dysphagia. Trismus is not pathognomonic for tetanus on its own and must be differentiated from the other causes, which include temporomandibular joint disease or subluxation, masticatory myositis, and retrobulbar abscess.

At least 50% of dogs progress within a median of 4 days (range 0–14 days) to recumbency with severe muscle spasms (Figure 14.81). Visual and tactile stimuli and placing the animal on its side often results in a further increase in muscle tone, resulting in muscle spasms. As



FIGURE 14.81 A young Bull Terrier exhibits generalized signs of tetanus with limb rigidity, creating a "sawhorse" stance and facial muscle abnormalities compatible with "risus sardonicus."

signs progress, the animal may have difficulty breathing and can develop a hiatal hernia and megaesophagus as a result of increased diaphragmatic tone. Both bradycardia and tachycardia have been described in dogs with tetanus due to effects of the toxin on the autonomic nervous system, in addition to dysuria, urinary retention, and constipation.

A tetanus severity classification system has been proposed in dogs: Class I dogs have only facial signs of tetanus; class II dogs have generalized rigidity or dysphagia, with or without class I signs; class III dogs have class I or II signs and are recumbent or have seizures; and class IV dogs have class I, II, or III signs as well as abnormal heart rate, respiratory rate, or blood pressure measurements. Survival rate decreases with severity class.

Cats are more likely to present with a focal form of the disease with signs limited to the area of the infection (e.g., monoparesis following distal limb injury, although this has also been reported in dogs).

Diagnosis

The diagnosis is usually presumptive and based on the presence of classic clinical signs. The presence of a wound or history of recent surgery are supportive of the diagnosis. Attempts can be made to culture the organism but are frequently unsuccessful due to low organism numbers and the need for anaerobic conditions. An infectious process may be suggested by the results of the complete blood count. Muscle enzymes may be elevated in patients with tetanus because of the persistent muscle spasticity; high activities of creatine kinase (1,599–18,405 U/L [reference range 61–394 U/L]) have been documented in more than 50% of dogs. CSF analysis is unremarkable. Radiographs may be helpful to identify involvement of the esophagus, diaphragm, and secondary changes in the lungs resulting from aspiration pneumonia. Attempts to isolate *C. tetani* from wounds often fails because of the low concentration of organisms and the requirement for strict anaerobic culture conditions at 37° C for at least 2 weeks. A Gram stain of a smear from an open wound may identify Gram-positive rods and dark-staining spheric endospores, but the morphology of the bacterium is nonspecific and similar to that of many other bacteria.

Management

There are three treatment strategies for dogs and cats with tetanus: (1) Toxins present in the body outside of the CNS should be neutralized; (2) organisms present in the body should be destroyed to prevent further toxin release; and (3) the effects of the toxin already in the CNS should be minimized. Intensive care management of affected animals is essential.

- **Toxin neutralization**

  Antitoxin neutralizes any toxin that is unbound to the CNS. Therefore, the timing of administration in relation to the onset of the disease is essential to its effectiveness. The antitoxin used can be either antitetanus equine serum or human tetanus immune globulin. Antitoxin should be administered intravenously (100–500 IU/kg, although a wide range of doses is cited by different authors) to inactivate any circulating toxin. A test dose of 0.1 mL of a 1:10,000 solution should be given subcutaneously 20–30 minutes prior to the intravenous dose to check for adverse reactions. A wheal at the site of injection may indicate that an anaphylactic reaction will develop. Epinephrine (0.1 mL/kg IV of the 1:10,000 dilution), glucocorticoids, and an antihistamine (e.g., diphenhydramine) should be readily available in case of an adverse reaction (or the latter two even given on a prophylactic basis. There has been no significant benefit in survival, severity of clinical signs, or duration of clinical signs shown for dogs treated with antitoxin.
- **Antimicrobial therapy**

  If the source of infection can be identified, it should be treated by surgical debridement (if necessary), flushing with hydrogen peroxide. Antimicrobials are essential to kill vegetative *C. tetani* organisms in order to reduce the amount of circulating toxin. Classically, penicillin G has been the drug of choice, either intravenously as an aqueous potassium or sodium salt or intramuscularly as the procaine salt (20,000–100,000 U/kg q.6–12 h. for 10 days in cats and dogs). However, metronidazole (7–10 mg/kg p.o. or IV q.8–12 h. for 10 days) has been shown superior to penicillin G in clinical tetanus because it achieves bactericidal therapeutic concentrations in anaerobic tissues. Other options include clindamycin (10 mg/kg p.o., IV, or IM q.8–12 h.) and tetracycline (22 mg/kg p.o. or IV q.8 h.) or doxycycline (5–10 mg/kg p.o. or IV q.12 h.).
- **Supportive care**

  Intensive nursing care is essential for successful treatment of patients with tetanus. The dog or cat should be isolated in a dark and quiet environment, with cotton wool balls placed in the external ear canals. Minimal handling is optimal, and all treatments, therefore, should be coordinated to occur together at set

times through the day. Complications occurring during treatment include aspiration pneumonia, upper respiratory tract obstruction requiring tracheostomy, hiatal hernia, hyperthermia, and coxofemoral luxation. Pressure sores or decubital ulcers should be prevented with appropriate soft or padded bedding and frequent turning.

Extensor tone can be reduced with a number of different drugs. Phenobarbital, pentobarbital, acepromazine, chlorpromazine, diazepam, and methocarbamol have all been advocated. These drugs also help to reduce patient anxiety. With severe signs such as generalized tonic–clonic seizure activity, generalized body stiffness, and opisthotonos, a propofol infusion may be necessary, but cardiovascular parameters should be monitored closely, and careful consideration should be given to whether the patient should be intubated and placed on positive-pressure ventilation. The use of magnesium sulfate ($MgSO_4$) infusions or supraphysiologic magnesium therapy has been documented as a potential adjunct therapy in the management of spastic paralysis in dogs with tetanus. A dose of 70 mg/kg over 30 minutes followed by an initial CRI of 100 mg/kg per day has been recommended for dogs based on human literature. The goal of this treatment is to increase total serum magnesium to 2–4 mmol/L (4.86–9.73 mg/dL) based on a target therapeutic range derived from the human literature.

If unable to prehend and swallow food, the animal may need to have a gastrostomy tube placed, and in some instances, a tracheostomy tube may also be necessary. Percutaneous gastrostomy tube placement may prevent the complications associated with nasogastric tube feeding, particularly the stress that may be associated with an indwelling intranasal tube. Gastrostomy- or gastrojejunostomy-assisted tube feeding also can reduce the risk of aspiration pneumonia, a potential complication in dogs with severe forms of tetanus and those that are recumbent for a prolonged period. If airway obstruction develops because of laryngeal spasm or a buildup of saliva or tracheal secretions, intubation and mechanical ventilation may be necessary. A tracheostomy often is performed in these patients to decrease the need for continuous anesthesia. Urinary and fecal retention occur in some patients with hypertonic anal and urinary sphincters. An indwelling urinary catheter may be beneficial in these patients, although the urine should be analyzed regularly for evidence of nosocomial infection.

Recovery is slow, and signs may take up to 4 months to resolve completely, although most animals dramatically improve within a month of starting treatment. Reported outcomes of tetanus vary. Most dogs that recover (58%–82%) show some improvement within 5–12 days, although the presence of autonomic abnormalities is a poor prognostic indicator. Median length of hospitalization for dogs has been reported to be 13 days (range 6–42 days). Mortality is likely related to the severity of clinical signs. One study reveals that all dogs with class I or II clinical signs survived, and only 58% of class III or IV signs survived. However, actual mortality may be difficult to estimate given the fact that long-term intensive management of these cases is associated with a significant financial burden for the owners; therefore, many animals are euthanized humanely. A full recovery may not be possible in at least 15% of dogs that survive, but continued improvement may be seen for 3–5 months. Cats are reported to recover well from localized tetanus, with some residual deficits remaining several months later.

At least 46% of surviving dogs in one large study developed abnormal "dream enactment," clinically consistent with rapid eye movement (REM) sleep disorder. Twitching, running, and vocalization were new sleep behaviors in 53, 80, and 60% of affected dogs. Clinically, probable REM sleep disorder was described as violent or "nightmare"-like in 36% affected dogs and like an epileptic seizure in 40% affected dogs. When trialed, antiepileptic medications were ineffective. Onset occurred before discharge in 25% cases. For dogs that developed REM sleep disorder after discharge, onset occurred within 2 weeks of discharge in 77% dogs. The clinical events did not worsen in severity or frequency in any dog and spontaneously resolved within 6 months in 43% cases.

TICK PARALYSIS

Definition/Overview

Attachment of a tick is associated with an acute onset of progressive diffuse neuromuscular disease. It is encountered commonly in the United States, and more severe forms occur in Australia and Africa.

Etiology

The ticks most commonly associated with tick paralysis in North America are the Rocky Mountain wood tick (*Dermacentor andersoni*), the American dog tick (*Dermacentor variabilis*), the lone star tick (*Amblyomma americanum*) and the Gulf Coast tick (*Amblyomma maculatum*). In Australia, tick paralysis is a common problem affecting both dogs and cats living along the east and southeastern coast reportedly due to *Ixodes holocyclus* and *Ixodes coronatus*.

Pathophysiology

Certain species of female ticks contain a toxin within their saliva that causes presynaptic blockade of acetylcholine release and a flaccid tetraplegia. Signs appear after the tick has been attached for 3–5 days and progress over 1–3 days. They usually resolve within an equal period following removal of the tick, except in the case of the Australian tick, in which signs can progress following tick removal.

Clinical Presentation

Ascending lower motor neuron paralysis develops within 5–9 days of tick attachment. One tick is sufficient to cause paralysis; large numbers of ticks are associated with increased severity of clinical signs and rapidity of

onset. Early signs are hindlimb weakness and ataxia, which progresses to tetraplegia over 1–3 days. Tendon (stretch) reflexes, such as the patellar reflex, are usually lost before withdrawal reflexes. Cranial nerves are rarely affected, but some animals may show changes in voice, suggesting laryngeal involvement, or facial and masticatory muscle weakness. Sensory, urethral, and sphincter functions are unaffected in dogs with American tick paralysis. If ticks remain in situ, death from respiratory paralysis can occur in 1–5 days.

Diagnosis

Appropriate clinical signs and the presence of an engorged tick together with rapid improvement after tick removal are sufficient for diagnosis.

Management

Removal of entire tick, including mouth parts, is necessary for treatment. Repeated searching of the whole body for further ticks should be undertaken. Long hair should be clipped to improve the efficacy of tick searches. Application of topical insecticidal solution is effective against ticks. Noticeable improvement occurs within 24 hours of tick removal, and the majority of cases are fully recovered within 1–3 days if all ticks are removed. Supportive care for paralysis should be provided. Prognosis is good if all ticks are removed, and animals do not require ventilatory support.

MYASTHENIA GRAVIS

Definition/Overview

Immune-mediated myasthenia gravis (MG) is a relatively common neuromuscular disease affecting dogs and, occasionally, cats. Acquired MG has been observed in dogs older than 3 months of all breeds but particularly in German Shepherd Dogs, Golden Retrievers, and Labrador Retrievers. In one report, the relative risk of acquired MG in different breeds of dog was highest in Akitas. Newfoundlands and Great Danes may be predisposed to a familial form of acquired MG. A bimodal age of onset (<5 years and >7 years) has also been reported in affected dogs, and spayed females may have heightened risk. In cats, Abyssinians and the closely related Somalis seem to be overrepresented, and gender is not a risk factor in cats.

Etiology

MG is an immune-mediated or less frequently a congenital disease.

Pathophysiology

MG is characterized by failure of neuromuscular transmission due to a reduction in the number of functional nicotinic AChRs on the postsynaptic membrane of the neuromuscular junction. This deficiency of functional receptors reduces the sensitivity of the postsynaptic membrane to the neurotransmitter acetylcholine. Acquired canine MG is an immune-mediated disease caused by production of autoantibodies (predominantly IgG) directed against muscle AChRs at the neuromuscular junction. Based on experimental and human clinical studies, MG involves both B and T cells. Complement-mediated destruction of the postsynaptic membrane of the neuromuscular junction and antibody-induced blockade of AChR function occur.

Congenital myasthenic syndromes (CMSs) are defined in dogs and cats as a clinically heterogeneous group of genetic disorders causing aberrant neuromuscular transmission. Congenital myasthenic syndromes have an onset at 2–16 weeks of age and are infrequently seen in dogs and cats. Congenital myasthenia gravis is thought to be an autosomal recessive trait in Jack Russell Terriers, Smooth Fox Terriers, and Springer Spaniels. A reversible form of congenital myasthenia gravis has been identified in young Smooth-haired Miniature Dachshunds, in which the clinical signs spontaneously resolve by 6 months of age. Congenital myasthenia gravis has also been reported in several cats. Despite efforts to classify CMSs in dogs and cats, many suspected CMSs presently cannot be classified because of a lack of identification of an underlying genetic mutation. Among these suspected CMSs, many are suspected to be postsynaptic because of a lack of postsynaptic AChR.

Clinical Presentation

Several forms of MG have been described in dogs including:

- *Focal MG:* Defined as weakness in >1 focal skeletal muscle group that does not involve the appendicular skeletal muscles. These focal skeletal muscle groups are facial, esophageal, pharyngeal, and laryngeal skeletal muscles. The predominant clinical signs are regurgitation associated with megaesophagus (note that the caudal two-thirds of the esophagus in dogs contains striated muscles), and dysphagia. Less commonly, other signs encountered are facial muscle weakness, a weak jaw tone, a weak gag reflex, and laryngeal paralysis. The incidence ranges from 26% to 43% of all cases of myasthenia gravis.
- *Generalized MG:* Defined as appendicular skeletal muscle weakness associated with severe exercise intolerance. This can occur with or without megaesophagus, facial or laryngeal muscle weakness and is reported in up to 57% of dogs with myasthenia gravis (Figure 14.82).
- *Acute fulminant MG:* Associated with a rapid onset of paralysis and megaesophagus and possibly including diaphragm and intercostal muscle fatigue. This may just represent a severe presentation of the generalized form but can present acutely.

Up to 15% of cats and 43% of dogs with MG may not have clinically detectable limb muscle weakness. Approximately 7% of dogs and 30% of cats with MG have generalized weakness without esophageal or

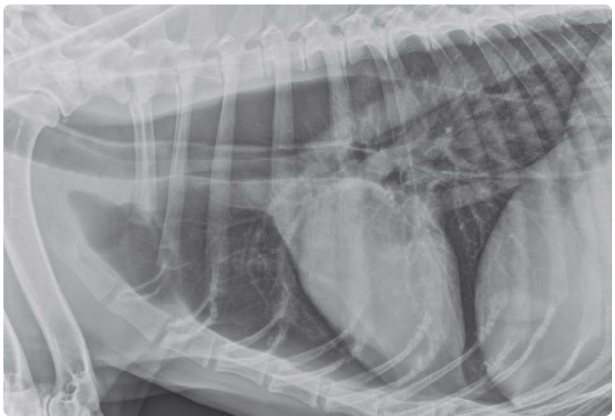


FIGURE 14.82 Lateral thoracic radiograph of a dog with megaesophagus.

pharyngeal dysfunction. Any one of the three forms of MG may be either nonthymoma associated or thymoma associated, which is considered a separate clinical form of the disease.[33,34] There is a greater incidence of mediastinal thymoma in cats with myasthenia gravis (15%–52%) than in dogs (3.4%).

While affected dogs may develop a stiff, choppy gait, in which the stride shortens until they crouch in sternal recumbency and rest their head on their forepaws, cats with MG are usually hypotonic, "floppy," and reluctant to walk. After rest, dogs walk normally for a short period before repeating the cycle. Many animals have facial weakness (repeated stimulation of the palpebral reflex causes it to diminish) and are unable to close their eyelids (accompanied by lack of menace and absent palpebral reflex). Third eyelids may be protruded. Neurologic examination may reveal normal sensation and intact tendon reflexes but diminished withdrawal reflexes, poor postural reactions, and proprioceptive deficits.

Diagnosis

A presumptive diagnosis of MG may be made by the resolution of muscle weakness following IV injection of edrophonium chloride (0.1 mg/kg in dogs, with a maximum 5 mg dose; 0.2–1.0 mg total dose in cats; Editors' Note: Drug currently unavailable). This test may be useful in diagnosing focal myasthenia if a decreased or absent palpebral reflex responds to edrophonium. A negative test does not rule out MG—either focal or generalized. Occasionally, this test causes a cholinergic crisis of bradycardia, profuse salivation, miosis, dyspnea, cyanosis, and limb tremors, which can be reversed with atropine (0.05 mg/kg IV). Electrodiagnostics in the form of repetitive stimulation and single-fiber EMG can assist in the diagnosis, although the tests lack sensitivity and specificity. However, lengthy anesthesia is necessary, and this may be contraindicated in a critical patient.

Diagnosis of MG is confirmed in both dogs and cats by the demonstration of circulating AChR antibodies in a serum sample. Reactive antibodies can usually be demonstrated in the sera of approximately 98% of dogs with acquired MG and in most affected cats. Antibody elevations in dogs and cats are specific for MG, whether it is acquired, paraneoplastic, or concurrent with another autoimmune disease. In the absence of immunosuppressive therapy, there is a good correlation in dogs between the clinical course of MG and the AChR antibody titer. Immunosuppressive therapy for longer than 7–10 days will lower antibody titers, so a thorough history is important to establish prior medication administration. Antibody titers may be negative early in the course of disease, and so retesting is suggested if clinical signs were recent in onset. Seronegative MG may occur if low-titer and high-affinity antibodies are bound to muscle AChRs in a range undetectable by the standard serum assay.

The diagnosis of CMSs is confirmed by the presence of exercise-related weakness in very young dogs for which muscle biopsy does not indicate a congenital muscle or peripheral nerve disease. The response to intravenous edrophonium is variable with an increase in muscle strength and a decremental response of the muscle action potential following repetitive nerve stimulation seen in animals with postsynaptic deficits, or no response seen in animals with presynaptic deficits and a deterioration of function seen following acetylcholinesterase inhibitors in synaptic CMSs. Biochemical quantification of acetylcholine receptor concentration in an external intercostal muscle specimen can be performed at a few research centers but is only useful in the postsynaptic CMSs. As this is not an immune-mediated disease, testing for acetylcholine receptor antibodies is not indicated. Genetic testing is available for most of the documented breeds affected.

Management

Treatment should begin with oral anticholinesterase drugs (pyridostigmine bromide 0.5–3 mg/kg q.12–8 h.). The drug dosage should be started at the low end to avoid cholinergic crisis and can then be modified based on response. As noted previously, cholinergic crisis manifests itself as a combination of bradycardia, profuse salivation, urination, diarrhea, dyspnea (bronchospasm, bronchosecretion), miosis, cyanosis, and limb tremors. If oral treatment is not possible due to severe regurgitation, injectable neostigmine can be given (0.04 mg/kg IM q.6 h.).

If limb muscle strength has not returned to normal following anticholinesterase treatment, or if intolerable side effects of cholinergic excess are noted, and if there is no evidence of aspiration pneumonia, alternate day low-dose corticosteroid therapy should be initiated (0.5 mg/kg p.o. q.48 h.) in the immune-mediated form of MG. Immunosuppressive dosages of corticosteroids should be avoided early in the disease, as this can exacerbate weakness, but the steroid dose can be increased every 2 weeks up to an immunosuppressive daily dose (2 mg/kg) if necessary. Once a state of clinical remission is achieved, the dose is reduced by 50% every 2–4 weeks while monitoring carefully for relapse. If there is no response to immunosuppressive doses of corticosteroids, azathioprine can be added to the regimen

(2 mg/kg p.o. q.24 h.). There are reports describing the successful short-term outcome in several dogs with severe myasthenia gravis treated with plasmapheresis.

Supportive care includes the elevation of food and water bowls or placement of a percutaneous endoscopic gastrostomy (PEG) tube. Many dogs can be fed with food presented as small balls; the animal is then kept in a vertical position for 10–20 minutes to assist with the passage of food into the stomach. Water must also be offered, in reduced quantities, on a more frequent basis and from an elevated position. Construction of a "vertical feeding" system (e.g., a Bailey chair) has been described by owners of dogs with myasthenia gravis. These maintain the dog in an upright position during and following eating. Famotidine administered orally or via a PEG tube (0.5–1.0 mg/kg q.12 h.) may reduce the nausea and gastrointestinal irritation caused by pyridostigmine. These side effects may also be prevented by diluting liquid pyridostigmine 50:50 with water. In addition, famotidine helps to reduce esophagitis due to acid reflux.

MYOPATHIES

NONINFLAMMATORY MYOPATHIES: ACQUIRED

ENDOCRINE MYOPATHIES

STEROID MYOPATHY

Definition/Overview

Chronic corticosteroid therapy may result in dramatic muscle atrophy and weakness, particularly in dogs. Steroid myopathy may be overlooked in patients receiving steroid treatment for disorders that produce weakness, such as inflammatory myopathies or CNS diseases.

Etiology

Chronic corticosteroid therapy.

Pathophysiology

The major actions of glucocorticoids are to increase muscle protein catabolism and inhibit synthesis of myofibrillar proteins. Protein synthesis is inhibited primarily in type 2 muscle fibers, and so net protein loss is greatest in these fibers. Inhibition of protein synthesis is dependent on the dose of steroids administered. Steroid myopathy is also associated with alterations in muscle carbohydrate metabolism, due in part to steroid-induced insulin resistance.

Clinical Presentation

Animals with steroid myopathy commonly have other clinical signs of glucocorticoid excess; skin and hair coat changes are typical. Patients rarely develop severe clinical weakness with <4 weeks of steroid administration. Muscle atrophy, particularly of the masticatory muscles, may occur within 2 weeks of steroid therapy (Figure 14.83). It has been reported that steroid myopathy is more common after administration of the fluorinated corticosteroids such as triamcinolone, betamethasone, and dexamethasone.



FIGURE 14.83 Marked hindlimb muscle atrophy is seen in this dog confirmed to have an underlying steroid myopathy.

Diagnosis

Diagnosis of steroid myopathy necessitates exclusion of other causes of generalized muscle disease, in addition to evidence of long-term steroid administration and muscle biopsy confirmation of disease. The typical pattern of type 2 fiber atrophy may be identified early in the course of steroid myopathy with muscle biopsy.

Management

The treatment of choice for iatrogenic steroid myopathy is steroid dose reduction. Obviously, this can only be achieved if the condition that warranted treatment with corticosteroids is safely controlled. Conversion to a nonfluorinated steroid preparation and alternate day treatment are recommended. Improvement may be seen but can take many weeks or longer. Because of the catabolic effect of corticosteroids, optimizing nutritional status is important. Protein supplementation in patients with a loss of muscle mass is recommended. Physical therapy or mild exercise may be useful in prevention and treatment of muscle weakness and wasting in patients receiving glucocorticoids. Androgens can partially antagonize the catabolic actions of glucocorticoids.

CUSHING'S MYOPATHY

Definition/Overview

A myopathy has been described in dogs with spontaneous hyperadrenocorticism. A pseudomyotonia is most often seen.

Etiology

Hyperadrenocorticism.

Pathophysiology

The myopathy found in Cushing's disease has been attributed to glucocorticoid excess, as described previously for steroid myopathy. It has been suggested that elevated levels of ACTH may also be myopathic.

Clinical Presentation

Most affected dogs are middle aged; females are predisposed. Poodles and the smaller breeds are also overrepresented. Affected dogs often, but not always, have characteristic signs of hyperadrenocorticism, in addition to generalized muscle atrophy, but with a stiff gait and hypertrophy of the proximal appendicular muscles. Of the cats that have been reported with Cushing's syndrome, the majority are middle aged or older (average 10–11 years) and are usually of mixed breed. Approximately 70% of the cats are female. No distinct myopathy has been reported in these cats, but muscle wasting is a prominent finding. Some dogs will have generalized muscle weakness and atrophy on presentation rather than generalized stiffness.

Diagnosis

Diagnosis necessitates exclusion of other causes of generalized muscle disease, in addition to biochemical confirmation of Cushing's disease and muscle biopsy evidence of type 2 myofiber atrophy. There may be mild serum CK elevation in some dogs. The pathologic changes have been described as dystrophic.

Management

Signs can resolve in some dogs over a period of months when they are treated for their primary disease, but deficits can persist. Improvement in motor function appears unlikely but may be inversely related to the duration of disease prior to therapy. Dietary and rehabilitation treatments should also be instituted, as for steroid myopathy.

HYPOTHYROID MYOPATHY

Definition/Overview

A myopathy occurs in dogs associated with spontaneous or experimentally induced hypothyroidism.

Etiology

Hypothyroidism.

Pathophysiology

In general, hypothyroidism affects carbohydrate, protein, and lipid metabolism within muscle. Muscle glycogenolysis is impaired, protein synthesis and degradation are decreased, causing net protein catabolism, and muscle uptake of triglycerides is reduced. Thyroid hormone imbalance has been determined to contribute to abnormalities of cellular energy generation in striated muscle through multiple carnitine-dependent mitochondrial biochemical pathways, supported in part by the fact that chronic hypothyroidism in dogs is associated with a marked reduction of skeletal muscle-free carnitine.

Clinical Presentation

Neuromuscular signs, including stiffness, weakness, reluctance to move, and muscle wasting, may be the first indication of an underlying endocrine disorder. Typical clinical signs of hypothyroidism, including lethargy, weight gain, seborrhea, and alopecia, may or may not be clinically evident.

Diagnosis

Serum CK concentrations may be normal, especially in the first 6 months of the disease, or significantly elevated. Aspartate aminotransferase and lactate dehydrogenase activities can also be elevated. Prominent histopathologic alterations include variation in muscle fiber size with type 2 fiber atrophy and an increased population of type 1 fibers, and multifocal nemaline rod inclusions.

Management

The only effective treatment is to restore the patient to a euthyroid state. Once this is achieved, the prognosis for recovery can be good and be achieved in a few weeks. It is reasonable to institute physical therapy to limit disuse atrophy and joint contractures. There is no evidence that dietary manipulation improves muscle function in this disease.

NONINFLAMMATORY MYOPATHIES: DYSTROPHIC

MUSCULAR DYSTROPHY

Definition/Overview

Muscular dystrophies are a heterogeneous group of inherited, degenerative, mostly noninflammatory disorders characterized by progressive muscle weakness, muscle atrophy or hypertrophy, gait abnormalities, and muscle contractures beginning in the first few months of life. While over 30 muscular dystrophies have been identified to date in humans, only a small number have been characterized in dogs and cats. The muscular dystrophies were originally characterized based on phenotypic features such as pattern of inheritance and the distribution of muscle involvement. With the advent of the molecular age, most have been shown to occur due to mutations of genes that code for proteins in the dystrophin–glycoprotein complex that spans the muscle cell membrane. Dystrophin and its associated glycoproteins

connect the contractile apparatus in the muscle to the sarcolemma, providing mechanical stability.

Etiology

Muscular dystrophy in dogs and cats is most commonly associated with dystrophin deficiency. In some cases, dystrophin is present but is abnormal.

Pathophysiology

Dystrophin links the myofiber cytoskeleton to the extracellular matrix and is crucial in stabilization of muscle fiber membranes during contraction. The dystrophin gene is located on the X chromosome; thus, dystrophin deficiency is an X-linked recessive trait transmitted by a female carrier. Females may be asymptomatic or expressing carriers or be homozygous for the disease, produced from mating carriers and affected males. Homozygous females have elevated CK levels and comparable histologic lesions to those seen in affected male dogs.

Clinical Presentation

Dystrophin deficiency has been documented in several breeds of dogs, including Golden Retriever, Rottweiler, German Short-haired Pointer, Irish Terrier, Groenendael Shepherd Dog, Japanese Spitz, Samoyed, Miniature Schnauzer, Brittany Spaniel, Rat Terrier, Old English Sheepdog, Pembroke Welsh Corgi, Cavalier King Charles Spaniel, Weimaraner, Labrador Retriever, Alaskan Malamute, Jack Russell Terrier, Lurcher, Australian Labradoodle, Border Collie, Miniature Poodle, Spanish Water Spaniel, Norfolk Terrier, and Labrador Retriever as well as in Domestic Shorthair cats. Clinical signs usually develop in the first 6 months of life and are rapidly progressive, although a slower disease course has been documented in some dogs. Affected dogs may demonstrate remarkable phenotypic variation, with some dogs dying within the first few days of life, and others living well into adulthood.

A deficiency of dystrophin in dogs manifests primarily in males, causing generally diffuse muscle atrophy and hypertrophy of certain muscle groups (cranial sartorius, semimembranosus, semitendinosus, and tongue muscles) and with generalized muscle hypertrophy or atrophy in cats (Figure 14.84). Affected animals can be weak at birth and ineffectual sucklers, necessitating nutritional supplementation. As affected animals age, they become more evidently exercise intolerant. Dogs have a characteristic plantigrade posture with the paws laterally rotated and tarsi held close together. While walking, they may advance the hindlimbs simultaneously (bunny hop) and abduct the forelimbs. Dysphagia, regurgitation, and dyspnea may occur as a result of hypertrophy of the lingual, pharyngeal, and esophageal musculature and the diaphragm. Cardiomyopathy may result in heart failure.

Diagnosis

A 6-minute walk test, defined as the distance an individual can walk in 6 minutes, is commonly used in muscular dystrophy clinical trials and has been employed in dogs to characterize cardiac and respiratory disease severity. The serum CK concentration is usually markedly elevated (10,000–100,000 IU/L). EMG reveals complex repetitive discharges. A dystrophic phenotype, characterized early in the course of disease by small group muscle fiber necrosis and regeneration, and more chronically by fibrosis and fatty deposition, is typically present on histopathology of muscle biopsy specimens. An absence of or decreased amount of dystrophin on immunohistochemistry and immunoblotting of muscle specimens confirms the diagnosis. Recently, MRI has been used to characterize the dystrophic muscle. Gene sequencing is routinely done in humans to identify specific mutations for the sake of genetic counseling and targeted therapies. However, mutations have been identified in only a few of the canine conditions.



FIGURE 14.84 Muscular dystrophy in a young cat showing excessive salivation associated with hypertrophy of its tongue. (*Courtesy of M. Schaer and F. Gaschen.*)

Management

There is no specific treatment. Prednisone (0.5 mg/kg q.24 h.) could have benefit in affected dogs. However, this has not been substantiated by clinical studies. If steroids are used, they should be combined with physical therapy. The prognosis is poor.

NONINFLAMMATORY MYOPATHIES: NONDYSTROPHIC CONGENITAL MYOPATHIES

The nondystrophic congenital myopathies are defined by distinctive morphologic abnormalities in skeletal muscle biopsies, including centronuclear and myotubular myopathies, the core myopathies, and protein accumulation myopathies, including nemaline rod and myofibrillar myopathies. The genetic basis for some of these myopathies is known in dogs.

CENTRONUCLEAR MYOPATHY (PREVIOUSLY KNOWN AS LABRADOR RETRIEVER MYOPATHY, TYPE 2 FIBER DEFICIENCY, AUTOSOMAL RECESSIVE MUSCULAR DYSTROPHY)

Definition/Overview

Centronuclear myopathies in humans are heterogeneous forms of inherited muscle disorders that share common clinical and histologic features. Hallmarks of the disease include generalized muscle weakness, ptosis, ophthalmoplegia externa, absence of the patellar reflex in Labrador Retrievers, muscular atrophy predominantly affecting type 1 myofibers, nuclei centralization, and pale central zones with variably staining granules.

Etiology

This is an autosomal recessively inherited myopathy. A short, interspersed repeat element (SINE) exonic insertion in the PTPLA gene leads to multiple splicing defects.

Pathophysiology

Historically, this disorder has been referred to as a polyneuropathy, muscular dystrophy, myotonia, and a hereditary myopathy. The precise etiology was unknown, and there was much debate about whether it represented a myopathy or a neuropathy, as characteristics of both were observed. Investigation of chronic pathologic changes in a group of Labrador Retrievers with a similar phenotype demonstrated that the muscle pathology became more obviously myopathic with time, and central nuclei were evident. The term centronuclear myopathy was proposed for this disease, as the majority of muscle fibers display centrally placed nuclei, with disorganized sarcoplasmic architecture over the long term.

Clinical Presentation

Yellow, chocolate, and black Labrador Retrievers from 8 weeks to 11 months of age exhibit a stiff "bunny-hopping" gait with an abnormal "low" head and neck posture and exercise intolerance. Tendon reflexes are absent or reduced. The signs are exacerbated by cold ambient temperature, exercise, or excitement but tend to stabilize at 1 year of age. Affected dogs often have reduced muscle mass and a poor conformation, and working strains of Labrador Retriever are overrepresented.

Diagnosis

Serum CK activity is normal or only mildly elevated. EMG reveals fibrillation potentials, positive sharp waves, and complex repetitive discharges. Nerve conduction studies are normal. Pathologic changes within muscle biopsy specimens are variable and can include both neuropathic and myopathic abnormalities. There is usually dramatic variation in myofiber size, with small and large group atrophy. A few fibers display centrally placed nuclei and this percentage increases over the long term. A type 2 fiber deficiency has been described. Genetic testing provides the definitive diagnosis, and a DNA-based test is now available for identification of affected dogs and carriers (http://www.labradorcnm.com).

Management

Supportive therapy and avoidance of cold are advised until the condition stabilizes. The disease itself is not lethal, and so the prognosis is fair, but dogs always have reduced exercise tolerance and will not be able to perform as working dogs. The condition tends to stabilize at approximately 1 year of age.

INHERITED MYOPATHY IN GREAT DANES (PREVIOUSLY NAMED CENTRAL CORE MYOPATHY, CORE-LIKE MYOPATHY)

Definition/Overview

A hereditary, noninflammatory myopathy with distinct histologic myopathic features has been described in young Great Dane dogs, affecting both sexes. While it was originally described as a "central core myopathy," the histochemical characteristics differ from this disease in humans. Now the disease is termed "inherited myopathy of Great Danes," potentially until an underlying cause has been identified.

Etiology

An autosomal recessive mode of inheritance is most likely. New unpublished studies have recently confirmed that this myopathy now belongs in the centronuclear/myotubular group of myopathies.

Clinical Presentation

Clinical dysfunction can be seen to affect both males and females from 6 to 19 months of age (median age of onset is 7 months), and consists of progressive muscle wasting, exercise intolerance, general body tremors, and collapse exacerbated by excitement or exercise. All affected dogs have fawn or brindle coat coloration. Affected dogs are usually stunted when compared to their littermates. The generalized muscle atrophy is usually mild to moderate and particularly affects the biceps femoris, quadriceps, temporalis, gluteal, supraspinatus, and infraspinatus muscles. The dogs "tuck" their legs under their abdomen and have an extended tail carriage. When they walk or run, they are short strided with a stiff hindlimb gait, beginning to "bunny hop" as they get faster. The tremors are present at rest and get worse with any movement or excitement. The neurologic examination is unremarkable, but some dogs have been described with reduced reflexes. Myalgia has not been described in any dogs.

Diagnosis

Serum CK activity has been noted to be normal to increased (up to 26-fold). EMG reveals fibrillations and positive sharp waves in all muscles. Diagnosis is easily made by examination of muscle biopsy specimens that show well-defined central cytoarchitectural changes that are highlighted by localization of oxidative enzyme activity.

Management

There is no known treatment at present, and the disease is usually progressive and fatal, although survival for up to 55 months has been described.

HYPOKALEMIC MYOPATHY

Definition/Overview

Hypokalemic myopathy is seen in cats and, very rarely, in dogs, resulting from one of the following: Reduced potassium intake, increased potassium entry into the cells, increased potassium loss from the body, familial disorder of electrolyte regulation (seen in Burmese kittens).

Etiology

Acute or chronic hypokalemia.

Pathophysiology

Hypokalemia significantly affects muscle membrane activity and, therefore, muscle function. The myocyte becomes increasingly refractory to depolarization in a hypokalemic environment. Eventually, the muscle cell membrane suddenly becomes permeable to sodium ions, and membrane hypopolarization occurs, inducing an acute onset of severe weakness. The familial disorder of electrolyte regulation (e.g., as seen in Burmese kittens) has been found to be due to a single nonsense mutation in the gene (WNK4) coding for lysine-deficient 4 protein kinase, an enzyme present primarily in the distal nephron. The underlying pathomechanism in affected cats is, therefore, likely to be a potassium-wasting nephropathy, as this enzyme is involved in complex sodium/potassium exchange mechanisms in the kidney.

Clinical Presentation

Clinical signs of muscle weakness in the cat become evident with any cause of potassium depletion and include generalized weakness and ventroflexion of the neck (Figures 14.85 and 14.86). The most severely affected patients exhibit profound exercise intolerance accompanied by collapse. The weakness can ultimately result in paralysis and is progressive until the potassium deficit is corrected. The neurologic examination is within normal limits.



FIGURE 14.85 Young kitten with hypokalemic myopathy showing its cervical muscular weakness. (*Courtesy of M. Schaer.*)

Diagnosis

The serum potassium level is often 1.5–3.5 mEq/L. Serum CK is often 500–10,000 IU/L. Chronic kidney disease and adrenocortical aldosteronomas in cats with urine loss of potassium should be ruled out with serum biochemistry and urine evaluations, as well as imaging assessments of the structure and function of the kidney and adrenal glands. The dietary potassium content should be investigated; diets should be at least 0.6% rich in potassium. Hyperthyroidism should also be ruled out. Electrophysiology may be normal or have areas of fibrillations and positive sharp waves. Histologic examination of muscle biopsies may be normal or show muscle fiber necrosis with little or no evidence of inflammation. It is worth mentioning that hypokalemia in Burmese cats is not always present concomitantly with the clinical signs, which are episodic, and this requires serial serum potassium measures. Fortunately, genetic testing for the mutation in the gene WNK4 is now available.

Management

Potassium gluconate (2–4 mEq p.o. q.12 h.) may be used in all animals. The dosage is adjusted until the serum



FIGURE 14.86 The same kitten 24 hours later after potassium supplementation. (*Courtesy of M. Schaer.*)

potassium levels are normal. Adequate diet may be enough if insufficient potassium was the initiating cause, but potassium supplementation may be needed for life in cats with renal disease. Spironolactone is helpful for treating aldosterone-secreting tumors and adrenocortical hyperplasia involving the zona glomerulosa. Adrenalectomy is a definitive treatment for the adrenal tumor unless metastasis has occurred. Severely affected cats may be treated with IV potassium chloride (0.2–0.4 mEq/kg/h diluted in IV fluids) with constant cardiac monitoring. Higher doses might even be required. Prognosis can be good if the potassium levels can be regulated or supplemented.

MYOTONIA CONGENITA

Definition/Overview

Myotonia is a clinical sign defined as prolonged contraction or delayed relaxation of a muscle after voluntary movement or after mechanical or electrical stimulation.

Etiology

Myotonia congenita is commonly due to diminished chloride conductance across the muscle membrane.

Pathophysiology

As the chloride channel contributes approximately two-thirds of the resting membrane conductance, a fall in chloride channel conductance significantly compromises the resting membrane potential. During normal muscle activation–depolarization, potassium ions accumulate in the sarcoplasmic reticulum and increase the probability of further depolarizations, which is "buffered" in the presence of normal high-chloride conductance. Loss of this conductance tips the balance toward potassium-induced after-depolarization bursts that manifest as myotonia. In some cases, this is due to genetic defects in skeletal muscle ion channels. Sodium, calcium, and potassium channel abnormalities have all been documented in people with similar muscle dysfunctions and likely exist in veterinary medicine.

Clinical Presentation

Myotonia is characterized by muscle stiffness without cramping and muscle dimpling after palpation. Congenital myotonia has been described in the Chow Chow (suspected autosomal recessive), Miniature Schnauzer (autosomal recessive), Australian Cattle Dog, Jack Russell Terrier, and in a series of related domestic kittens. Dental and craniofacial abnormalities were exhibited in affected Miniature Schnauzers. Single cases of congenital myotonia have been reported in a Great Dane, a Staffordshire Terrier, and a Cocker Spaniel. In dogs, clinical signs of muscle stiffness are evident at the time of first ambulation and are progressive; however, the signs can improve with exercise. Myotonia is accompanied by difficulty in rising, splaying of the limbs, a "bunny-hopping" gait, muscle hypertrophy, regurgitation, and stridor. Hypertrophied skeletal muscles are painless on palpation. Similar clinical signs have been documented in cats.

Diagnosis

Routine laboratory evaluations, including serum CK concentration, are usually normal. Electrophysiologic findings are characterized by waxing and waning myotonic discharges sounding like a "revving" motorcycle. Muscle biopsy evaluation may reveal muscle hypertrophy or a type 1 fiber predominance without inflammation. For detection of the mutant allele in affected and carrier Miniature Schnauzers, a DNA-based test on whole blood has been developed and is available at the University of Pennsylvania. A novel mutation of the CLCN1 gene associated with hereditary myotonia has also been identified in the Australian Cattle dog, and a DNA test is now available.

Management

Treatment is directed at decreasing the repetitive activity in the muscle by using antagonists to voltage-gated sodium channels. These drugs include extended-release procainamide (40–50 mg/kg p.o. q.8–12 h.), quinidine, phenytoin, and mexiletine (8.3 mg/kg p.o. q.8 h.). The treatment has been documented to improve but not normalize the condition; therefore, the prognosis depends on the severity of the clinical signs in the individual animal.

MISCELLANEOUS MYOPATHIES AND CAUSES OF COLLAPSE

EXERCISE-INDUCED COLLAPSE IN LABRADOR RETRIEVERS

Definition/Overview

A syndrome of exercise intolerance and collapse has been observed in young adult (often 7 months to 2 years old) Labrador Retrievers of either sex and any color, especially those used in field trials. This genetic condition has also been detected in Chesapeake Bay Retrievers, Curly-coated Retrievers, Boykin Spaniels, Pembroke Welsh Corgis, and mixed-breed dogs thought to be Labrador Retriever crosses A similar syndrome has been seen in working Border Collies, Golden Retrievers, and Australian Shepherd Dogs, although it is likely that a different genetic mutation is responsible.

Etiology

A genetic mutation identified in the dynamin 1 gene (DNM1) is responsible for this disorder in Labrador Retrievers.

Pathophysiology

Dynamin 1 is expressed almost exclusively in the brain and spinal cord where it plays a key role in synaptic

vesicle endocytosis at the presynaptic terminal membrane. The mutant protein results in a temperature dependent reversible loss of motor function. It appears that this is an autosomal recessive disease.

Clinical Signs

Affected dogs are normal at rest and with normal activity. They are usually very well muscled, athletic, and excitable. The earliest gait abnormalities seen in exercising dogs with exercise-induced collapse (EIC) usually include a "rocking" or forced gait, with a wide-based hindlimb stance. Dogs that can still walk after exercise exhibit a characteristic crouched hindlimb gait with long strides and a base-wide posture when turning. Ataxia is usually noted after 5–15 minutes of strenuous activity, often followed by an episode of collapse, panting, and distress. Patellar reflexes are lost during this time, and this finding may persist beyond recovery to a normal gait. The dogs usually return to normal after 10–20 minutes of rest, especially if passive cooling actions such as fans are used. A small percentage of dogs have died during the exercise period. Although dramatic elevations in body temperature after exercise (>41.5°C) have been reported, normal Labrador Retrievers demonstrate similar such elevations without collapse. Affected dogs are significantly more tachycardic and have more severe respiratory alkalosis after exercise compared with normal dogs. Although a few dogs with EIC have been documented with mild elevations in serum CK levels after exercise, they are not compatible with dystrophic or myonecrotic muscle. Muscle biopsy characteristics and sequential lactate and pyruvate concentrations are normal when evaluated.

Affected Border Collies develop abnormal mentation and/or an abnormal gait during evaluation. All dogs have postexercise elevations in rectal temperature, pulse rate, arterial blood pH, PaO2, and lactate and decreased $PaCO_2$ and bicarbonate, as expected with strenuous exercise, but there are no significant differences between affected dogs and normal dogs. Electrocardiography demonstrates sinus tachycardia in all dogs following exercise. Needle electromyography is normal, and evaluation of muscle biopsy cryosections using a standard panel of histochemical stains and reactions is normal. Genetic testing excludes the dynamin-1-related exercise-induced collapse mutation and the V547A malignant hyperthermia mutation as the cause of this syndrome. Although a genetic basis is suspected, the cause of collapse in this breed is not yet determined.

Diagnosis

Apart from severe alkalosis on arterial blood gas analysis, all clinicopathologic (including lactate-to-pyruvate ratios), electrophysiologic, and histopathologic tests are normal. A genetic test is now available for identification of affected and carrier dogs of the Labrador Retriever, Chesapeake Bay Retriever, and Curly-coated Retriever breeds (http://www.vdl.umn.edu/services-and-fees/canine-neuromuscular/index.htm).

Management

The condition is not progressive, and so a normal life span should be expected if the dogs are not heavily exercised. Exercise restriction is the only advice given at this time regarding treatment, especially when ambient temperatures are high. Hunting dogs may be less affected in cold weather. Genetic testing can be used to guide breeding programs.

FIBROTIC MYOPATHY

Definition/Overview

This acquired, usually nonpainful disorder associated with a fibrous band within a muscle has been reported sporadically in dogs affecting specific muscle groups, including the muscles of the medial thigh (gracilis, semimembranosus, or semitendinosus), sartorius, infraspinatus, and iliopsoas. It is most commonly seen in German Shepherd Dogs, usually male, with an age range from 8 months to 9 years. Similar disorders have been reported in the Dobermann, Rottweiler, St. Bernard, Boxer, and Old English Sheepdog. Fibrotic myopathy of the semitendinosus has been reported in a cat.

Etiology

Active dogs seem to be susceptible to this disorder, and recent studies in dogs suggest that fibrotic myopathy may be related to muscle injury from excessive activity, including jumping and sprinting.

Pathophysiology

Fibrotic myopathy has been called gracilis or semitendinosus myopathy, although any of the hamstring muscles can be affected, and a similar disease has been described affecting the infraspinatus, sartorius, and iliopsoas muscles. A fibrous band can be palpated within the affected muscle belly and can extend the length of the muscle. It is proposed that muscle strain causes inflammation, edema, and localized hemorrhage, which leads to fibrosis. Increased angulation (flexion) at the stifle in normal German Shepherd Dogs may predispose these dogs to increased hamstring stress during physical activity, explaining their overrepresentation.

Clinical Presentation

This may be a unilateral or bilateral disease, and signs depend on the muscle group involved. While onset in some dogs is acute, the gait deficit appears to be insidious in most dogs and is best seen when dogs are "trotting."

- *Gracilis myopathy:* In dogs with gracilis and/or semimembranosus or semitendinosus muscle involvement, the hindlimb gait is characterized by a shortened stride

with a rapid medial rotation of the paw, external rotation of the hock, and internal rotation of the stifle during the mid-to-late swing phase of the stride, resulting in the paw being slapped to the ground prematurely. The gait anomaly results from restricted abduction of the coxofemoral joint and reduced extension of the stifle and hock.

- *Iliopsoas fibrotic myopathy:* This has been associated with chronic progressive lameness, flexion contracture of the coxofemoral joints, severe pain, and decreased femoral reflexes.
- *Infraspinatus myopathy:* Fibrotic contracture of the infraspinatus muscle, a rare musculotendinous disorder mainly affecting hunting dogs, begins as an acute onset of a painful nonweight-bearing lameness. Following this onset, the initial pain and lameness improve over a period of 1–4 weeks, after which a characteristic circumducted gait abnormality develops in the forelimb accompanied by elbow adduction with external rotation of the distal part of both forelimbs.

Diagnosis

The gait is characteristic of the disease and neurologic examination is usually normal. Tight fibrous cords are palpable in affected muscles. Atrophy or swelling may be associated with this disease when affecting the infraspinatus muscles. Serum CK levels may be normal or moderately elevated in some animals. Absence of myoelectrical activity in the band during EMG evaluation is consistent with total replacement of muscle fibers by dense connective tissue. Ultrasonography, CT, and MRI can all be useful for diagnosing muscle fibrosis in the specific muscles affected by this disease.

Management

Prognosis is guarded to poor, since the condition in dogs tends to recur within several months following surgical resection of the fibrous band, or transection, partial excision, or complete resection of the affected muscle. However, tenectomy has been described to improve gait and provide pain relief associated with iliopsoas muscle contracture, as it has with bilateral infraspinatus contractures. Nonsurgical treatment (e.g., corticosteroids, NSAIDs, acupuncture) is usually ineffective. Nonsurgical rehabilitation, including therapeutic ultrasound and cross-fiber friction massage, resulted in mild improvement in several dogs (slight increase in range of motion of the stifle and less crossing-over of hindlimbs). However, gracilis and semitendinosus fibrosis does not appear to be painful and simply causes a gait deficit. Dogs can live with these diseases without a problem.

EXERTIONAL RHABDOMYOLYSIS, MALIGNANT HYPERTHERMIA, AND RHABDOMYOLYSIS

Definition/Overview

Rhabdomyolysis is a clinical syndrome consisting of acute muscle necrosis with swollen painful muscles causing weakness and collapse. With the exception of racing Greyhounds and sled dogs, exertional rhabdomyolysis (ER) is rare. Malignant hyperthermia (MH) has been reported in various breeds of immature and mature dogs: St. Bernards, Border Collies, Labrador Retrievers, Pointers, Spaniels, Greyhounds, and animals crossbred with Dobermanns.

Etiology

MH is a hereditary disorder of skeletal muscle, with collapsing episodes triggered by exposure to halothane, depolarizing muscle relaxants, and occasionally stress or exercise. Rhabdomyolysis may also occur sporadically in dogs as a complication of prolonged convulsive seizures (and extreme muscle exertion), infections including babesiosis and neosporosis, heat stroke, and MH. Rhabdomyolysis has also been reported following various intoxications and envenomations and as an idiopathic disorder in dogs.

Pathophysiology

In racing Greyhounds exhibiting ER, severe lactic acidosis leading to muscle cell swelling, local ischemia, muscle cell necrosis, and myoglobinuria (**Figure 14.84**) with nephropathy has been proposed as a likely sequence of events in the pathogenesis. The final common pathophysiologic mechanism resulting from direct injury to the sarcolemma or failure of energy supply to the muscle is an uncontrolled rise in free intracellular calcium concentration and activation of calcium-dependent proteases. These abnormalities result in destruction of myofibrils and lysosomal digestion of muscle fiber contents (myonecrosis). In MH, the underlying defect in calcium (Ca) homeostasis occurs at the level of the skeletal muscle sarcoplasmic reticulum, where there is hypersensitive and heightened ligand-gating of the calcium-release channel. Most variants of MH are known to be caused by a mutation in the gene on chromosome 1 encoding the skeletal muscle calcium release channel (ryanodine receptor 1: RYR1).

Clinical Presentation

Clinical signs of ER may occur during or within 24–48 hours of a race or trial and are characterized by extreme distress, hyperpnea, and generalized muscle pain, especially over the back and hindquarters, which may appear swollen and firm. Limbs may be rigidly tonic, and affected dogs may have a "hunchback" appearance and refuse to walk. Myoglobinuria and death within 48 hours are common in severe, acute cases. Typical manifestations of collapse associated with MH include a rapidly progressive elevation in body temperature, tachycardia, hypercarbia, and rhabdomyolysis.

Diagnosis

Clinical signs associated with an acute episode of exertion should prompt suspicion. Serum CK may be



FIGURE 14.87 A urine sample showing myoglobinuria. (*Courtesy of M. Schaer.*)

markedly elevated. Urinalysis should be performed to rule out subsequent myoglobinuria (Figure 14.87). EMG investigation will be normal in acute muscle disease. Muscle biopsy will confirm rhabdomyolysis, but as time is of the essence for the treatment of this disease, it is rarely advised.

Management

Treatment for rhabdomyolysis is mainly supportive, with intensive fluid therapy being necessary to maintain normal renal function. The systemic complications of rhabdomyolysis should be identified and individually addressed. Multimodal drug therapy, including dantrolene, analgesics, antibiotics, and mannitol, has been described with a beneficial effect. Frequent blood gas analyses, biochemistry, and urine analyses are advised to monitor systemic acid–base status as well as kidney function. The prognosis is guarded.

It is essential to remove triggering agents in the treatment of MH. This needs to be combined with symptomatic treatment. Stomach lavage with iced water, body surface cooling, and IV administration of cold isotonic saline solution may be beneficial. Dantrolene can prevent a MH crisis or reverse anesthetic-induced MH if given early enough (3–5 mg/kg IV). As for rhabdomyolysis, the prognosis is guarded.

INFLAMMATORY MYOPATHIES: INFECTIOUS

Definition/Overview

Infection can occasionally cause diffuse muscle and/or nerve disease and may be part of a systemic disease.

Etiology

Inflammatory myopathies have been associated with protozoal, viral, rickettsial, and, rarely, bacterial infections.

Pathophysiology

Infections causing myopathies in dogs and cats are usually multisystemic. Protozoal and viral infections often become clinical in young animals in situations of immune compromise. Older animals may have concurrent infections or neoplastic diseases affecting local immunocompetence.

Clinical Presentation

Signs seen in these patients are not specific but represent diffuse muscle disease. They include marked weight loss, weakness, exercise intolerance, generalized muscle atrophy, muscle pain (myalgia), and, in the late stages of disease, contractures, and recumbency.

Diagnosis

Diagnosis of an inflammatory myopathy necessitates muscle biopsy. Elevations of serum CK and abnormal needle EMG can be nonspecific findings. Definitive etiologic diagnosis may be difficult as it relies on the identification of organisms within the tissues, specifically with molecular or immunohistochemical methods; however, *Toxoplasma* and *Neospora* spp. are often seen within the muscle. The interpretation of serologic titers is particularly difficult in the acute stages of disease because a single positive result only implies exposure to the disease, rather than clinical infection.

Management

The prognosis for most infectious inflammatory myopathies is guarded, but partial function may remain if treatment is initiated early in the course of the disease. Clindamycin treatment is recommended for protozoal myositis, and this has been reported to be successful but may require months of administration. If CNS infection is suspected, additional antimicrobials should be considered such as the trimethoprim–sulfa drugs. If treatment is not initiated until the disease has reached a state of recumbency, it is unlikely that the patient will walk again. Intense physiotherapy may be needed in addition to specific antibiotics, especially in young patients that are continuing to grow in the face of severe muscle contractures caused by the infections.

INFLAMMATORY MYOPATHIES: IMMUNE-MEDIATED

IDIOPATHIC POLYMYOSITIS

Definition/Overview

Idiopathic polymyositis is a generalized inflammatory myopathy affecting dogs and, less commonly, cats that is not associated with any other systemic connective tissue disease or infectious cause.

Etiology

Immune-mediated dysfunction.

Pathophysiology

Tissue inflammation arises due to immune-mediated damage by CD8+ T lymphocytes. Several genes involved with innate and adaptive immunity are upregulated in this disease, as are those involved in proinflammatory and anti-inflammatory pathways. Circulating autoantibodies against an unidentified sarcolemmal antigen supporting a humoral immune component have been reported in Newfoundlands and Boxers. Autoantibodies to a 42-kDa molecule in striated muscle have been documented in Pembroke Welsh Corgis.

Clinical Presentation

Progressive exercise intolerance with acute exacerbation of weakness may occur, but the disease may initially be episodic; marked weight loss is often reported by the owner. A stiff, uncomfortable gait in all limbs is often accompanied by an arched thoracolumbar spine (kyphosis) and a ventroflexed neck. Commonly, multiple skeletal muscles are affected, but it can manifest as a focal disease affecting pharyngeal, laryngeal, esophageal, or, infrequently, tongue muscle groups, causing dysphagia, dysphonia, and stridor or regurgitation. Myalgia may be present, but this is not a consistent finding. Pyrexia may be a feature of the disease or a consequence of aspiration pneumonia. Any age and breed of dog and cat may be affected. However, breed-specific variants of polymyositis affect Newfoundlands, Boxers, Pembroke Welsh Corgis, and, recently, Hungarian Vizslas. The disease affecting Vizslas is marked by pharyngeal dysphagia, megaesophagus, and masticatory muscle atrophy, although exercise intolerance has also been described. Dysphagia and megaesophagus are more commonly seen in Newfoundlands with inflammatory myopathy when compared with other dogs. Corgis present with severe tongue atrophy, facial muscular atrophy, and occasional gait abnormalities.

Diagnosis

Diagnosis is based on identification of at least three of the following, including a confirmatory muscle biopsy:

- Appropriate clinical signs.
- Elevation of serum CK concentration (at least 5–10 times the upper reference range) (CK can be low in end-stage disease). CK is not always elevated during active muscle disease; this seems to depend on distribution of cellular infiltrates and degree of muscle damage.
- Compatible electrophysiologic findings.
- Negative infectious disease titers.
- Inflammatory muscle biopsy (critical for the diagnosis); demonstration of mononuclear cell infiltration into muscle and invasion of cells into apparently non-necrotic fibers.

Management

Early and aggressive institution of immunosuppressive therapy is essential for a good clinical outcome. The prognosis can be good unless there is concurrent megaesophagus or pharyngeal dysfunction, or if therapy is not initiated until after there has been severe myofiber loss or fibrosis. Robust muscle regeneration has been documented in the face of significant inflammation and fibrosis, suggesting that muscle can survive if treatment can be initiated prior to regenerative capacity of the muscle being exhausted. Long-term treatment is usually required. The serum CK concentration should be monitored, and immunosuppressive therapy continued until the CK returns to the reference range and clinical signs have resolved.

RECOMMENDED FURTHER READINGS

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CHAPTER 15

Musculoskeletal Disorders and Injuries

Matthew D. Johnson, Mitchell S. Gillick, and Steven M. Fox

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INTRODUCTION

These are exciting times in veterinary medicine, particularly for those with an interest in musculoskeletal disorders. As a result of an ever-expanding knowledge base, pets are living longer, and the human–animal bond has never been stronger. Senior dogs are becoming recognized as a group with special needs, and multimodal pain management has become a foundation of our practice ethics. The continued understanding of cyclooxygenase-1 and cyclooxygenase-2 has led to development of numerous nonsteroidal anti-inflammatory drugs (NSAIDs), which have become the cornerstone in the treatment of pain and inflammation. Nutritional management, exercise, and physical therapy, long ignored in veterinary medicine, are now recognized as very important treatment adjuncts. Disease processes are being recognized as more complex than previously appreciated, and it follows that treatment must embrace similar complexity. The quest for greater understanding must always be a driving force for the practitioner.

History

Making a clinical diagnosis is often assisted by noting the correlation of clinical signs to a time course (Figure 15.1). This can only be done by recording an accurate history. Whereas traumatic injuries present with an acute severity that rapidly diminishes, autoimmune diseases are often episodic in clinical presentation, and neoplasia generally presents with vague signs that become progressively worse with time.

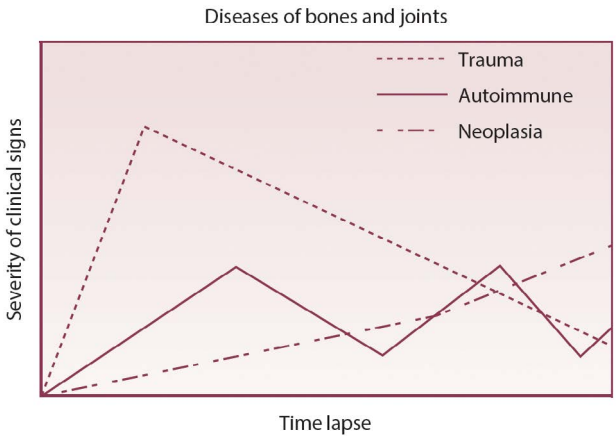


FIGURE 15.1 The correlation between clinical signs and a time course.

Examination

Dogs and cats with skeletal diseases most often present with lameness, swelling, or a combination of the two. After recording a thorough history and conducting a comprehensive physical examination, diagnostic imaging is often the next step in diagnostic aid. While radiography is often the most informative diagnostic aid, musculoskeletal ultrasound has been gaining in popularity in complementing radiography in the diagnosis of various orthopedic conditions. To determine the most probable cause of the underlying problem, the clinician must identify the pathophysiologic disease mechanisms involved that are associated with the clinical presentation and, thereafter, derive a diagnosis. Trying to

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determine a cause of the problem without identifying the pathophysiologic disease mechanisms involved leads to an overdependence on diagnosis by previous experience, thereby restricting the capacity to diagnose disease processes never personally encountered.

The problem-oriented medical record is designed for a logical approach to problem solving. Additionally, to avoid overlooking possible differential diagnoses, many find it helpful to screen for disease processes using the DAMNIT acronym of pathophysiology:

- Degenerative disorders
- Anomalies
- Metabolic disorders
- Neoplasia, nutritional disorders
- Inflammation (infectious or noninfectious), immune disorders, iatrogenic disorders, idiopathic
- Toxicity (endogenous or exogenous), trauma (internal or external)

The following conditions should be considered under the heading of musculoskeletal disorders:

- *Degenerative and developmental disorders:* Degenerative joint disease (DJD), canine hip dysplasia, intervertebral disc disease, cauda equina syndrome, cranial cruciate disease, medial patella luxation (MPL), elbow dysplasia (ununited anconeal process, fragmented coronoid process)
- *Anomalies:* Agenesis, luxation, ectrodactyly, osteochondrodysplasia, growth arrests, growth plate disorders, retained cartilage core
- *Metabolic disorders:* Hyperparathyroidism, hyperadrenocorticism
- *Neoplasia:* Osteosarcoma, chondrosarcoma, hemangiosarcoma, fibrosarcoma, synovial cell sarcoma
- *Nutritional disorders:* Nutritional hyperthyroidism, hypervitaminosis A, hypovitaminosis D
- *Infection/inflammation:* Osteomyelitis, discospondylitis, septic/suppurative arthritis
- *Immune disorders:* Immune-mediated polyarthritis, erosive and nonerosive arthritis, systemic lupus erythematosus (SLE)
- *Iatrogenic disorders:* Synostosis, sequestra
- *Idiopathic:* Avascular necrosis of the femoral head (Legg–Calvé–Perthes disease), hypertrophic osteopathy, bone cyst, multiple cartilaginous exostoses, osteochondrosis, panosteitis, craniomandibular osteopathy, hypertrophic osteodystrophy, idiopathic polyarthritis
- *Toxicity:* Lead poisoning
- *Trauma:* Fracture, muscle, tendon, and ligament injuries:
  - Common calcaneal tendinopathy, biceps tendinopathy, collateral ligament injury (stifle, tarsus)

Many skeletal diseases are predisposed to specific areas of long bones, which makes disease rule outs logical by region of bone affected (Figure 15.2). Bone diseases that affect the epiphysis include infectious arthritis (with

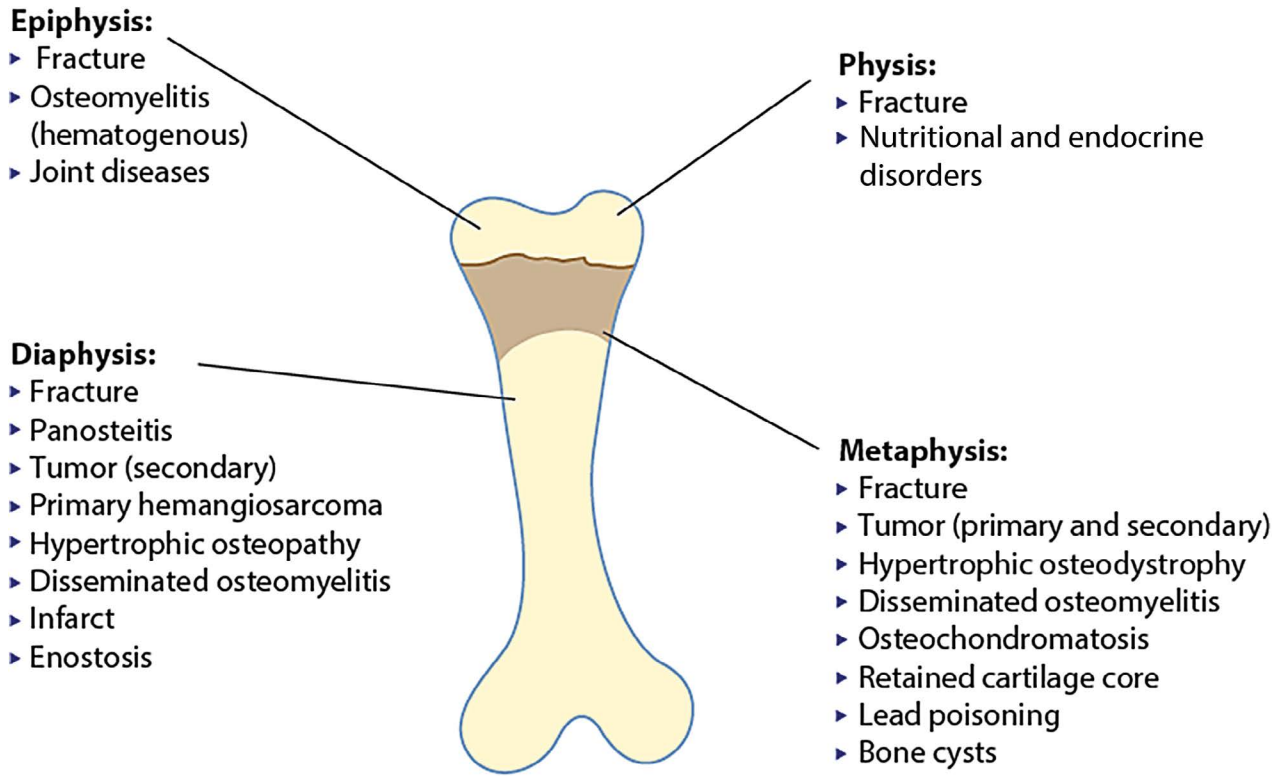


FIGURE 15.2 Bone diseases affecting long bones.

extension to subchondral bone), joint tumors (fibrosarcoma, synovial sarcoma [with extension to adjacent bone]), osteochondrosis (proximal humerus, medial humeral condyle, lateral or medial trochlear ridges, lateral femoral condyle, distal ulnar epiphysis "retained cartilage core"), osteoarthrosis (with subchondral bone sclerosis and/or epiphyseal "cysts"), primary bone tumors (with extension to the epiphysis), and erosive polyarthritis (rheumatoid [with periarticular and subchondral bone lysis]). Alterations of the physis may be seen with traumatic injury or fracture, hematogenous dissemination of infection, and nutritional or endocrine disorders. Diseases that may affect the metaphysis include primary bone tumors (osteogenic sarcoma, chondrosarcoma, and fibrosarcoma), primary hemangiosarcoma of bone, disseminated osteomyelitis, metastatic tumors, and hypertrophic osteodystrophy. Lesions of the diaphysis can result from canine panosteitis, metastatic tumors, bone infarction, disseminated osteomyelitis, primary hemangiosarcoma of bone, and hypertrophic osteopathy (hypertrophic pulmonary osteoarthropathy). It must be appreciated that some skeletal diseases are characterized by unpredictable anatomic location and variable distribution.

DEGENERATIVE DISORDERS

DEGENERATIVE JOINT DISEASE

Definition/Overview

DJD is a total joint disease with joint cartilage degeneration. Surface fibrillation and fissures ultimately result from an initial increase in cartilage swelling followed by dehydration and reduction in concentration of matrix proteoglycan. This leads to deformation under loading, with less elastic return and, consequently, more contact pressure on subchondral bone (Figure 15.3).

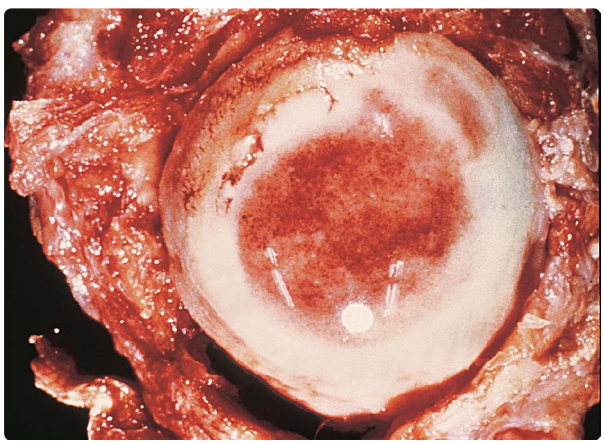


FIGURE 15.3 Eburnation of the femoral head resulting from DJD. Chondromalacia attributed to a decrease in sulfated mucopolysaccharide content is the earliest sign of degeneration, followed by fibrillation exposure of the collagen framework through the loss of ground substance. Fibrillation progresses to eburnation as subchondral bone becomes sclerotic from mechanical pressure and/or the effect of the synovial fluid.

Pathophysiology

Autoimmunity and the phagocytosis of immune complexes, leading to the release of substances deleterious to the affected joint, play an important role in the pathogenesis of DJD, although the exact role of specific immune responses is not known.

Clinical Presentation

Affected animals usually present with lameness or gait change. Once the affected joints are identified and examined, radiographs are taken to support the diagnosis.

Diagnosis

Characteristic radiographic features of DJD include subchondral bony sclerosis, subchondral cyst formation, joint space narrowing, and intra-articular or periarticular osteophyte formation. Arthroscopy can be both diagnostic and a treatment option. Arthroscopically observed morphologic changes give the clinician an appreciation for early treatment of these disorders.

Management

Treatment goals are to alleviate discomfort, retard the development of further deterioration, and, ideally, restore affected joints to as near normal as possible. Optimal management is with implementation of a multimodal regimen (Figure 15.4), which is best approached through the six points of two overlapping triangles, one representing nonmedical treatment and the other medical treatment (Figures 15.5a, b and 15.6). Surgical intervention may be appropriate, especially in correcting conditions of instability.

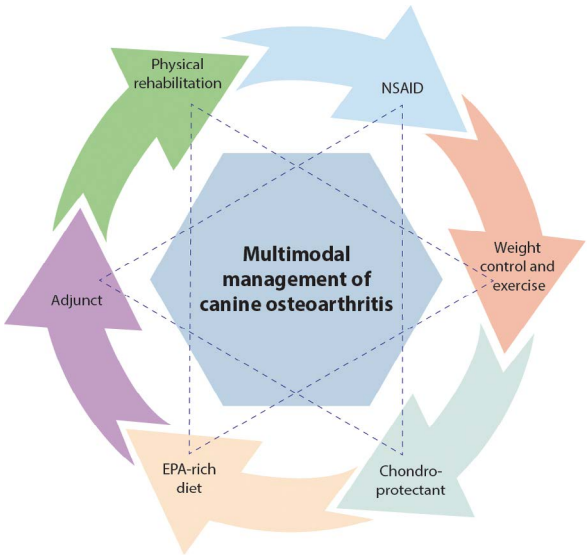


FIGURE 15.4 The multimodal management of canine osteoarthritis integrates six different elements: NSAIDs, weight control and exercise, a chondroprotectant, an eicosapentaenoic acid-rich diet, an adjunct, and physical rehabilitation. (*From Fox SM (2013).* Pain Management in Small Animal Medicine. *CRC Press, Boca Raton.*)

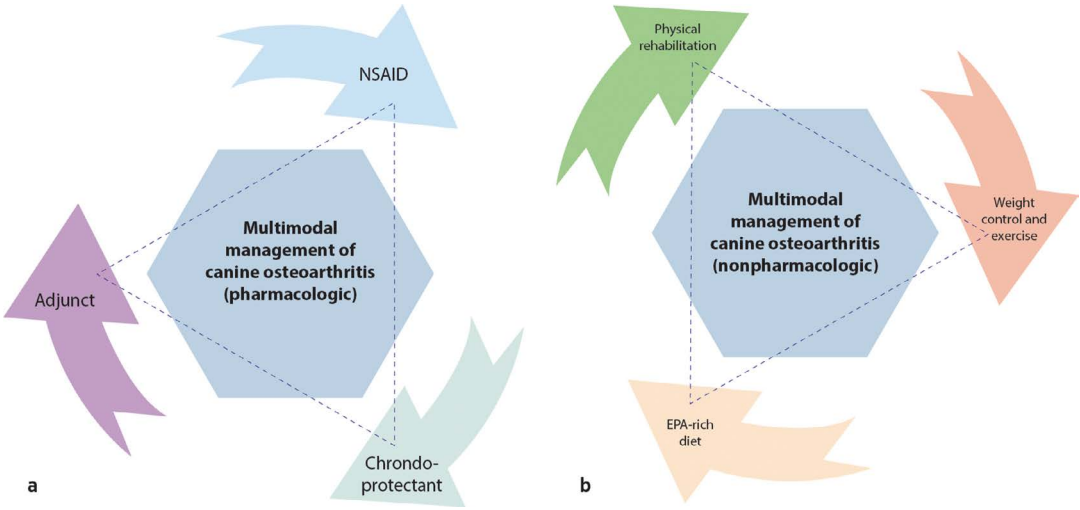


FIGURE 15.5 **(a)** The pharmacologic (medical) management of osteoarthritis is achieved with a NSAID, a chondroprotectant, and analgesic adjuncts. **(b)** The nonpharmaceutical management of osteoarthritis comprises weight control/exercise, an eicosapentaenoic acid-rich diet, and physical rehabilitation. (*From Fox SM (2013).* Pain Management in Small Animal Medicine. *CRC Press, Boca Raton.*)

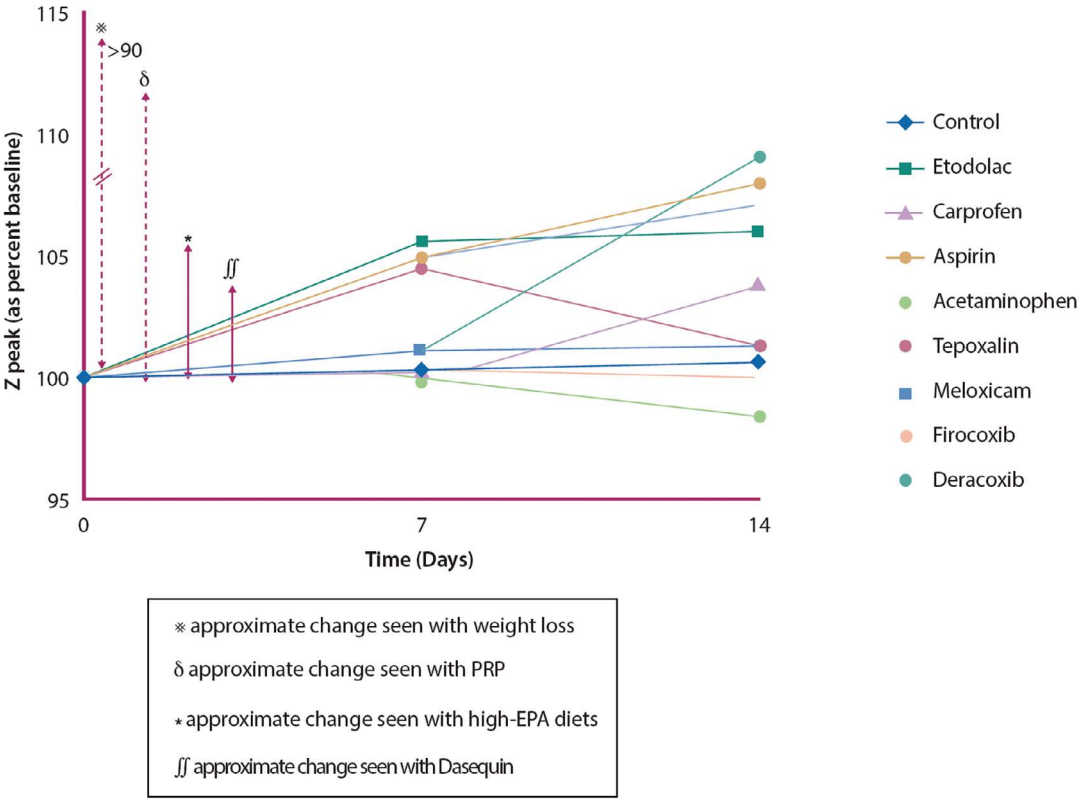


FIGURE 15.6 Relative efficacy of several contemporary NSAIDs used in veterinary medicine to treat osteoarthritis as assessed by force plate gait analysis (FPGA). Every dog in this study responded to a NSAID, but not every dog responded to each NSAID. Comparative responses from different treatment modalities (different studies) are further superimposed on this NSAID response graphic. All the studies used FPGA for assessment. Millis DL (2006). Nonsteroidal anti-inflammatory drugs, disease-modifying drugs, and osteoarthritis. A multimodal approach to treating osteoarthritis. *Symposium Proceedings, Western Veterinary Conference*. (Comparing relative efficacy of various NSAIDs by force plate gait analysis in cruciate deficient dogs.)

※ Clinician's Update™ (2005). Canine osteoarthritis: Overview, therapies, & nutrition. *Supplement to NAVC Clinician's Brief®*. April 2005.

δ Fahie MA, Ortolano GA, Guercio V, et al. (2013). A randomized controlled trial of the efficacy of autologous platelet therapy for the treatment of osteoarthritis in dogs. *J Am Vet Med Assoc* 243(9):1291–1297.

* Millis DL (2005). Effects of feeding omega-3 fatty acids on force plate gait analysis in dogs with osteoarthritis: 3-month feeding study, 2003. *Hill's Clinical Evidence Report.* Technical Information Services.

∬ Millis DL (2010). Dasuquin's efficacy may be similar to that of NSAIDs in dogs. Joint Health: A roundtable discussion. Supplement. *Vet Med* 105(11):10.

Two recent additions to the adjunct modality in consideration for management of canine DJD are implementation of a piprant-class drug and radiosynoviorthesis. In 2013, the World Health Organization defined a newly recognized class of drug that acts as a prostaglandin receptor antagonist. The prototypic drug grapiprant is an analgesic, anti-inflammatory agent that acts as an EP4 prostaglandin receptor antagonist. Radiosynoviorthesis is an intra-articular radionuclide therapy, for which Sn-117m is showing promise for its therapeutic effects in animal models of inflammatory arthritis.

HIP DYSPLASIA

Definition/Overview

Hip dysplasia, a developmental and progressively degenerative disorder characterized by hip laxity, pain, and development of osteoarthritis. It is more common in large breeds of dogs, but small breed dogs as well as cats can also be severely affected. Nongenetic risk factors include nutrition, growth rate, body size, exercise, and muscle mass.

Etiology

Although the cause of hip dysplasia is unknown, it has a hereditary basis. It is considered to be a polygenic trait, with expression determined by both genetic and environmental factors.

Pathophysiology

At birth, the hip is normal. With development, increased laxity and/or changes to the congruity of the femoral head and the acetabulum result in increased amounts of synovial fluid and hypertrophy of the round ligament of the head of the femur. Articular cartilage deteriorates, synovitis ensues, and the joint capsule thickens. With further progression of joint incongruity, bone changes occur, and osteophytes form surrounding the joint (Figure 15.7). Discomfort in the early stages of the disease is associated with stretching or tearing of fibers in the joint capsule and the round ligament, while that in advanced disease is from osteoarthritis (Figures 15.8 and 15.9).

Clinical Presentation

Signs of decreased activity and various degrees of joint discomfort are seen at two stages of the afflicted dog's life, between 4 and 12 months of age, and over 5 years. Affected dogs will often bunny hop (run with both hindlimbs moving together), prefer to sit rather than stand, demonstrate decreased mobility and range of motion, posture abnormally to defecate or urinate, and may show changes in eating trends and behavior.

Differential Diagnosis

Degenerative myelopathy, lumbosacral disease, stifle instability, fracture, luxation, iliopsoas muscle strain.

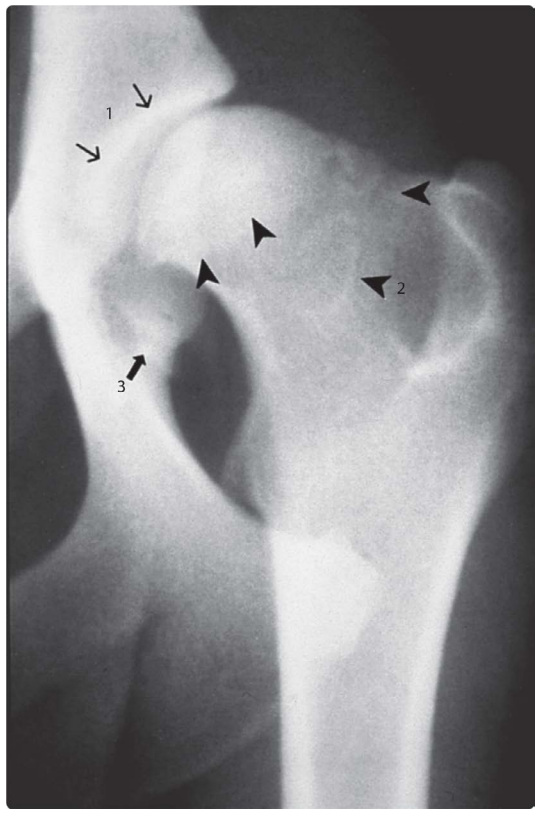


FIGURE 15.7 Moderate hip dysplasia. Less than 40% dorsal rim acetabular cover of the femoral head and secondary changes: (1) Sclerosis of the cranial acetabular margin; (2) osteophyte buildup at femoral neck capsule attachment (Morgan's line or caudolateral curvilinear osteophyte); and (3) caudal acetabular rim osteophyte deposition.

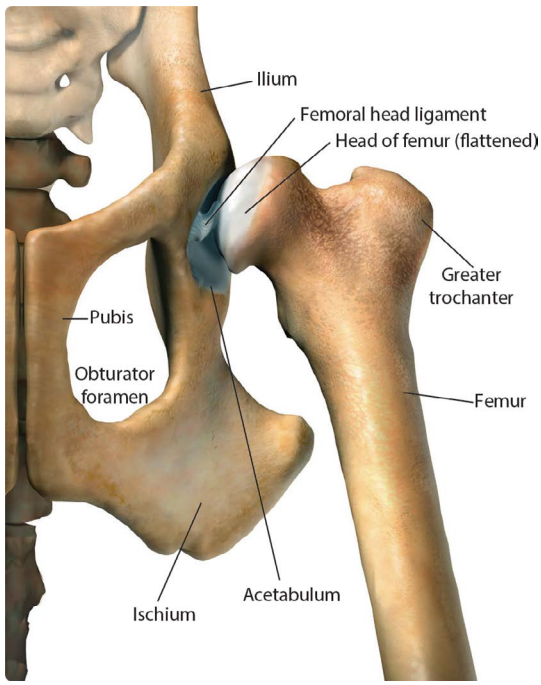


FIGURE 15.8 Illustration of hip dysplasia showing femoral head luxation, shallow acetabulum, and femoral head conformation change.

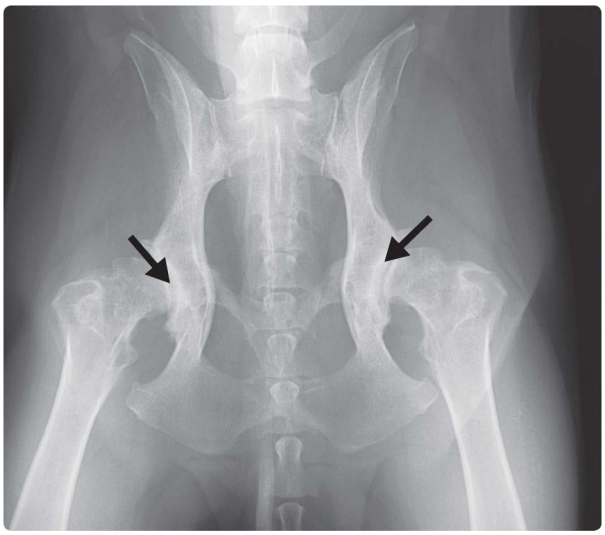


FIGURE 15.9 Radiograph of hip dysplasia showing poor acetabular cover to the femoral head (arrows).

Diagnosis

Diagnosis is made by physical (Figures 15.10 and 15.11) and radiographic examination. Comparing a lame limb with the contralateral limb and observing the dog ambulate at different gaits and on different surfaces, as well as on steps, can be helpful during the physical examination. It should be noted that often patient sedation is required to best evaluate for presence of an Ortolani sign.

Management

Available treatments (conservative or surgical) vary widely depending on the age of the animal, the pathologic condition of the joint, the expectation of function, the surgical skill of the clinician, and the financial resources of the owner. Conservative management consists of weight loss, formulated exercises, EPA-rich diets, and judicious use of analgesics and NSAIDs. Nutraceuticals have gained popularity as adjunct therapy for DJD; however, their evidence base remains indecisive.

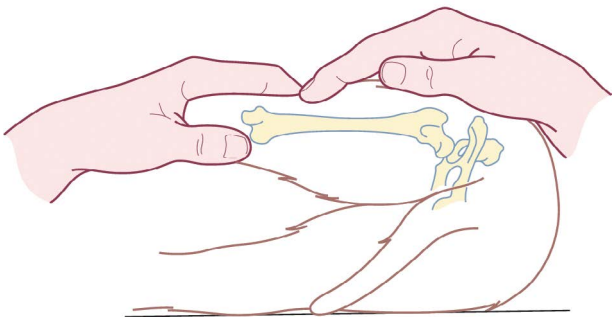


FIGURE 15.10 Physical examination for the Ortolani sign. The coxofemoral joint is subluxated by driving the femoral shaft dorsal to the long axis of the spine. (*Adapted from Fox SM (1987). A symposium on hip dysplasia.* Veterinary Medicine *82(7):683–716.*)

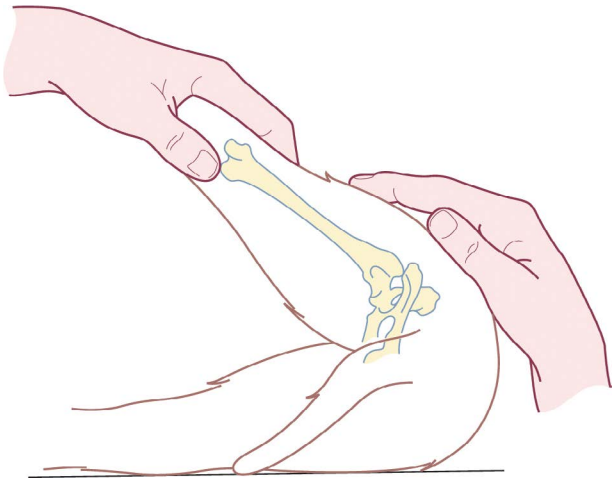


FIGURE 15.11 Physical examination for the Ortolani sign, with the coxofemoral joint subluxated, the femur is abducted until the femoral head "clunks" back into the acetabulum. The palpable (and often audible) clunk is considered a positive Ortolani sign. (*Adapted from Fox SM (1987). A symposium on hip dysplasia.* Veterinary Medicine *82(7):683–716.*)

For the immature animal, pectineal myectomy, pubic symphysiodesis, pelvic osteotomy, and femoral osteotomy are procedures frequently performed, while femoral head and neck excision and total hip replacement are most often performed in the mature animal. With the exception of pectineal myectomy and femoral head and neck excision, these surgeries require both special equipment and training.

ELBOW DYSPLASIA: UNUNITED ANCONEAL PROCESS/FRAGMENTED CORONOID PROCESS

Definition/Overview

The term general term elbow dysplasia is applied to several developmental conditions of the elbow that may occur individually or in combination. Conditions encompassing elbow dysplasia include ununited anconeal process (UAP), fragmented coronoid process (FCP), osteochondrosis of the humeral condyle, and elbow incongruity (Figure 15.12).

Etiology

Because these two diseases, together with osteochondritis dissecans (OCD) of the medial humeral condyle, overlap, a common etiology of osteochondrosis has been proposed. Skeletally immature large and giant breed dogs are affected, and the condition is often bilateral. The etiology of UAP and FCP is most often accepted to be incongruous growth of the radius and ulna. Incongruent development between the semilunar notch of the ulnar and humeral condyle may also contribute to the development of conditions of elbow dysplasia. The

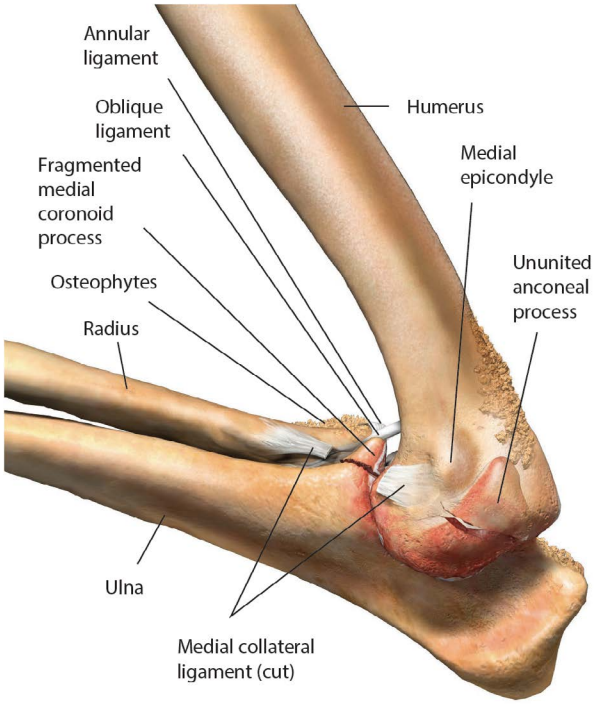


FIGURE 15.12 Elbow dysplasia is often a manifestation of FCP and/or UAP.

anconeus develops from a separate ossification center only in large dogs and will normally come to union with the parent ulna by 20 weeks of age. If this union has not occurred by this time, it is considered ununited.

Pathophysiology

It is proposed that if the radius grows faster than the ulna in large breed dogs, it places abnormal distractive forces on the anconeus through the distal end of the humerus, destabilizing the cartilaginous attachment of the anconeus to the ulna and, therefore, preventing its normal ossification. Similarly, a narrow semilunar notch would put abnormal strain on either the anconeal process or coronoid process (or both) during weight bearing, potentially resulting in development of FCP or UAP.

In contrast, if the ulna grows faster than the radius, more weight than normal is placed on the medial ulnar coronoid. Normally, the coronoid processes together with the radial head bear the compressive forces from the distal humerus. With asynchronous growth, the lateral aspect of the medial ulnar coronoid suffers damage and can become fragmented.

Clinical Presentation

Both UAP and FCP lead to forelimb lameness with an abnormal gait. Affected dogs tend to stand with the elbow abducted and feet pointed inwards but can also occasionally stand with elbow adducted with feet pointed outward. Joint effusion may be present, and the dog resents deep elbow palpation and elbow manipulation, especially hyperextension and pronation of the antebrachium.

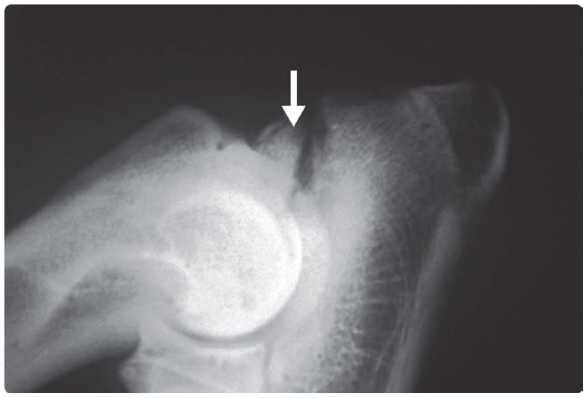


FIGURE 15.13 Ununited anconeal process (arrow) is best demonstrated in a hyperflexed lateral radiograph, which avoids the overlapping density of the medial humeral epicondyle. A diagnosis is made when the anconeus has not fused by 5 months of age.

Differential Diagnosis

Luxation/subluxation, OCD (humeral head), biceps brachii muscle/tendon disease, panosteitis.

Diagnosis

UAP is diagnosed radiographically by a hyperflexed lateral radiograph of the elbow revealing failure of the anconeal process to fuse with the proximal ulna in a dog older than 5 months of age (Figure 15.13).

Primary lesions associated with a fragmented medial coronoid process are extremely difficult to see radiographically (Figures 15.14 and 15.15). Blunting of the coronoid process and secondary changes such as osteophyte deposition proximal to the anconeal process, caudal to the distal humeral condyle, and anterior to the radial head are radiographic findings consistent with a fragmented medial coronoid process of long standing (Figure 15.16). Due to overlapping bones of the elbow combined with low sensitivity for mild changes in the elbow, survey radiographs can be very insensitive in detecting FCP or elbow incongruity. Therefore, a presumptive diagnosis of fragmented medial coronoid process is often made based on breed,

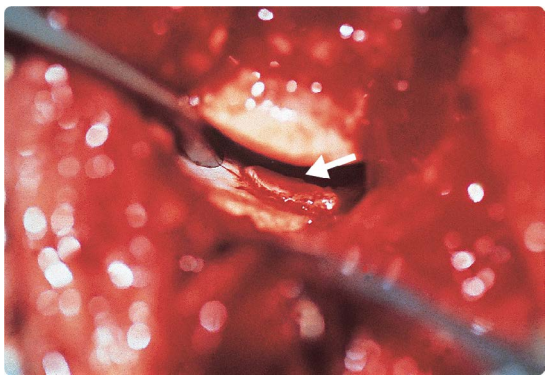


FIGURE 15.14 The separate coronoid fragment is rarely identified because it usually occurs on the lateral aspect of the medial coronoid process. An intraoperative view (arrow).



FIGURE 15.15 The separate coronoid fragment is rarely identified because it usually occurs on the lateral aspect of the medial coronoid process. Sequential views made along an arc around the elbow joint demonstrate the difficulty with radiographic identification of the coronoid lesion, as other bony structures always silhouette this area. The presence of secondary joint disease may be the only radiographic evidence of the fragmented coronoid. Periarticular osteophytes may be observed on the proximal margin of the anconeal process, coronoid process, medial humeral epicondyle, or cranial proximal radius. Sclerosis of the subchondral bone of the ulnar trochlear notch, a widened humeral–ulnar trochlear notch, and a widened humeral–ulnar joint space may be observed. Comparison radiographs of both elbows are extremely helpful because the lesions are often subtle.



FIGURE 15.16 Radiographic signs of elbow dysplasia include osteophyte deposition within the anconeal process, at the leading edge of the radial head, and on the medial humeral condyle, as well as sclerosis of the trochlear notch of the ulna.

age, history, clinical signs, and physical examination. CT imaging is required for a more definitive diagnosis of elbow dysplasia due to its increased sensitivity and multiplanar imaging capability. When CT imaging is unavailable, the diagnosis of FCP is often one of exclusion. Although CT can give detailed imaging of the bones of the elbow, arthroscopy is the gold standard to determine cartilage status and degree of severity of progression of degeneration in dogs with elbow dysplasia. More recently, nanoscopes have been developed, which can be used as a bedside diagnostic imaging tool for the identification of a FCP. Patients typically only require sedation as these scopes are typically the diameter of a 16- to 18-gauge needle.

Management

Treatment for UAP is surgical, either removal or attachment of the process. Surgery to include fragment removal and lesion curettage is the treatment of choice for FCP. Distal and proximal ulnar osteotomies are also performed in certain situations in addition to arthroscopy and UAP removal (**Figure 15.17a, b**). Prognosis for both

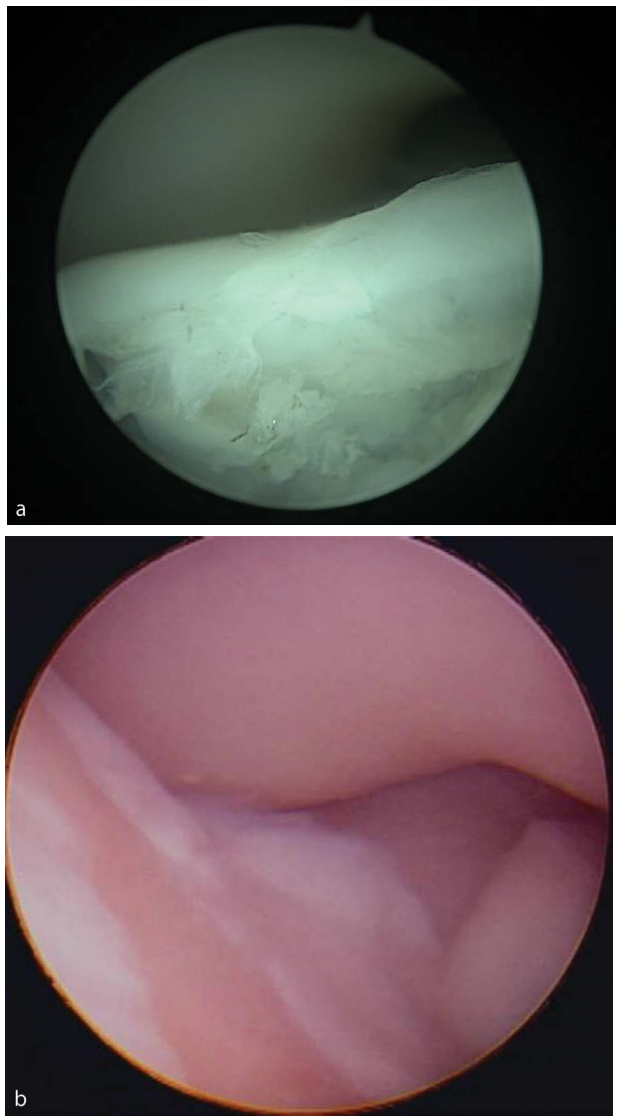


FIGURE 15.17 Arthroscopic images of different left elbows. **(a)** Fragment is in foreground, and humeral condyle is seen in the background. **(b)** The fragmented coronoid is seen in the lower right. Full-thickness cartilage erosion is noted on the ulna in the foreground.

conditions is dependent on the severity of secondary changes at the time of treatment. Total and partial elbow replacement procedures are available and are proving to be viable options for treating end-stage elbow arthritis.

Conservative management consists of weight loss, exercise modification, NSAIDs and analgesics such as gabapentin. Chondroprotectants are also used, often in combination with NSAIDs.

Intra-articular therapies have also been used with moderate success. Intra-articular therapies include hyaluronic acid, platelet-rich plasma, autologous stem cells, and corticosteroids. These therapies may reduce the use of daily NSAIDs therapy but require sedation and ability to perform arthrocentesis. Joint cytology is recommended to accompany joint injections to monitor progression of disease process.

OSTEOCHONDROSIS

Definition/Overview

Osteochondrosis is an endochondral ossification defect, the term denoting a dissecting lesion between articular cartilage and underlying bone. Once articular cartilage dissects free from the underlying calcified tissue, the lesion of OCD has formed.

Etiology

The etiology of the disease is multifactorial, with genetic, nutritional, and environmental contributions.

Pathophysiology

Osteochondrosis is the culmination of the failure of normal endochondral ossification. Failure of the ossification process leads to thickened area of cartilage. The process is thought to begin secondary to disruption of normal blood supply to the cartilage anlage. The abnormally thick cartilage results in poor nutrient diffusion to the chondrocytes and eventual chondrocyte death. The thickened area of cartilage is susceptible to damage caused by normal weight-bearing forces. Fissures may form leading to separation of the cartilage from the subchondral done. Osteochondritis dissecans (OCD) is the term used once the cartilaginous flap has formed with the resultant joint inflammation and lameness.

Clinical Presentation

Clinical signs of lameness appear between 4 and 12 months of age, mostly in large and giant breeds of dogs. Bones affected include the humeral head, medial humeral condyle, femoral condyles, and talus.

Differential Diagnosis

Intra-articular (osteochondral) fractures, elbow dysplasia, panosteitis, periarticular ligamentous injury, cranial cruciate injury, biceps tenosynovitis.

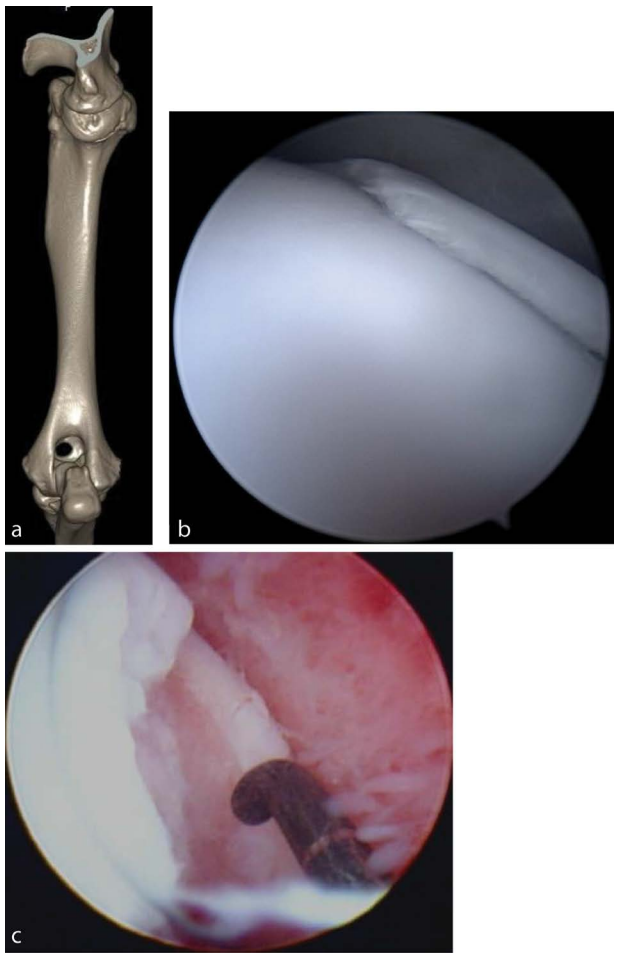


FIGURE 15.18 Arthroscopic images of a shoulder OCD lesion. **(a)** 3D reconstruction from CT imaging of a humeral head OCD lesion in the caudal central region. **(b)** Lesion as it is initially seen. **(c)** The OCD flap is being lifted by an arthroscopic probe prior to removal.

Diagnosis

The typical lesion appears radiographically as a flattened or concave radiolucent defect in the subchondral bone immediately beneath the articular cartilage (Figure 15.18a–c). Free-floating, mineralized cartilage fragments ("joint mice") may also be present within the affected joint (Figures 15.19 and 15.20).

Management

Treatment is surgical. Pain and lameness in a dog with radiographic evidence of osteochondrosis are an indication for surgical exploration. All loose cartilage fragments, including joint mice, are removed from the joint, and the lesion is curettaged to stimulate the articular surface defect to heal by fibrocartilage formation. Although clinical severity is not correlated with radiographic findings, the prognosis is based on secondary changes. Shoulder and stifle lesions typically yield a better prognosis than elbow and tarsus lesions. Resurfacing techniques using allografts, autografts, and synthetic grafts are also used to fill in the defect. Although not

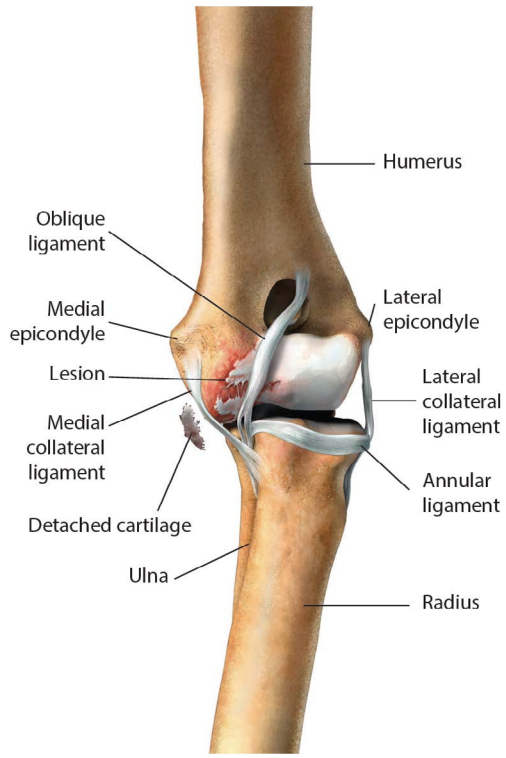


FIGURE 15.19 Osteochondrosis lesion of the humeral condyle. Lesion is typically found on the trochlea of the humerus.

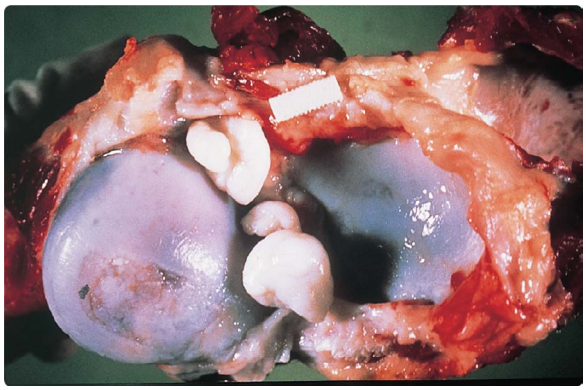


FIGURE 15.20 Humeral head osteochondrosis appears grossly with fibrillation and eburnation and may include joint mice, as seen in this case. Also note the thickened joint capsule, which might manifest clinically as restricted range of motion.

curative, NSAIDs are useful to treat symptomatically the pain associated with DJD.

RETAINED ENDOCHONDRAL CARTILAGE CORE

Definition/Overview

Retained endochondral cartilage core occurs in the distal ulnar metaphysis of immature large and giant breed dogs, appearing as a radiolucent inverted cone.

Etiology

The etiology of the disorder is not well understood but is thought to be similar to disruption of endochondral ossification (osteochondrosis) of the physis instead of the more typical development of osteochondrosis of the epiphysis. The core is a result of improper mineralization (Figure 15.21). Fortunately, most cases of retained endochondral cartilage core do not persist long enough to produce a deformity. This same condition may be seen in the lateral femoral condyle, leading to genu valgum, a predisposition to "knock-knees" and lateral patellar luxation.

Pathophysiology

In Great Dane pups, formation of cartilage core in the distal ulnar and tibial metaphyses has been associated with feeding excess calcium.

Clinical Presentation

The condition is often self-resolving and an incidental radiographic finding; however, it may be associated with varying degrees of growth retardation after 5 months of age.



FIGURE 15.21 Histologically, retained cartilage core, as seen here, is a failure of normal endochondral ossification within the distal ulna. Radiographically, an inverted radiolucent cone may be observed extending proximally from the distal ulnar physis into the metaphysis. This condition may lead to deformation of the carpus as is seen in the condition radius curvus.

Diagnosis

Radiography of the distal ulna. A radiolucent core of cartilage 5–10 mm wide and 2–6 cm long extending from the distal ulnar physis into metaphyseal bone is pathognomonic.

Management

Corrective/reconstructive surgery is the treatment of choice for deformities resulting from retained endochondral cartilage core.

CRANIAL CRUCIATE LIGAMENT RUPTURE

Definition/Overview

Rupture of the cranial cruciate ligament (Figure 15.22) is frequently associated with hindlimb lameness in dogs (especially large breeds of older, overweight females), contributing to its recognition as the major cause of stifle joint DJD. Injury leaves the animal with partial to complete instability of the joint (Figure 15.23).

Etiology

The history varies from dogs presenting with acute signs of hindlimb lameness to patients with a chronic course of intermittent lameness, often culminating in a more acute exacerbation. Degeneration of the ligament is poorly understood but may be affected by age, breed, sex hormones, body weight, conformational abnormalities, immune-mediated processes, and limb immobilization or loss of tone due to irregular use. There is also speculation that excessive (>35°) tibial plateau angle is an etiologic factor.

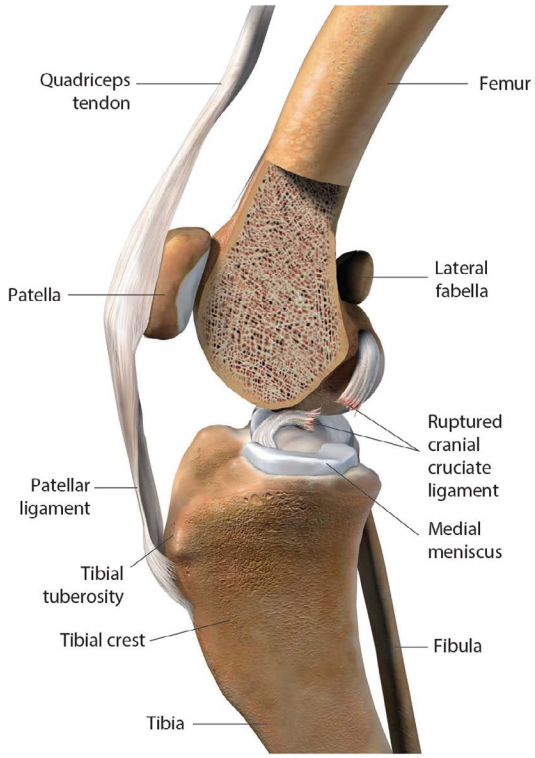


FIGURE 15.22 Illustration depicting a torn cranial cruciate ligament.

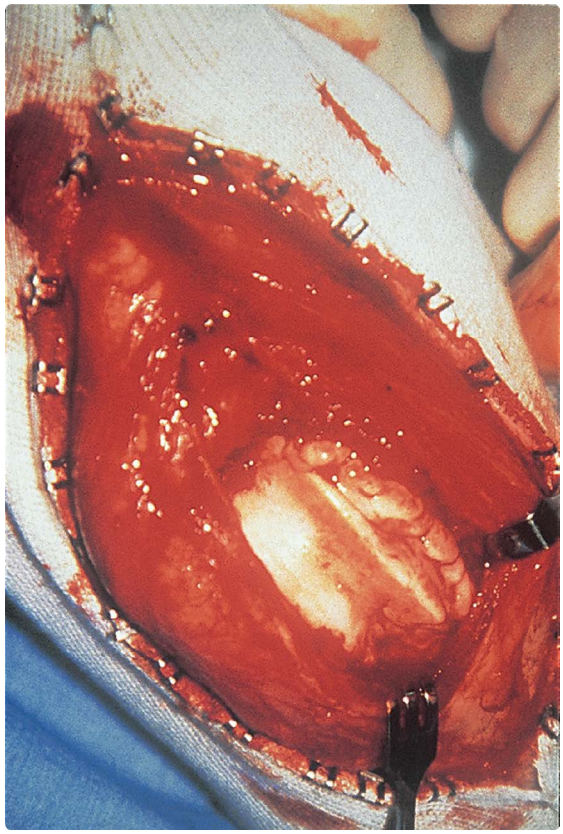


FIGURE 15.23 Cranial cruciate ligament rupture is a common presentation in clinical practice. In larger breeds of dog, surgical stabilization is important in order to minimize the progression of degenerative joint disease, demonstrated by osteophyte deposition on the lateral aspect of this femoral condyle. (*Courtesy of the late M.S. Bloomberg.*)

Pathophysiology

Immune-mediated arthritis, lymphocytic–plasmacytic synovitis, and septic arthritis may predispose the ligament to rupture. Cranial cruciate ligament strength deteriorates with aging, correlating with loss of fiber bundle organization and metaplastic changes of cellular elements. Tears may occur in total or in part (approximately 30% of patients with stifle lameness), and osteoarthritis soon follows. Cranial cruciate ligament compromise results in additional stress on the menisci, which frequently tear (>50% of patients), thus further contributing to joint osteoarthritis.

Clinical Presentation

A common presenting sign is lameness of the hindlimb. Acute traumatic ligament rupture is accompanied by severe lameness and occasional non-weight-bearing.



FIGURE 15.24 Osteochondritis dissecans of the femoral condyle is a differential diagnosis for stifle lameness; however, the condition does not present with cranial drawer motion.

Lameness subsides in 3–5 weeks as muscle atrophy progresses. In contrast, dogs with chronic disease have a more insidious history of lameness, often intermittent and exacerbated by exercise. Joint effusion is characteristic. Subtle weight shifts during standing and difficulty rising can also suggest cruciate disease.

Differential Diagnosis

Patellar luxation, meniscal injury, collateral ligament compromise, hip dysplasia, skeletally immature dog (have some degree of drawer sign), osteochondrosis of the femoral condyle (Figure 15.24), neoplasia (synovial cell sarcoma).

Diagnosis

High-quality radiographs can be suggestive for cranial cruciate ligament compromise and often demonstrate joint effusion and early signs of DJD (Figures 15.25–15.28). Joint effusion may cause cranial displacement of the infrapatellar fat pad, and osteophyte deposition is commonly observed on the distal pole of the patella in more chronic cases. A bow-legged conformation, internal rotation of the tibia, or straight stifle increases suspicion of cruciate disease. Thickening of the medial joint capsule (medial buttress) is characteristic of long-standing disease. The most consistent physical exam finding is pain on hyperextension of the stifle. Cranial drawer



FIGURE 15.25 Radiograph showing the relative displacement of the fat pad in mild cranial cruciate ligament rupture. (*Courtesy of B. Poteet.*)



FIGURE 15.26 Radiograph showing the relative displacement of the fat pad in moderate cranial cruciate ligament rupture. (*Courtesy of B. Poteet.*)



FIGURE 15.27 Radiograph showing the relative displacement of the fat pad in severe cranial cruciate ligament rupture. (*Courtesy of B. Poteet.*)



FIGURE 15.28 Radiograph showing the normal joint. (*Courtesy of B. Poteet.*)

motion is one of the hallmarks of cruciate compromise and may be detected by the cranial drawer test in either flexion or extension. The tibial compression test is also diagnostic and very sensitive. Partial tears of the craniomedial band of the ligament are identified by palpation when cranial tibial displacement is prevented by extension, but abnormal cranial drawer motion is evident in flexion. Due to periarticular fibrosis, cranial drawer motion may be difficult to elicit in dogs with chronic cruciate disease. In young, growing dogs, "puppy drawer" may be found. This drawer is differentiated by lack of stifle effusion or pain and is due to normal laxity in the ligament until skeletal maturity is reached. This drawer sign has a distinct endpoint since the ligament is intact.

Management

Treatment options are influenced by the animal's weight, age, intended use, concurrent medical problems, economic considerations, and veterinary surgical training. Dogs >15 kg body weight clearly benefit from surgical therapy. Smaller dogs and cats respond favorably to surgical interventions similar to larger dogs but may clinically appear to do well with conservative management as long as they have unilateral disease.

Conservative therapy includes weight loss/management, activity modification, nutritional joint supplements, and careful use of NSAID analgesics. Leash walking, swimming rehabilitation are appropriate exercise activities. The objectives of surgery are joint stabilization, early return to function and minimizing secondary DJD.

A myriad of surgical methods for joint stabilization have been described, suggesting that no one method is ideal. At present, extracapsular stabilization, tibial plateau leveling osteotomy (TPLO) techniques, and tibial tuberosity advancement are in favor. Recent studies have shown some long-term clinical advantages with the TPLO procedure with regard to range of motion

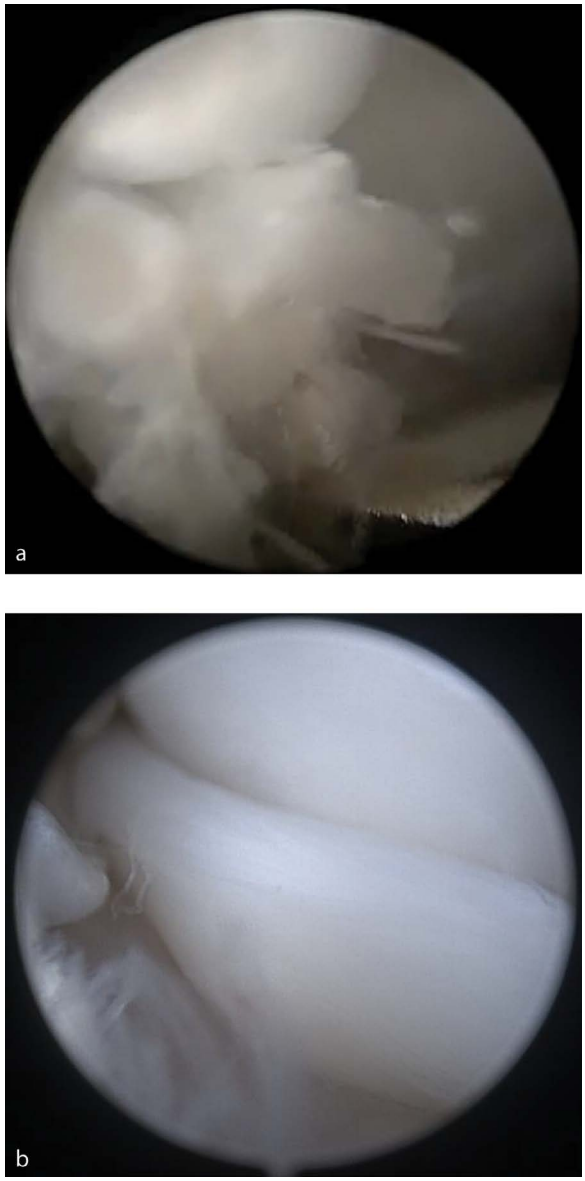


FIGURE 15.29 Images taken during stifle arthroscopy showing torn cruciate fibers **(a)** and **(b)** a cranially displaced bucket handle tear of the medial meniscus.

and overall function. Irrespective of the technique for stabilization, the joint must be inspected for meniscal damage either by an arthrotomy or arthroscopy. The frequency of meniscal damage (**Figure 15.29a, b**) increases with chronicity and is as great as 80% in dogs with complete tears.

DEVELOPMENTAL LUXATIONS

Definition/Overview

Most joint luxations are traumatic, although congenital/developmental luxations (**Figure 15.30**) do occur in both dogs and cats. Femoropatellar luxation is frequently diagnosed in small dogs and occasionally in



FIGURE 15.30 Congenital joint luxations, such as this elbow, often accompany other anomalies and are best treated by "salvage" procedures.

large dogs and cats (Figures 15.31 and 15.32). The condition varies from complete, irreducible luxation of the patella and severe lameness to mild instability without

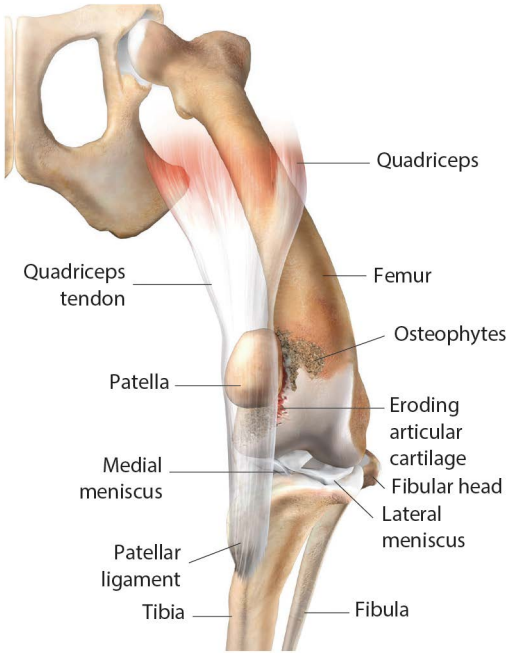


FIGURE 15.31 Illustration of medial patella luxation, a common developmental anomaly in small breed dogs.



FIGURE 15.32 Radiograph of medial patella luxation, a common developmental anomaly in small breed dogs.

associated clinical signs. Grading is made from 1 to 4 based on the severity of the condition and clinical signs.

Etiology

In dogs, the smaller breeds are more commonly affected with luxations owing to disruption of supporting joint structures or anatomic developmental failures. The changes noted during development are difficult to attribute causation. For instance, with the development of a shallow or concave trochlear groove in small dogs, it is unclear if the lack of a groove contributes to patella luxation or if the development of patella luxation results in abnormal groove formation.

Pathophysiology

Multifactorial developmental abnormalities can contribute to development of patella luxation. Abnormal growth of the distal femur (femoral varus), underdeveloped trochlear groove, medially directed growth of the tibial tuberosity, soft tissue restrictions (contracted musculature or medially displaced origin of the rectus femoris), and lack of supporting joint structures (such as the fabellopatellar ligament) have all been found to be responsible, individually or more commonly in combination, for development of patella luxation. In doing so, the patella rides over the trochlear ridge (with medial more common than lateral). Articular cartilage of both the ridge and the articular surface of the patella may become eburnated down to subchondral bone. Ultimately, DJD leads to chronic osteoarthritis. In grades 3 and 4, severe bony deformities may be present, including marked internal tibial rotation and an S-shaped curve of the distal femur and proximal tibia.

Clinical Presentation

Grade 1 luxations are often incidental findings during physical examination, where the patella can be manually luxated but spontaneously reduces back into the groove. Grade 2 luxations typically present with a history of intermittent lameness, resolving spontaneously with patella reduction. Owners often report that the dog suddenly skips and carries the limb without apparent pain, flexes and extends the joint several times, and is then able to bear weight normally thereafter. In this case, the animal is allowing the patella to pop back into place by forcing the limb into extension. With a grade 3 luxation, the patella remains outside the trochlear groove but during examination can be replaced into the groove; however, it immediately re-luxates once manipulation is ceased. The owner frequently reports that the dog shows a "crouched" gait, since the dog often uses the limb in a semiflexed, internally rotated position. Grade 4 is a nonreducible luxation of the patella. The tibia is often rotated internally from 60 to 90 degrees relative to the sagittal plane, and limb disfiguration often accompanies abnormal gait. Patella luxation often occurs bilaterally.

Differential Diagnosis

Premature physeal closure, cranial cruciate ligament rupture, collateral ligament disruption, tibial tubercle avulsion fracture, patellar tendon rupture.

Diagnosis

Diagnosis is most often apparent on physical examination, and it can be confirmed radiographically. Acute lameness in a dog with chronic luxation is usually caused by rupture of the cranial cruciate ligament, as cranial stifle support from the straight patella ligament is lacking. Every small-breed dog should be examined for patella luxation.

Radiographic images should be obtained to assess for abnormal bone morphology or the occurrence of comorbidities such as hip dysplasia or cranial cruciate disease. True craniocaudal images of the femur are necessary to accurately assess femoral varus. These images are obtained via horizontal beam imaging or positioning the patient such that the femur is parallel to the radiographic imaging table.

Management

Surgical correction for developmental luxations in growing animals is often disappointing due to the rapid anatomic changes in the growing dog and inevitable DJD. Once past the rapid growth phase, or after skeletal maturity, surgical correction of patella luxation is often rewarding. Surgical methods include sulcoplasty, block or wedge recession trochleoplasty, tibial tuberosity transposition, and antirotational techniques. For severe patella luxations, corrective osteotomies of the distal femur or proximal tibia maybe needed as well. Uncomplicated traumatic luxations most often carry a favorable prognosis if treated promptly.

CHRONIC DEGENERATIVE TENDINOPATHIES

Definition/Overview

Degenerative tendinopathies typically have an insidious onset that may go unnoticed until severe changes have occurred or an intermittent occurrence with inability to localize source of lameness or showed improvement with rest and anti-inflammatory medications. The two most common chronic tendinopathies occur in the common calcaneal tendon and the proximal biceps tendon.

Etiology

The etiology of degenerative tendinopathy is poorly understood but is suspected to most commonly be secondary to repetitive use injury. Chronic strain may cause microfiber damage due to the innate low density of tendon vascularity. This results in poor reparative response leading to increased parenchymal damage and worsening of tendon injury. Tendon pathology typically leads to tendon thickening, with or without accompanying inflammation. These changes lead to decreased compliance and increased stiffness of the tendon resulting in pain and lameness. With time, chronic inflammation can lead to increased vascularity and mineralization (**Figures 15.33–15.35**).

Pathophysiology

Chronic tendinopathies are commonly thought to be due to repetitive use/overuse. These injuries often have an insidious onset and can be quite advanced at the time of presentation, evidenced by the significant changes found at the time of diagnosis, including tendon thickening and mineralization along with changes at the bony insertion of the tendon as well as enthesophyte formation.

Clinical Presentation

Weight bearing lameness of the affected limb is common. For a common calcaneal tendon injury, a "dropped hock" with or without excessive digit flexion may be noted during weight bearing. With an affected but still intact tendon, plantigrade stance may not be noted; however, the distance from calcaneus to the ground will be less than the contralateral side (if unaffected).

For biceps tenosynovitis, pain is commonly elicited upon shoulder flexion with elbow extension. Because the biceps muscle crosses the shoulder and elbow, this positioning is essential to cause appropriate stretch of the effected muscle and tendon. Reduction in shoulder extension may be noted. This is likely due to concurrent joint inflammation, since the bicipital tendon of origin is within the joint capsule. Conversely, primary arthritides of the shoulder joint can secondarily affect the biceps tendon, giving a positive examination finding for biceps pain due to inflammation without true tendon injury.

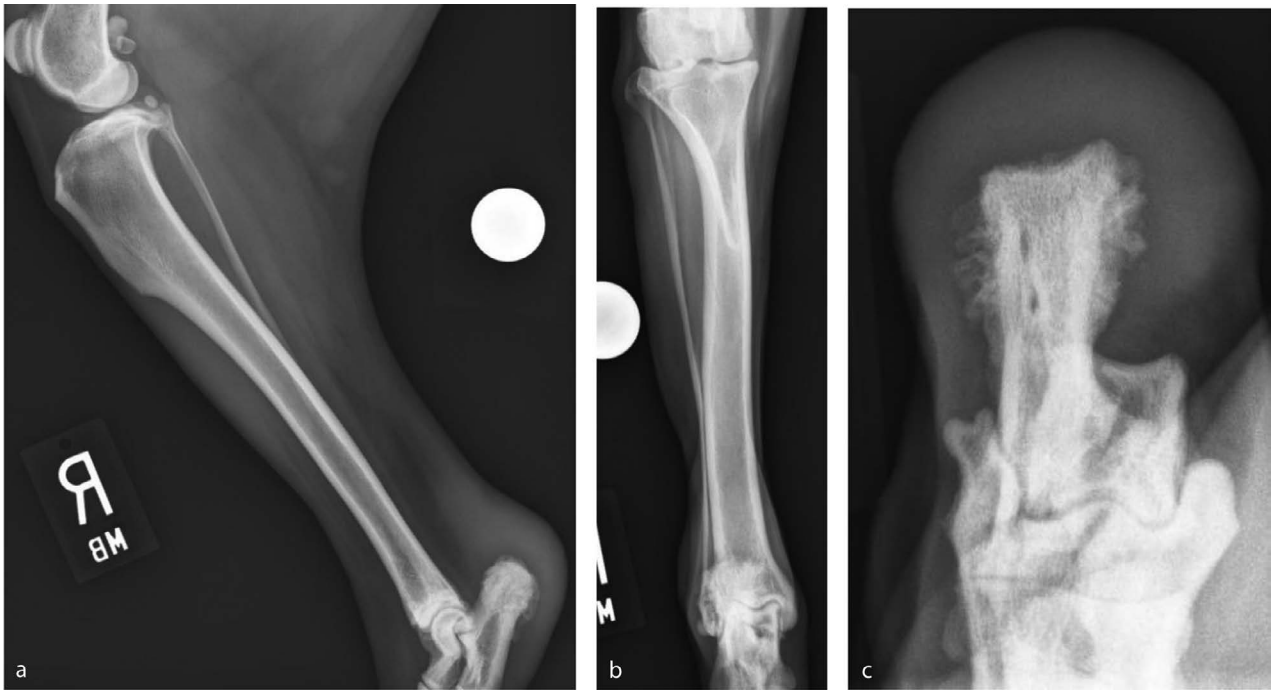


FIGURE 15.33 (a, b) Lateral and craniocaudal radiographic projections of a dog with chronic common calcaneal tendinopathy revealing marked soft tissue swelling in the region of the calcaneus extending proximally. **(c)** A skyline projection of the calcaneus highlighting the extensive soft tissue thickening and periosteal reaction in the region of tendon insertion on the calcaneus.

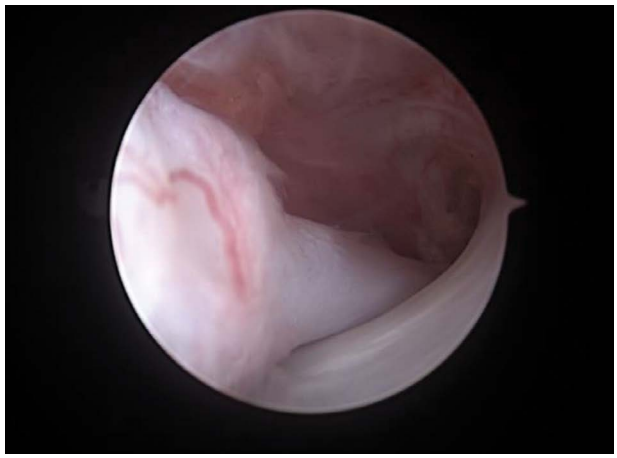


FIGURE 15.34 Arthroscopic image of partially torn biceps tendons. Image of acute tear with a majority of the tendon still intact.

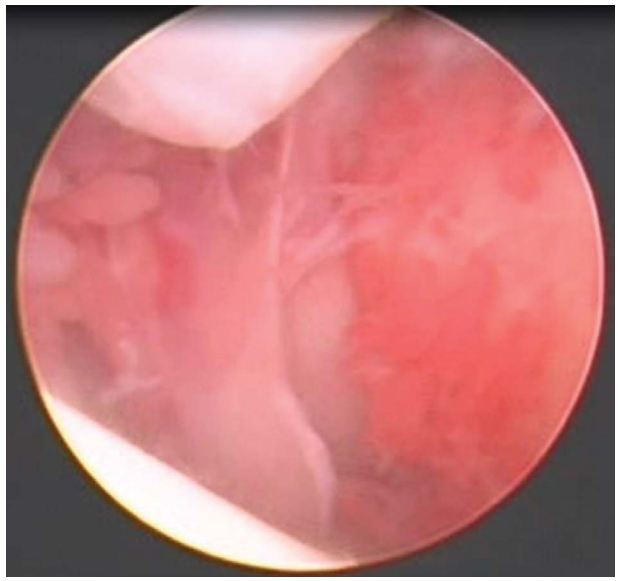


FIGURE 15.35 Arthroscopic image of partially torn biceps tendons. Image shows a more chronic biceps tendon with a near complete rupture of the tendon.

Differential Diagnosis

Common calcaneal tendon: Acute tendon rupture, calcaneal fracture, superficial digital tendon luxation
Biceps tenosynovitis: OCD, medial shoulder instability, neoplasia, primary shoulder arthritides (septic joint, severe DJD)

Diagnosis

Diagnosis of chronic tendinopathy is generally achieved via a combination of physical examination findings along with confirmatory diagnostic imaging, typically musculoskeletal ultrasound. Physical examination findings include tendon thickening, pain with direct palpation of the tendon, and reduced range of motion. The calcaneal tendon develops thickening at its insertion on the calcaneus. The thickening extends proximally, generally corresponding the degree of severity of injury to

the tendon. While the biceps tendon may develop thickening, it is generally not to the extent that is palpable upon examination. Pain on tendon stretch is due to the loss of compliance in the tendon. For the common calcaneal tendon, this is accomplished with the stifle kept in extension while attempting to flex the tarsus. For the biceps tendon, this is accomplished by keeping the elbow in extension while flexing the shoulder.

Management

Chronic tendinopathies can often be resolved with conservative management. Successful treatment of chronic tendinopathies typically involves joint immobilization to reduce tendon strain along with activity modification. Additional therapies are utilized to improve healing within the tendon, including PRP injection, shockwave therapy, therapeutic ultrasound, and/or cross-frictional massage.

Joint immobilization is initially done in cases of common calcaneal tendinopathy. Immobilization doesn't completely eliminate tendon strain because the gastrocnemius muscle can still contract creating tension in the tendon; however, immobilization does maintain the joint in extension, placing the muscle in the contracted position that limits the amount of tension that can be generated. Following 2-4 weeks of immobilization, controlled range of motion is initiated either via an orthotic device with a controlled range-of-motion hinge design. Alternatively, splinting with progressive flexion at the tarsus and periodic sedated range of motion has been utilized.

ANOMALIES

ECTRODACTYLY

Definition/Overview

Skeletal growth disorders that are apparent at birth or manifest later in young animals are of two main types: Generalized dysplasias and localized malformations of individual bones. Ectrodactyly (Gr. ectro = congenital absence) (split hand or lobster claw deformity) is an abnormal limb development with metacarpal bone separation (Figure 15.36), digit contracture, digit aplasia, metacarpal hypoplasia, and metacarpal fusions. The condition is usually unilateral.

Etiology

In the cat, ectrodactyly is caused by a dominant gene with variable expression.

Pathophysiology

The cleft between metacarpal bones may terminate just below the carpus or extend proximally through the carpus, separating the radius and ulna entirely.



FIGURE 15.36 A number of congenital anomalies may affect the digits. Here, a syndactyly of digits 2, 3 and 4, 5 is seen, as metacarpals 3 and 4 are separated at the level of the metacarpal heads. (*Courtesy of the late M.S. Bloomberg.*)

Clinical Presentation

Ectrodactyly presents as absence of the central digit or incomplete fusion of three digits. There are many variations of this condition, but typically, the third digit and metacarpal bone are absent, which produces a deep cleft dividing the paw into ulnar and radial parts. Concomitant congenital elbow luxation is common.

Differential Diagnosis

Congenital amputation.

Diagnosis

Diagnosis is made by physical examination and supporting radiographs.

Management

Reconstructive surgery or arthrodesis can improve function.

OSTEOCHONDRODYSPLASIA

Definition/Overview

Osteochondrodysplasia is an abnormality of cartilage or bone growth and development. In achondroplasia, endochondral ossification of all long bones is retarded, resulting in shortened and deformed limbs. Hypochondroplasia is similar to achondroplasia; however, the condition is less severe. The Bulldog, Boston Terrier, Pug, Pekingese, Japanese Spaniel, and Shih Tzu are achondroplastic, while the Dachshund, Basset Hound, Beagle, Welsh Corgi, Dandi Dinmont Terrier, Scottish Terrier, and Skye Terrier are hypochondroplastic.

Etiology

In most osteochondrodysplasias, there is a known or suspected genetic basis, and autosomal recessive inheritance is common.

Pathophysiology

There are several syndromes of chondrodystrophia fetalis in animals, some of them inherited, and all of them result in disproportionate dwarfism. Dwarfism of chondrodystrophia fetalis is differentiated from primordial dwarfism by disproportionate body form. As a result of an endochondral ossification defect, one or more long bones grows in retardation.

Clinical Presentation

Animals may exhibit dwarfism, and there may be reduced limb length relative to the trunk because of the discrepant development of the axial and appendicular skeleton.

Differential Diagnosis

When the condition affects one or more limbs, particularly the forelimbs, bilateral premature closure of the physes (radial/ulnar) can be a differential diagnosis of concern. Genetic anomalies tend to be symmetrical. Premature physeal closure can be bilateral, and closure of the distal ulnar physis is more sensitive to insult than the radial physis.

Diagnosis

Serial radiography of the long bone physes during the rapid growth phase is often diagnostic for premature physeal closure as a differential.

Management

Corrective osteotomies and bone-lengthening procedures can yield good outcomes; however, correction of severe deformities is often best addressed with staged procedures to maintain associated joint congruities until growth rate is diminished. Once growth is diminished, final correction can be attempted. If severe and not addressed early, the results are often unrewarding.

GROWTH DEFORMITIES

Definition/Overview

Chondrodysplasia is responsible for most growth deformities in dogs. Trauma is the most common origin of acquired growth deformities due to the exuberant nature of puppies. Unilateral growth deformities are most commonly secondary to trauma, whereas bilateral deformities are more likely to be congenital/developmental.

Etiology

Long bones grow in length through the process of endochondral ossification, which occurs at the growth plate or physis. Alterations in this normal process can lead to growth deformities, which are most frequently seen in the antebrachium. The most common cause of premature growth cessation is trauma to the distal ulnar physeal growth plate. Large and giant breeds are most commonly affected.

Pes varus is a growth abnormality of the distal tibia and fibula most commonly seen in Dachshunds. It can be unilateral or bilateral and is thought to be secondary to asymmetrical premature closure of the distal tibial physis. Trauma is potentially a cause in non-Dachshund breed but is generally believed to be a genetic condition in Dachshunds.

Pathophysiology

Following trauma, asymmetric growth of the physis leads to valgus (Figure 15.37) or varus (Figure 15.38) deformation of the limb. The severity of disfigurement is dependent on the growth potential remaining after the physeal trauma. The antebrachium is predisposed to growth deformity because of the two-bone system and the architecture of the distal ulnar physis.



FIGURE 15.37 Valgus deformation of the carpus resulting from premature closure of the distal ulnar physes.

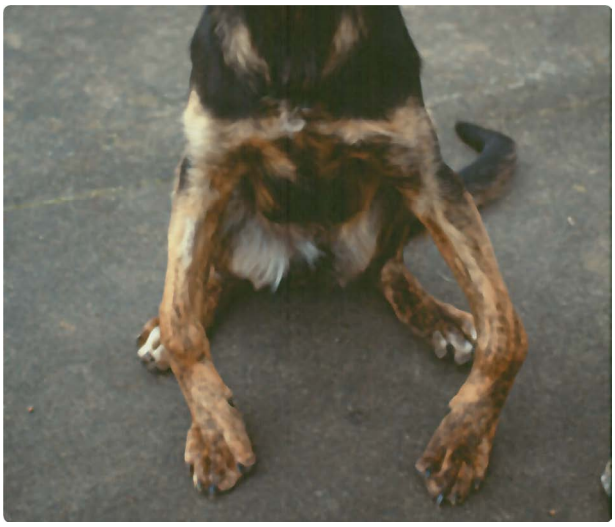


FIGURE 15.38 Young dog with varus deformation of the carpal joints resulting from premature closure of the distal radial physes.

Clinical Presentation

Three deformities of the radius result from premature closure of the distal ulnar physis: Lateral deviation (valgus), cranial bowing (curvus) (Figure 15.39), and external rotation (supination). Caudolateral subluxation of the radial carpal joint results, with stretching of the medial soft tissue supporting structures. The radial head may also luxate the humeral condyles from the trochlear notch of the ulna. Abnormal articulations resulting in irreversible degenerative osteoarthritis in the carpal and elbow joints may be sequelae. In the severe condition, the patient appears to be walking on its mediopalmar metacarpals. Elbow luxation can be very painful for the patients.

As the name implies, pes varus results in a varus deviation of the distal tibia and fibula. Additionally, internal rotation of the distal tibia is commonly seen. Fortunately, abnormalities of the proximal tibia and fibula do not accompany this condition.

Differential Diagnosis

Congenital deformity, ligamentous trauma, luxation, fracture.

Diagnosis

For the antebrachium, diagnosis is by radiography of the carpal and elbow joints (Figures 15.40 and 15.41), comparing them with the contralateral limb if that limb is normal. The condition is predictable when closure of the distal ulnar physis precedes that of the distal radial physis and significant growth remains before skeletal maturation.

For hindlimb, orthogonal images of the tibia and fibula to include the tarsus are compared to those of the contralateral limb. Closure of the medial distal tibia

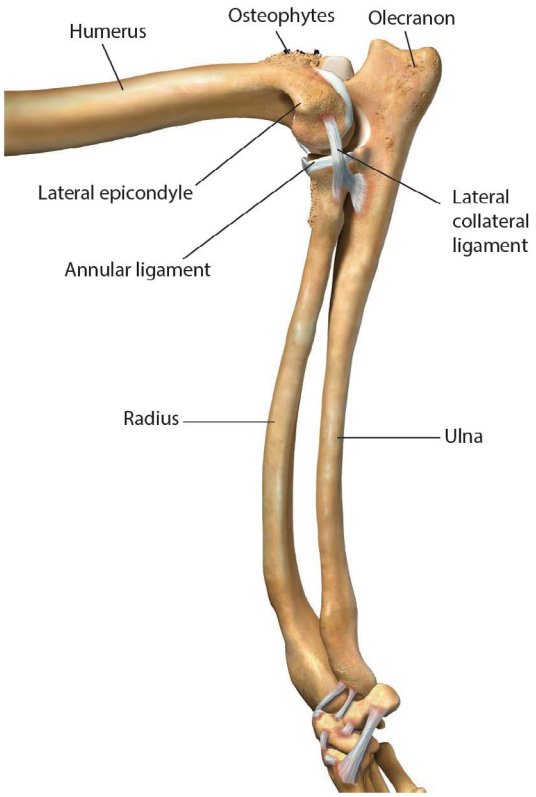


FIGURE 15.39 Radius curvus can lead to disfigurement of the entire antebrachium, including the elbow and the carpus.



FIGURE 15.40 Craniocaudal projection showing some of the radiographic changes commonly seen with premature closure of the distal ulnar growth plate: Valgus deviation of the distal radius, external rotation of the distal antebrachium, mild elbow incongruity, and mild radiocarpal subluxation.



FIGURE 15.41 Medial lateral projection showing some of the radiographic changes commonly seen with premature closure of the distal ulnar growth plate: Valgus deviation of the distal radius, external rotation of the distal antebrachium, mild elbow incongruity, and mild radiocarpal subluxation.

epiphysis may be noted on craniocaudal images but more commonly is presumed based on the pattern of growth abnormality.

Management

ADVANCED SURGICAL RECONSTRUCTION

Early identification and intervention with distal ulnar ostectomy to "uncouple" the distal radial growth have significant positive benefit to limiting elbow incongruity and irreversible degenerative changes. Distal ulnar ostectomy may or may not positively benefit the remaining growth of the distal radius. A secondary corrective procedure may be required after growth potential has subsided.

Pes varus does not commonly result in the same debilitating sequela of the antebrachial growth disturbances. Pes varus can be addressed once growth has subsided but also requires advanced reconstructive interventions.

METABOLIC DISORDERS

PANOSTEITIS

Definition/Overview

Panosteitis is a disease of the fatty bone marrow, with secondary involvement of bone.

Etiology

The cause is poorly understood; some authors have implicated a viral role.

Pathophysiology

Medullary endostosis and occasional subperiosteal new bone formation are characteristic of this self-limiting disease in young, large, or giant breeds of dogs, which may last up to 18 months. Pain may be due to disturbance of endosteal and periosteal elements, vascular congestion, or high intramedullary pressure. German Shepherd Dogs are most commonly affected.

Clinical Presentation

Clinical signs of lameness usually appear in immature dogs, with a prevalence in males, but onset has been documented as late as 5 years of age. Episodic lameness lasts 2–3 weeks, with bouts persisting for 2–9 months. Lameness may range from mild to severe, involve one or more bones, and be persistent or intermittent. Other signs include anorexia, lethargy, pyrexia, and weight loss. The ulna is most commonly affected, although the radius, humerus, femur, and tibia may also show involvement.

Clinical signs are usually associated with pain, which can be elicited with deep palpation of the affected bone and often self-resolves by the time the dog reaches 18–20 months of age. Mild depression, inappetence, and weight loss may occur in severely affected patients.

Differential Diagnosis

Osteochondrosis, elbow dysplasia, fractures, ligamentous injury, immune-mediated arthritides, Lyme disease, bacterial endocarditis.

Diagnosis

The earliest radiographic abnormality seen is an increase in intramedullary density (Figures 15.42–15.45). Initially unifocal with indistinct margins, lesions coalesce as the disease progresses. There is no correlation between radiographic signs, degree of lameness, and amount of pain elicited on deep palpation of the limb. Often, radiographic signs lag behind clinical signs by weeks.

Management

Treatment with analgesics (NSAIDs) and supportive care yields excellent results, although the course of treatment may be prolonged.

CRANIOMANDIBULAR OSTEOPATHY

Definition/Overview

Craniomandibular osteopathy is a proliferative nonneoplastic disease of the flat bones in the skull, where



FIGURE 15.42 Radiographic findings of panosteitis center around the nutrient foramina. The early phase begins with an increase in endosteal and medullary density, with blurring of the normal trabecular pattern. In the second phase, the densities tend to coalesce, become patchy and mottled, and fill the medullary canal. After 4–6 weeks, the medullary canal regains a normal or decreased density, and cortical thickening may persist. A differential diagnosis list should include bone neoplasm and hematogenous osteomyelitis.

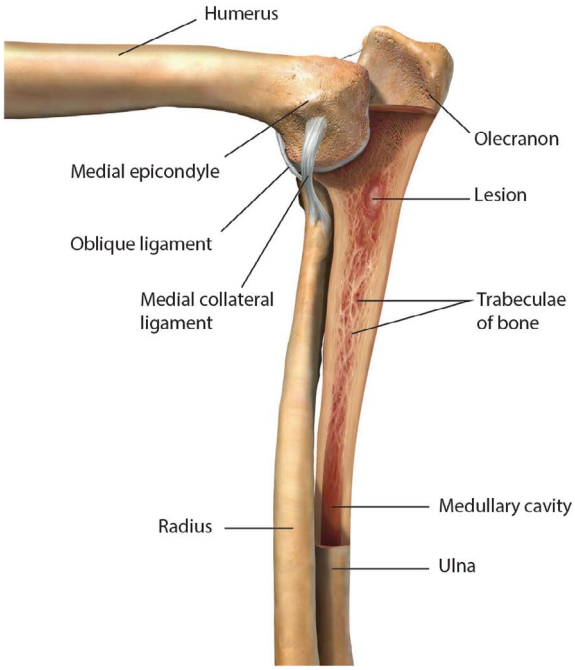


FIGURE 15.43 A schematic drawing of panosteitis showing increased density of the ulnar medullary canal.



FIGURE 15.44 A lateral radiograph of an ulna affected with panosteitis showing areas of increased density within the medullary canal. The disease is most commonly seen in long bones such as the tibia and ulna.



FIGURE 15.45 A craniocaudal radiograph of an ulna affected with panosteitis showing areas of increased density within the medullary canal. The disease is most commonly seen in long bones such as the tibia and ulna.

mandibular lamellar bone is resorbed, and juvenile bone is produced. Scottish Terriers and West Highland White Terriers between 3 and 6 months of age are most commonly affected (Figure 15.46).

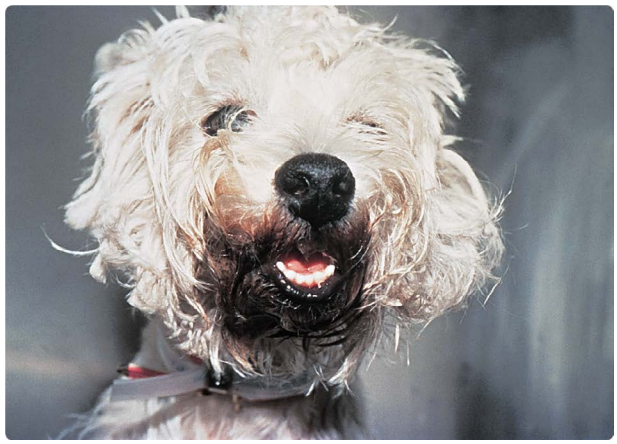


FIGURE 15.46 This young West Highland White Terrier has severe osteoproliferative pathology involving the mandible and temporomandibular joint. (*Courtesy of M. Schaer.*)

Etiology

The condition is inherited in West Highland White Terriers, and there may be a genetic predisposition in Scottish Terriers. However, as the condition occurs sporadically in other breeds, there may be several causes.

Pathophysiology

The disease is characterized by resorption of existing lamellae, vascular fibrous stroma in place of marrow spaces, proliferation of coarse trabecular bone beyond normal periosteal boundaries, and infiltration by inflammatory cells at the periphery of new bone. New primitive bone shows a mosaic pattern of cement lines.

Clinical Presentation

Animals are usually presented because of pain on opening the mouth, although lethargy, anorexia, pyrexia, excess salivation, prehension difficulties, lymphadenopathy, temporal muscle atrophy, weight loss, and dehydration may also be seen. The clinical course may fluctuate, with periods of remission and exacerbation.

Differential Diagnosis

Osteomyelitis, traumatic periostitis, temporomandibular joint ankyloses, neoplasia.

Diagnosis

Skull radiographs demonstrate bilaterally symmetrical periosteal lesions involving the mandible and temporal bones. Osseous proliferation of the mandible or tympanic bulla and periosteal new bone formation may be seen around the temporomandibular junction (Figure 15.47).

Management

Craniomandibular osteopathy is a self-limiting disease for which treatment is directed at supporting the animal (including analgesic therapy) until the condition regresses. In severely affected nonresolving cases, resection of the condyloid process of the mandible or a partial hemimandibulectomy may be considered. NSAID treatment can reduce pain and discomfort. The poorest prognosis is associated with deposition of bone surrounding the temporomandibular joint. Prolonged glucocorticoid therapy can slow disease progression and totally restore normalcy, if started early.

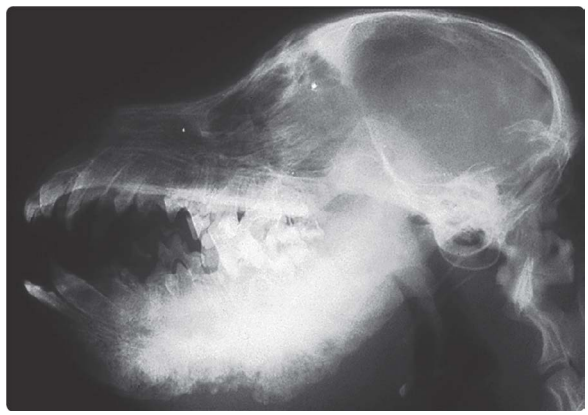


FIGURE 15.47 Lateral radiograph showing pronounced mandibular periosteal proliferation. (*Courtesy of M. Schaer.*)

HYPERTROPHIC OSTEODYSTROPHY

Definition/Overview

Hypertrophic osteodystrophy (HOD; metaphyseal osteopathy) is a metaphyseal bone disease of immature large and giant breeds of dogs. Although all bones are susceptible, the distal radius and ulna are most commonly affected. Metaphyses are widened due to perimetaphyseal swelling and bone deposition.

Etiology

The cause of the disease is unknown. Hypotheses, including the influence of hypovitaminosis C, dietary oversupplementation, and infectious organisms, have not been validated. HOD has been diagnosed in several different dog breeds. Weimaraners appear to have a strong heritable predisposition, and an immune mechanism is likely involved.

Pathophysiology

The pathogenesis is obscure; however, a disturbance of the metaphyseal blood supply leads to a failure or delay in ossification of the hypertrophic zone of the metaphyseal growth plate. The disease is usually bilaterally symmetrical and episodic. Some cases recover within a few days, but others have one or more relapses over several weeks before recovery.

Clinical Presentation

Presenting signs involve some degree of lameness where the metaphyseal region of the long bones may be



FIGURE 15.48 This approximately 2- to 3-month-old Weimaraner puppy suffered from severe debilitating effects of hypertrophic osteodystrophy. (*Courtesy of M. Schaer.*)

swollen, warm, and painful on palpation (Figure 15.48). The disease may be accompanied by depression, inappetence, and variable pyrexia.

Differential Diagnosis

Panosteitis, elbow dysplasia, OCD, polyarthritis, septic metaphysitis, retained cartilage core, canine osteochondrodysplasia.

Diagnosis

Necrosis and resorption of the metaphyseal trabeculae may be seen radiographically as an irregular radiolucent line in the metaphyses adjacent to the growth plates (Figure 15.49). Subperiosteal new bone formation (likely hematoma mineralization) may be mild or extensive in the area of the metaphyseal growth plate.

Management

Treatment is largely supportive with rest, analgesics, anti-inflammatory drugs, and attention to a proper diet. Vitamin C supplementation has no efficacy. Antibiotics may be indicated for treatment of secondary infection, if identified. Animals with mild lesions have a good-to-excellent prognosis, while the severely affected carry a guarded prognosis (death and euthanasia are not uncommon). There is no specific treatment for the disease, although anti-inflammatory analgesia (NSAIDs) can be palliative and physical rehabilitation activities may be beneficial. In one study of Weimaraners, treatment with corticosteroids was superior to treatment with NSAIDs, suggesting that the immune suppressive action of corticosteroids may be preferential for achieving remission.

HYPERADRENOCORTICISM

See also Chapter 12.

Definition/Overview

Hyperadrenocorticism is found in the presence of Cushing's disease or with chronic excessive administration of glucocorticoids.



FIGURE 15.49 This approximately 2- to 3-month-old Weimaraner puppy from Figure 15.48 suffered from severe debilitating effects of hypertrophic osteodystrophy. Note the marked radiographic swelling of the carpal metaphyseal region. Bacterial physitis with sepsis was also present. (*Courtesy of M. Schaer.*)

Etiology

There are several recognized causes of hyperadrenocorticism: A pituitary tumor, which synthesizes and secretes excess adrenocorticotrophic hormone (pituitary-dependent hyperadrenocorticism [PDH]); adrenocortical tumors, which randomly secrete excessive cortisol independently of the pituitary (adrenocortical dependent); and administration of excessive glucocorticoids (e.g., drugs for skin, ear, and eye conditions [iatrogenic]).

Pathophysiology

Osteoporosis of the spine and long bones can be associated with this disease in dogs, as calcium absorption from the gut, urinary excretion of calcium, normal production of bone matrix, and fibroblast as well as osteoblast proliferation and differentiation are affected.

Clinical Presentation

Poodles, Dachshunds, Boston Terriers, Boxers, and Beagles have been reported to be at higher risk than other breeds. In general, endogenous hyperadrenocorticism affects middle-aged to old animals; however, the iatrogenic form can be seen in young dogs. Severity of

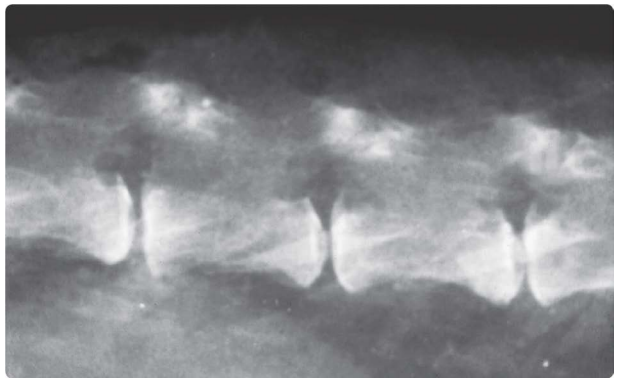


FIGURE 15.50 Lumbar vertebrae showing osteopenia. (*Courtesy of M. Schaer.*)

signs varies depending on the duration and degree of cortisol excess. The most apparent signs are polyuria, polydipsia, polyphagia, and a pendulous abdomen. Lethargy, muscle weakness, muscle atrophy, panting, obesity, hyperpigmentation, calcinosis cutis, and facial nerve palsy can also occur. Cats show similar signs and are commonly poorly controlled diabetics as well.

Differential Diagnosis

Hypothyroidism, acromegaly, renal disease, hepatopathy, diabetes mellitus, ligament rupture.

Diagnosis

Radiography will reveal the extent of bone involvement (Figure 15.50). A urine cortisol-to-creatinine ratio is a very practical screening test. A diagnosis of hyperadrenocorticism is made by dexamethasone suppression testing or ACTH response testing. Abdominal radiography, ultrasonography, CT, and MRI are all useful in differentiating PDH from adrenal tumors.

Management

Surgery is usually not an option for PDH. Medical management for treating both PDH and adrenal tumors in dogs is with o, p'-DDD. Trilostane is now used commonly for treating PDH in dogs and cats; it can also be used to treat functional adrenocortical tumors in cats.

NEOPLASIA

Bone neoplasms may arise from bone tissue elements, or they may invade bone by local extension or distant metastasis. Most primary bone tumors are malignant. While the most frequent clinical signs in dogs and cats with appendicular bone tumors are pain or lameness referable to the primary tumor, signs of axial skeletal neoplasms reflect the tumor location. Radiographic findings such as periosteal new bone formation and bone destruction may support a diagnosis of neoplasia, but a definitive diagnosis is made histologically from a bone biopsy. Primary bone tumors and bone metastases are infrequent in cats.

PRIMARY BONE TUMORS

The most common primary bone tumors among dogs and cats include osteosarcoma, parosteal osteosarcoma in the cat, chondrosarcoma, and fibrosarcoma. Clinical signs and physical exam findings are usually quite similar among these tumor types.

Definition/Overview of Primary Bone Tumors

Osteosarcoma is the most frequently reported (70%–80%) primary bone tumor in cats. Solitary osteolytic metaphyseal long bone lesions in older cats are considered osteosarcoma until proven otherwise; these lesions tend to be less aggressive than canine osteosarcoma.

Osteosarcoma is the most common (85%) bone tumor in the dog. At greatest risk are the Saint Bernard, Great Dane, Golden Retriever, Irish Setter, Dobermann, and German Shepherd Dog.

Parosteal osteosarcoma is the second most common bone tumor in the cat.

Chondrosarcoma is the second most common bone tumor in dogs (Figure 15.51). Lesions can originate in the ribs (most common primary rib tumor), long bones, extraskeletal sites, nasal cavity, vertebrae, facial bones, pelvis, digits, and os penis. The nasal cavity is commonly affected. This tumor is uncommon in cats.

Primary fibrosarcoma of bone originates from the fibrous components of the medulla and is the third most common primary bone neoplasm in dogs. Primary fibrosarcoma of bone is rare in cats. Parosteal or soft tissue



FIGURE 15.51 Chondrosarcoma of the proximal scapula characterized by both destruction and proliferation. (*Courtesy of I.A. Robertson.*)

origin is more common, and axial skeleton sites are more common than appendicular sites. This neoplasm tends to be locally invasive but late to metastasize.

Etiology

The cause of primary bone tumors is generally unknown. The association of osteosarcoma with metaphyseal bone, however, suggests that neoplastic transformation may result from aberrant bone growth or differentiation. Some dogs may be genetically predisposed, as mutation and inactivation of the p53 tumor suppressor gene have been found. Chondrosarcoma lesions can occur in cases of multiple cartilaginous exostosis.

Pathophysiology

No specific pathophysiologic pathways have been identified in primary bone tumors; however, each of them do have some differences in respect to tumor development location and destruction of bone. Osteosarcomas have been reported at locations where metallic implants have been used for fracture fixation, as well as at previous fracture sites or where there is chronic inflammation. In parosteal osteosarcomas, typically, the lesions appear as a mixed proliferative or lytic pattern in the metaphyseal region of the affected bone. The formation of periosteal bone in adjacent tissue leads to the development of a Codman triangle, comprising proliferation of the periosteum and mild destruction of cortical tissue.

Chondrosarcomas develop anaplastic cartilage cells between and within the tumors that show various stages of differentiation and maturation. Metastasis may occur in any tissue but most commonly affects lung tissue.

Fibrosarcomas are fibroblastic tumors that produce bundles of collagenous fibers but no neoplastic bone, osteoid, or cartilage either in the primary tumor or its metastases. It is often difficult to determine if the tumor is primarily a bone neoplasm or a soft tissue neoplasm invading bone. Fibrosarcomas produce bone lysis with minimal reactive bone response.

Clinical Presentation

Typical presentation for primary bone tumors is lameness or pain over the affected bone. Often a firm swelling is noted in locations with sufficient muscular tissue. The ability to detect the tumor on palpation may be challenging, only becoming apparent after chronic muscle wasting or after pathologic fracture has occurred.

Most osteosarcomas originate in the metaphyses of long bones, with a higher frequency in the forelimbs. Tumors are most prevalent away from the elbow and around the stifle. Animals usually present with swelling and lameness of the affected limb. Swelling may or may not involve soft tissue. The tumor is seen arising on the outer surface of the cortex of the humerus, femur, frontal bones, and ramus of the mandible. Although osteosarcomas generally do not cross articular cartilage, adjacent bones can be affected but generally through periarticular soft tissue or if the tumor is a telangiectatic osteosarcoma. Owing to the sudden onset of swelling and pain, a nonneoplastic orthopedic problem can be mistakenly assumed.

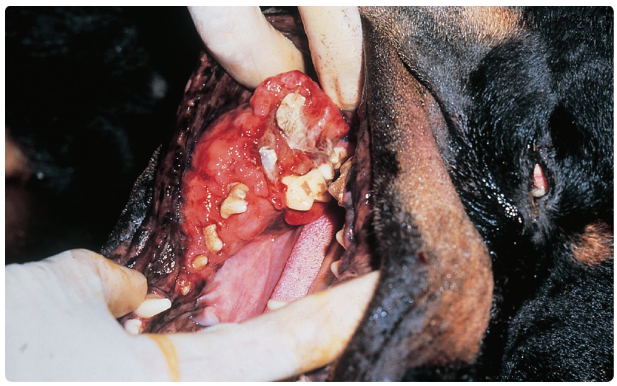


FIGURE 15.52 Mandibular fibrosarcoma in an 8-year-old Rottweiler.

Parosteal osteosarcoma the lesions are slow growing, but affected sites can elicit pain.

Chondrosarcoma occurs commonly in ribs, nasal bones, and the pelvis. Pain on palpation of the lesion is common, and swelling may occur at the tumor site. Intrathoracic extension of tumors may give rise to pleural effusion.

Animals with oral fibrosarcoma lesions (Figure 15.52) usually present with fleshy, pink, firm, sessile masses in the palate or gingiva, which deeply infiltrate soft tissue and bone. Long bones may have swelling, typically at a metaphyseal site, and the site is often painful to palpation.

Differential Diagnosis

Metastatic lesion, other primary bone tumor, osteomyelitis. Osteosarcoma should be ruled out in any large-breed dog presenting with sudden lameness.

Diagnosis

For any suspected bone tumor, the definitive diagnosis is made by a bone biopsy. In some cases, with a primary lytic appearance, the diagnosis may be made by fine-needle aspirate and cytology. For osteosarcoma, a presumptive diagnosis can be made by radiography, which may reveal a Codman's triangle and the proliferative or lytic pattern of the metaphyseal bone region (Figure 15.53). Pain is often elicited with deep palpation over the site. If treatment is considered, the extent of disease metastasis should be determined by a radiographic survey of the thorax or skeleton. A small percentage (5%–10%) of affected animals have detectable lung lesions.

Radiographically, parosteal tumors appear less aggressive than periosteal tumors. The lesions are moderately well circumscribed, and lysis of the cortex is usually mild. Biopsy specimens must be evaluated carefully for areas of tumor cells, as lesions may be misdiagnosed as reactive bone, chondroma, or osteoma.



FIGURE 15.53 Osteosarcomas may produce a localized soft tissue swelling containing mineralized foci. In this case, the carpus was swollen. There is extensive bony destruction, with the cortex eroded at several sites.

For suspected fibrosarcomas, biopsy specimens should be carefully examined, as it is difficult to distinguish fibroblastic osteosarcoma from fibrosarcoma.

Management

Wide surgical excision or amputation is the treatment of choice for most primary bone tumors. In the case of parosteal osteosarcomas, amputation may be curative due to their slow growth and do not tend to metastasize early. Most primary bone tumors grow rapidly, and treatment is often unrewarding. Cisplatin is the chemotherapy of choice for treatment of osteosarcoma in dogs (toxic to cats). However, microscopic metastasis is common by the time of diagnosis. Survival is <6 months with limb amputation and <18 months if there is additional chemotherapy. Osteosarcoma in cats is less aggressive, and amputation alone yields a median survival of >4 years. Since osteosarcoma is often associated with considerable pain, management with NSAIDs may be appropriate for dogs. Furthermore, there is some speculation that COX-2-specific NSAIDs manifest antitumor mechanisms. Adjunctive analgesics such as opioids, N-methyl-d-aspartate antagonists, and ion-channel regulators may be necessary to control the pain.

For chondrosarcomas, the prognosis is guarded to good if complete excision of the tumor is accomplished. Chemotherapy with cisplatin is appropriate for nonresectable tumors; however, response of chondrosarcomas to radiation and chemotherapy is poor. Regarding fibrosarcomas, the best treatment is wide surgical excision with an overall guarded prognosis. There is no suggestion that chemotherapy may be advantageous.

VASCULAR TUMORS OF BONE

Definition/Overview

Primary vascular tumors of bone are infrequently encountered, but they are virtually all malignant. Any bone may be affected, but the axial skeleton is more frequently affected than the appendicular skeleton. Hemangiosarcoma of the bone is more common in the dog than in the cat, and the German Shepherd Dog is most frequently at risk.

Etiology

Hemangiosarcoma is a malignancy of vascular endothelial cells or their precursors.

Pathophysiology

These tumors rapidly metastasize via hematogenous routes to the liver and lungs. They can rupture, leading to acute hemorrhage and sudden death.

Clinical Presentation

History and presenting signs are similar to those for osteosarcoma. Osteolysis is the dominant radiographic feature.

Differential Diagnosis

Telangiectatic osteosarcoma (Figures 15.54–15.56).



FIGURE 15.54 This dog was lame on her right hindlimb for several weeks before she had a sudden onset of hemorrhagic swelling in the thigh muscle region. Radiographs (not shown) showed considerable osteolysis of the femur. The primary differential diagnosis included a hemangiosarcoma. (*Courtesy of M. Schaer.*)

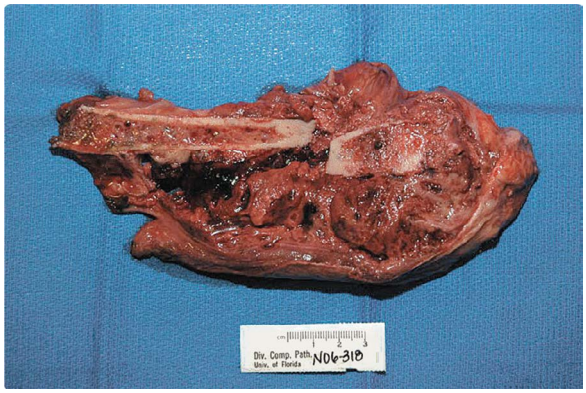


FIGURE 15.55 Gross necropsy of the same dog in **Figure 15.54** showed the lesion to be a telangiectatic osteosarcoma. (*Courtesy of M. Schaer.*)

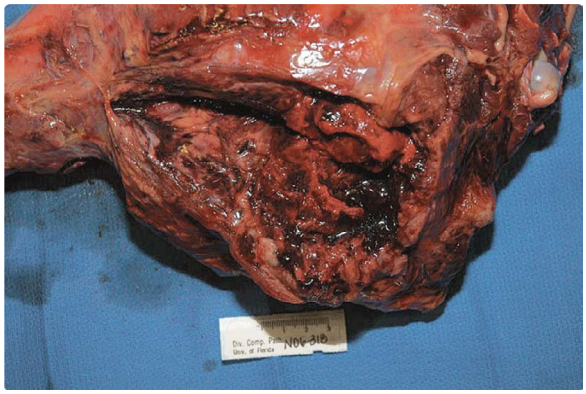


FIGURE 15.56 There was considerable hemorrhage into the thigh muscles. (*Courtesy of M. Schaer.*)



FIGURE 15.57 Pelvic hemangiosarcoma. This lesion is characterized by soft tissue swelling and periosteal proliferation.

Diagnosis

Radiographically, hemangiosarcomas show massive destruction, often involving one-half or more of the entire bone shaft. Destruction tends to remain confined within the medullary cavity with both proximal and distal expansion. Marked periosteal new bone formation is not characteristic but may be seen (**Figure 15.57**), and pathologic fractures may occur. Hemangiosarcomas often have vascular spaces, and biopsy for diagnosis may be nondiagnostic. Therefore, it is prudent to biopsy at the periphery of the tumor to obtain distinct cores of tissue.

Management

Affected dogs must be thoroughly staged with thoracic and abdominal radiography, bone scintigraphy, or bone survey radiography. Prognosis is poor irrespective of surgical excision and adjunct chemotherapy.

SYNOVIAL CELL SARCOMA

Definition/Overview

Synovial cell sarcoma is the most frequent tumor of soft tissue that involves adjacent bones.

Etiology

This tumor may arise from precursor mesenchymal cells outside the synovial membrane of articular structures.

Pathophysiology

The biological behavior of this tumor is variable. Synovial cell sarcoma is a disease of middle-aged to older dogs and is rarely reported in cats. Joints most commonly involved are the stifle, elbow, carpus, tibiotarsal, and phalangeal joints. Nearly half of affected patients ultimately develop metastasis involving the lungs or regional lymph nodes.

Clinical Presentation

Examination of the affected joint may reveal swelling, pain, and a decreased range of motion. Joint swelling typically involves both sides of the joint.

Differential Diagnosis

Primary bone tumor, osteoarthritis, osteomyelitis, villonodular synovitis.



FIGURE 15.58 Synovial cell sarcoma with soft tissue swelling of the elbow and erosion of the olecranon (proximal ulna) (arrow). Synovial cell sarcoma is most often seen in the elbow and stifle. The tumor usually crosses the joint space. The lesion is predominantly osteolytic, periosteal proliferation is minimal, and soft tissue mineralization is rare. (*Courtesy of A.M. Walker.*)

Diagnosis

Radiographic evidence of a destructive lesion involving bones on both sides of a joint suggests synovial sarcoma, and both the stifle and the elbow are sites of predilection (Figures 15.58–15.61). A biopsy of both the soft tissue lesion and associated bone is diagnostic. Regional lymph node cytology may also be diagnostic.



FIGURE 15.59 Cranial-caudal radiographic lesions diagnosed as synovial cell sarcoma of the tarsometatarsal joint. (*Courtesy of B. Poteet.*)



FIGURE 15.60 Lateral radiographic lesions diagnosed as synovial cell sarcoma of the tarsometatarsal joint. (*Courtesy of B. Poteet.*)

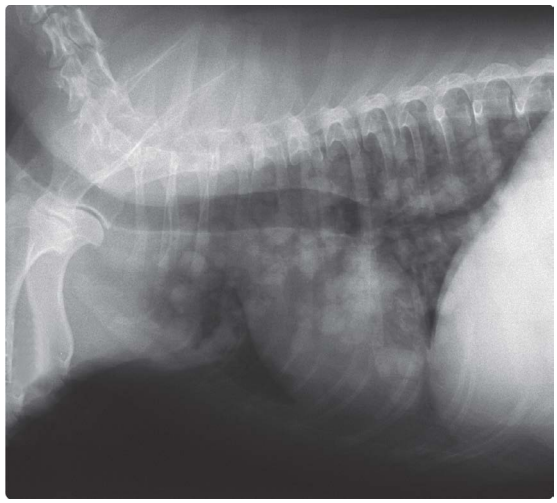


FIGURE 15.61 A lateral thoracic radiograph of the same dog from Figures 15.59 and 15.60 showing metastatic lesions in the thorax. (*Courtesy of B. Poteet.*)

Management

The prognosis after surgery is variable, with recurrence being not uncommon. Survival after excisional biopsy and combination chemotherapy has been reported; however, metastasis occurs in up to 50% of cases.

SQUAMOUS CELL CARCINOMA

Definition/Overview

Squamous cell carcinoma (SCC) is a common tumor involving the skin in both the dog and cat, and it is a common feline neoplasm involving bone. SCCs are usually found in nonpigmented or lightly pigmented skin.

Etiology

Primary lesions occur on the skin and may arise de novo or from overexposure to sunlight. Cats are predisposed to this type of cancer because of a lack of skin pigmentation and a desire to seek sunlight. The lesions are highly erosive and deeply infiltrative and, although late to metastasize, may spread to bone. SCC in cats occurs frequently in the oral cavity and less frequently involves the digits.

Pathophysiology

Unknown; however, SCC can metastasize almost anywhere.

Clinical Presentation

The most common cutaneous locations for SCC in the dog are the toes, scrotum, nose, limbs, and anus, while the nose, eyelids, lips, and pinnae are common locations in the cat. Lesions vary from a red firm plaque to a cauliflower-like ulceration, and they may appear as sequelae to crusts, ulcers, or masses that may have been present for months and been unresponsive to conservative treatment. SCC located deep to teeth can be a reason for premature tooth loosening.

Differential Diagnosis

Draining abscessation, nail bed infection/osteomyelitis, eosinophilic granuloma, mast cell tumor, cutaneous lymphosarcoma.

Diagnosis

Biopsy or cytology.

Management

Superficial tumors are treated by surgery, cryosurgery, or irradiation. Digits with tumor involvement should be amputated. Adjunct chemotherapy or radiation therapy has provided remission (generally only for a short duration) where surgical excision is incomplete, the mass is nonresectable, or the patient has metastasis. When lesions are advanced and bone involvement is present, the prognosis is guarded.

NUTRITIONAL DISORDERS

RICKETS/OSTEOMALACIA

Definition/Overview

Inadequate supplies of cholecalciferol or vitamin D result in rickets or osteomalacia (adult equivalent), diseases affecting the hypertrophic zone of metaphyseal growth plates.

Etiology

Likely causes include dietary deficiency (hypovitaminosis D), impaired absorption or an inadequate concentration of minerals from the diet, and an inborn error in the metabolism of vitamin D. Dogs and cats are mainly dependent on vitamin D from their diet due to an inability to synthesize cholecalciferol in skin exposed to ultraviolet light.

Pathophysiology

There is a failure of mineralization of cartilage and osteoid. The costochondral junctions and metaphyses may be enlarged so that the joints appear swollen.

Clinical Presentation

Immature animals with rickets or mature animals with osteomalacia may be presented with lameness, difficulty rising, a stiff gait, limb bowing, pathologic fractures, or sudden paralysis.

Differential Diagnosis

Hyperparathyroidism.

Diagnosis

Radiographic signs may be similar to hyperparathyroidism and commonly include radiolucent cortical bone due to poor mineralization, thin cortices, bowed diaphyses, and a loss of lamina dura dentes.

Management

Treatment consists of proper dietary supplementation with adequate but not excessive amounts of calcium, phosphorus, and vitamin D and repair of any pathologic fractures.

HYPERVITAMINOSIS A

Definition/Overview

Hypervitaminosis A is a disease of cats that consume large amounts of raw liver.

Etiology

Excessive and prolonged intake of vitamin A either from supplements or liver-rich diets.

Pathophysiology

The condition is characterized by cervical and thoracic bridging exostoses and limb joint periarticular ankylosis, especially in the elbow.

Clinical Presentation

Animals may present with irritability, poor grooming, lethargy, depression, gingivitis, and lameness. In the

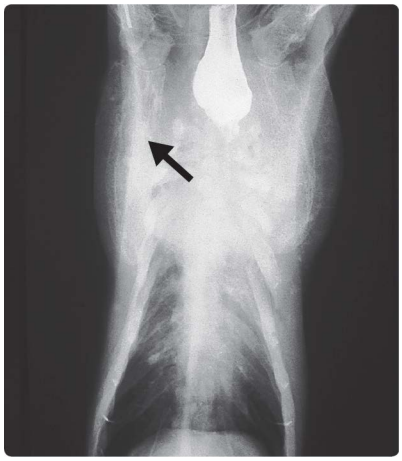


FIGURE 15.62 Thoracic rhabdomyosarcoma and long-standing hypervitaminosis A. The tumor caused esophageal obstruction, as shown on this barium esophagram. The hypervitaminosis A causes the bony proliferation, as shown by the arrow. (*Courtesy of M. Schaer.*)

early stages, the lesions are painful, and they may ankylose, leading to abnormal posture and neck stiffness.

Differential Diagnosis

Nutritional secondary hyperparathyroidism, hypovitaminosis D.

Diagnosis

Radiographically, there is evidence of exostoses and enthesophytes in the cranial and thoracic vertebrae, particularly in older affected animals (Figures 15.62–15.64). There may also be enthesophytes around limb joints (e.g., the elbow or shoulder).

Management

Treatment is aimed at avoidance of excess vitamin A. In elderly cats, despite bone remodeling, there may be

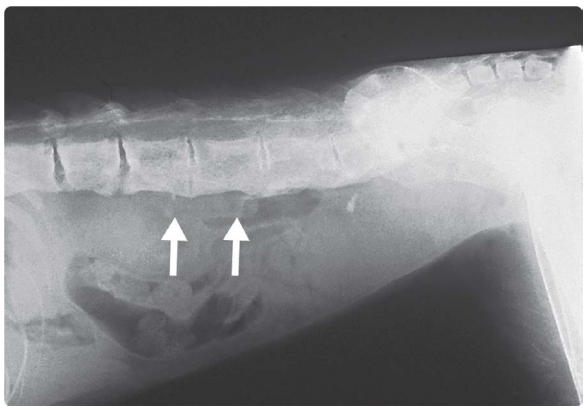


FIGURE 15.63 Radiograph from an aged cat with thoracic rhabdomyosarcoma and long-standing hypervitaminosis A. Note the characteristic hypervitaminosis A-induced bone thickening involving the lumbar vertebrae and pelvis. (*Courtesy of M. Schaer.*)



FIGURE 15.64 Postmortem specimen from an aged cat with thoracic rhabdomyosarcoma and long-standing hypervitaminosis A. Note the characteristic bone thickening involving the scapulae (arrows). (*Courtesy of M. Schaer.*)

rigidity from ankylosis. In young animals, bone growth may be permanently affected.

INFECTION/INFLAMMATION

SUPPURATIVE OSTEOMYELITIS

Definition/Overview

Suppurative osteomyelitis is a bacterial (rarely fungal) contamination of bone leading to the formation of purulent discharge.

Etiology

About half of infections are caused by *Staphylococcus aureus*, whereas polymicrobial infections can be caused by *Streptococcus* spp. and Gram-negative bacteria such as *Pseudomonas* spp., *Klebsiella* spp., *Escherichia coli*, and *Proteus* spp. Sometimes, anaerobic bacteria are involved. Bone is relatively resistant to infection unless there is a concurrent soft tissue injury, bone necrosis, sequestration, fracture instability, implanted foreign material, altered host defenses, or some combination.

Pathophysiology

Associated soft tissue changes can be observed as early as 24 hours. These changes include swelling and loss of fascial planes, and a fistulous tract may eventually develop as a consequence. Bone changes, bony lysis, areas of periosteal new bone formation, or presence of a sequestrum do not become apparent until 10–14 days after introduction of the infection.

Clinical Presentation

In acute conditions, animals may present with signs of systemic illness, including inappetence, dullness, weight loss, and pyrexia. Affected periosteum and surrounding



FIGURE 15.65 A postoperative lateral view of osteomyelitis involving the ulna.

muscle may appear swollen, painful, and feel hot. In chronic conditions, animals may present with fibrosis, muscle atrophy, lymphadenopathy, and contracture.

Differential Diagnosis

Neoplasia, bone cysts, HOD, medullary bone infarction.

Diagnosis

Diagnosis is usually determined from the history, physical examination, microbiology, and radiology. In acute cases, radiography reveals swelling of soft tissue (Figures 15.65 and 15.66) but no osseous changes, whereas in chronic cases, there is evidence of formation of periosteal new bone, which appears as radially oriented, spiculated, and extensive growth. Bone resorption leads to lysis of the medulla, rounding of the ends of fractured bones, and thinning of the cortex. Osteomyelitis can virtually be diagnosed by the presence of sequestra. Bacterial culture should confirm the diagnosis and dictate antibacterial selection.



FIGURE 15.66 The same dog as Figure 15.65 on a cranial-caudal projection.

Management

Drugs that readily cross the capillary membrane of bone and are widely distributed in interstitial fluid include beta-lactams (cephalosporins, penicillins), aminoglycosides, and quinolones. Acute osteomyelitis is usually cured after 4–6 weeks of antibacterial treatment, whereas such treatment is pointless in chronic cases without débridement and surgical removal of sequestra and/or associated implants. Antibiotic-impregnated, absorbable or nonabsorbable beads, or delayed release gels have been used in both acute and chronic cases. Recurrence of infection may require repeated sequestrectomy, débridement, microbiologic culturing, drainage, fracture stabilization, or bone grafting.

INFLAMMATORY ARTHRITIDES

Definition/Overview

Suppurative arthritis is an inflammatory disease of the joints characterized by cellular infiltrates and inflammatory changes in the synovial membrane and synovial fluid. Bacterial infective arthritis is the most common manifestation of septic arthritis; however, fungal agents have also been implicated. Clinical manifestations are due to both persistent inflammatory reactions resulting from deposition and phagocytosis of immune complexes and release of damaging lysosomal enzymes within the joint. The cause and source of immune complexes are unknown.

Noninfective inflammatory arthropathies, including the immune-mediated arthritides, are subdivided as erosive and nonerosive. Erosive arthritides include canine rheumatoid arthritis (RA) and erosive polyarthritis of Greyhounds. Canine rheumatoid arthritis (RA) is a progressive inflammatory polyarthropathy characterized by erosion and destructive changes in the joint that involves both cellular and immune interactions. Characteristic signs are generalized stiffness and shifting limb lameness accompanying systemic signs such as fever, lethargy, and inappetence. The most severely affected joints are the carpal, tarsal, and interphalangeal joints, although the stifle, elbow, and hip are also commonly affected.

Erosive polyarthritis is a specific disease entity in the young Greyhound (Figures 15.67 and 15.68) and mature cats. Chronic progressive polyarthritis of cats is etiologically linked to feline syncytium-forming virus, a common retrovirus infection, and all cats with this disease are serologically and virologically positive for this infection (high incidence of false-positive tests). Cats can also acquire a calicivirus-associated arthritis from natural infection and by vaccination.

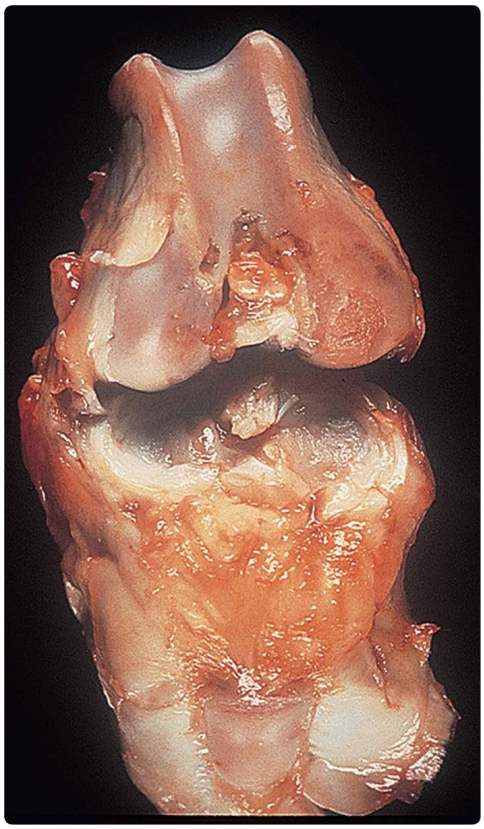


FIGURE 15.67 Gross specimen from a Greyhound with erosive polyarthritis. The cartilage of the trochlear groove has a rough surface, and the red and blue caste to the cartilage identifies the subchondral bone beneath thin, translucent cartilage. The synovium is hypertrophic. (*Courtesy of the late M.S. Bloomberg.*)

Nonerosive arthritides can be further subdivided as follows:

- Systemic lupus erythematosus
- Plasmacytic–lymphocytic synovitis
- Polyarthritis / polymyositis syndrome
- Idiopathic polyarthritis

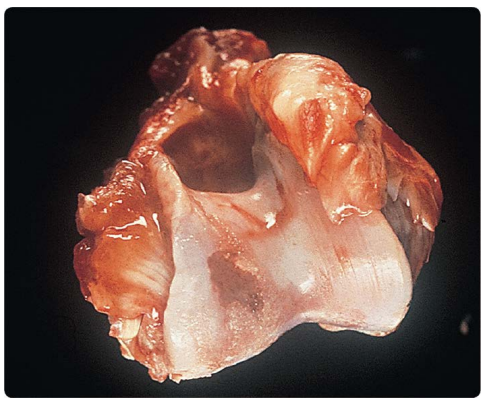


FIGURE 15.68 Gross specimen from a Greyhound with erosive polyarthritis. The distal humerus has a granular, rough cartilaginous surface with linear score marks, cartilage cracks, and a deep erosion. (*Courtesy of the late M.S. Bloomberg.*)

- Drug-induced arthritis
- Hepatopathic arthritis
- Enteropathic arthritis
- Arthritis associated with malignant neoplasia

SLE is a multisystem autoimmune disease characterized by the formation of autoantibodies against a wide array of self-antigens and circulating immune complexes. Although polyarthritis is a frequent feature of SLE in both dogs and cats, it is more likely to be a predominant clinical disease in dogs, whereas cats tend to manifest other systemic signs.

Etiology

Septic Arthritis

Joints are common destinations for blood-borne microbial pathogens because the synovium and the subchondral bone are highly perfused. Additionally, the synovium is a highly phagocytic organ and is, therefore, a common site for trapping blood-borne microbes and immune complexes. In contrast to dogs, infectious arthritis is less common in cats due to infrequent urinary tract and skin infections. Organisms commonly involved in joint infections in dogs include *Staphylococcus* spp., *Streptococcus* spp., *Erysipelothrix* spp., *Corynebacterium* spp., coliforms, *Pasteurella* spp., *Salmonella* spp., and, occasionally, *B. canis*. In cats, the usual offending organisms are *Pasteurella multocida* and hemolytic strains of *E. coli*.

Erosive Arthritis

In RA, immune complexes in the synovium and synovial fluid probably initiate the inflammatory reaction.

Nonerosive Arthritis

Etiologically diverse, nonerosive, noninfectious arthritis occurs in both dogs and cats. Immune complexes in the synovial membrane (resulting in a type 3 immune reaction) are believed to result in joint disease. In idiopathic nondeforming arthritis, the origin and nature of the antigens in the complexes are unknown. The antigens in SLE are of nuclear origin. The antigens in enteropathic arthritis probably originate from the inflamed bowel, and antigens in arthritis secondary to chronic infectious disease or neoplasia originate from the offending microorganisms or from the tumor cells. The cause of SLE is unknown.

Polyarthritis may be a manifestation of drug-induced vasculitis. Fever and stiffness may be seen from the time of first administration or as late as 3 weeks after drug initiation. Skin rash may or may not occur concurrently. Intolerance to trimethoprim–sulfa, penicillins, erythromycin, lincomycin, and cephalosporins is most common. Drug withdrawal yields rapid resolution of signs.

Pathophysiology

Septic Arthritis

Damaged joints, such as joints with chronic degenerative joint disease, are more likely to accommodate

blood-borne pathogens. Larger dogs, older dogs, and proximal rather than distal joints are more commonly affected by degenerative joint disease. Prostatitis, cystitis, pyelonephritis, pyodermas, and oral infections can all be accompanied by septicemia, leading to septic arthritis. Complications include osteomyelitis, fibrous or bony ankylosis, and secondary joint disease.

Erosive Arthritis

Canine RA is more severe in the carpal and tarsal joints. In the early stages, the disease is often accompanied by fever, malaise, anorexia, and lymphadenopathy, while renal amyloidosis can be a complication of long-standing disease. In the central region of the joint, pannus arising from granulation tissue in the underlying marrow cavity causes cartilage destruction. Ankylosis in advanced lesions is common in the intercarpal and intertarsal joints.

Nonerosive Arthritis

This joint disease tends to be cyclic, affecting one or more joints. Biopsy of the synovial membranes shows a nonvillous hyperplasia, sparse mononuclear cell infiltrates, moderate neutrophil infiltrate, and fibrin exudation.

In SLE, the production of autoantibodies to nonorgan-specific nuclear and cytoplasmic antigens and to cell- and organ-specific antigens results from an immunoregulatory defect. Resultant immune complexes are deposited in the glomerular basement membrane, synovial membrane, skin, blood vessels, and other sites. Complement is activated by the immune complexes, leading to tissue injury and inflammation. Furthermore, a direct cytotoxic effect of autoantibodies against membrane-bound antigens contributes to tissue damage.

Clinical Presentation

Septic Arthritis

Animals with septic arthritis are usually painful upon palpation and have significant lameness often severe enough to be nonweight-bearing. Redness and swelling may be observed in the overlying skin and soft tissue. Fever is common. Pointing abscessation and draining tracts may also be present (Figure 15.69).

Erosive Arthritis

Canine RA is a disease of mainly small dogs, manifesting initially as a shifting lameness with soft tissue swelling around involved joints. The disease is often accompanied by fever, malaise, anorexia, and lymphadenopathy in the early stages, while renal amyloidosis can complicate long-standing disease. Excessive amounts of synovial fluid may be present, which is generally discolored and turbid and yields a typically poor and friable mucin clot.

Nonerosive Arthritis

The clinical and radiographic findings of polyarthritis demonstrate the inflammatory nature of the disease and simulate those of RA (narrowed joint space, periarticular osteophytes, subchondral sclerosis, and capsular swelling). The history is one of cyclic fever, including anorexia, lameness, stiffness, and malaise. Muscle atrophy may also be noted.



FIGURE 15.69 This patient had been treated with high doses of prednisone for an earlier diagnosis of pemphigus vulgaris. The immunosuppressive doses of this drug very likely predisposed this patient to a monoarticular *Salmonella* spp. joint infection that responded well to aspiration and intensive antimicrobial treatment. (*Courtesy of M. Schaer.*)

Differential Diagnosis

Septic Arthritis

Lyme disease (*Borrelia burgdorferi*), mycoplasmosis (often associated with immunocompromise), rickettsiosis (polyarthritis is a prominent feature), ehrlichiosis (nonerosive polyarthritis, always thrombocytopenia, triad of thrombocytopenia, fever, and lymphadenopathy).

Erosive Arthritis

Neoplasia, immunologic cause.

Nonerosive Arthritis

Neoplasia, infectious disease, trauma.

Diagnosis

Septic Arthritis

Synovial fluid from septic joints is often bloody, and the presence of toxic, ruptured, and degranulated neutrophils should suggest a bacterial infection. Although slight periosteal proliferation of bone adjacent to the joint space may be seen in late-stage arthritis, early stages are characterized by thickened synovial membrane, distended joint capsule with displacement of adjacent fascial planes, and widening of the joint space from joint effusion. Aspiration of the joint is necessary for a diagnosis by cytology and culture. Positive bacterial culture is low, with only 30% cases resulting in positive culture, even in cases that have bacteria noted



FIGURE 15.70 A cranial-caudal radiographic projection of the carpus of a 7-year-old male Whippet showing erosive polyarthritis. Radiographic investigations of patients with polyarthritis often reveal slightly large joints with soft tissue swelling, periarticular osteophytes, osteolysis of the distal portion of the radius and radial carpal bone, and loss of joint space. (*Courtesy of A.M. Walker.*)

on cytologic examination. Joint cytology supportive of a septic cause should be treated as such despite negative bacteria culture results unless proven otherwise by other diagnostic testing.

Erosive Arthritis

No single test can diagnose canine RA, including the presence of rheumatoid factors in the blood. A prominent radiographic lesion is the progressive destruction of subchondral bone in the more central areas and at the area of synovium attachment (Figures 15.70 and 15.71). A characteristic finding in canine RA is the presence in synovial fluid of mononuclear cells containing IgG.



FIGURE 15.71 The same dog as Figure 15.70 on lateral projection. (*Courtesy of A.M. Walker.*)

Nonerosive Arthritis

Diagnosis is complicated by the cyclic nature of the disease; therefore, consideration must be made of a clinical history with antibiotic-nonresponsive cyclic fever, malaise, anorexia, and lameness. Joint fluid with a neutrophilia of 5,000–100,000 cells/μL yet sterile for bacteria, viruses, *Mycoplasma*, and *Chlamydia* is diagnostic. Diagnosis of SLE is based on a positive ANA or lupus erythematosus test, or both, and two major signs of polyarthritis, proteinuria, dermatitis, hemolytic anemia, leukopenia, thrombocytopenia, or polymyositis.

Management

Septic Arthritis

Treatment of bacterial arthritis is dictated by identification of the causative organism and determination of antibiotic sensitivities. Concurrent cultures of joint fluid, serum, and urine may optimize isolation of the pathogen(s). In the absence of positive bacteria culture, empiric antibiotic therapy is chosen and response to therapy gauged. Generally, continued administration of appropriate antibiotics for 2 weeks or more after the resolution of clinical signs is curative. Drainage of the suppurative exudate helps prevent lysosomal-caused joint damage. Most cases of bacterial arthritis are monoarticular.

Erosive Arthritis

Treatment of RA with corticosteroids, anti-inflammatories, and gold salts has been used, but the effect is merely palliative. If the condition is identified in the early stages, it can be arrested with combination immunosuppressive drug therapy, whereas in advanced conditions, adjunctive joint arthrodesis may be necessary.

Nonerosive Arthritis

Glucocorticoids alone or in combination with immunosuppressive drugs provide remission; however, recurrence of illness is common when therapy is discontinued. Treatment of SLE is directed at controlling the abnormal immune response and reducing the inflammation. Corticosteroids are the foundation of treatment with adjunctive cytotoxic immunosuppressive drugs for additional improvement or when the patient is steroid intolerant.

The most commonly encountered immune disorders affecting the skeletal system are SLE and immune-mediated polyarthropathy. When there is doubt as to whether an arthritis is due to a tick-borne or immune etiology, it is rational to first treat with tetracycline or doxycycline for at least 5 days before initiating treatment with immunosuppressive therapy. A favorable response is expected in 2–4 days if the arthritis is due to spirochetes or rickettsiae.

IATROGENIC DISORDERS

SYNOSTOSIS

Definition/Overview

Synostosis of the radius and ulna is not a developmental disease but rather a sequela following fracture of the mid to proximal radius and ulna. This condition can be of clinical significance in growing animals.

Etiology

A restriction in the relative growth of the proximal ulna is usually associated with a callus spanning the radius and the ulna. This can occur following inadequate or delayed stabilization of a fracture; however, it can also occur despite satisfactory stabilization of a diaphyseal radius/ulna fracture, especially in young dogs with prolific bone healing potential.

Pathophysiology

Synostosis can be associated with a bridging callus following inadequate reduction of radial or ulnar fractures. The condition may also be caused by transfixation of both bones with pins or screws during internal fixation before skeletal maturity. Where considerable growth follows transfixation, the normal growth of the proximal radius is not matched by the proximal ulna, resulting in the radial head continuing the lengthen resulting in elbow incongruity with proximal displacement of the humeral condyles and trochlear notch deformation.

Clinical Presentation

Synostosis presents as an antebrachial deformity that may also include luxation or subluxation of the elbow joint.

Differential Diagnosis

Traumatic premature physeal closure.

Diagnosis

Radiographic finding is of bone bridging two synchronously growing bones, such as the radius and ulna in a growing animal (Figure 15.72).

Management

Treatment of synostosis is based on the degree of malformation and the potential for further bone growth. Surgery consists of removal of the growth constraint and realignment of the elbow joint if appropriate. Bridging callus can be resected, and the defect filled with autogenous fat graft to prevent reformation.



FIGURE 15.72 Synostosis of the radius and ulna in a young German Shepherd Dog. The synostosis (within the diaphysis) resulted in elbow incongruity and a UAP due to disproportionate growth of the proximal portion of the radius ("long radius") relative to the ulna. (*Courtesy of the late M.S. Bloomberg.*)

IDIOPATHIC DISORDERS

LEGG–CALVÉ–PERTHES DISEASE

Definition/Overview

Legg–Calvé–Perthes disease (aseptic necrosis of the femoral head) is a disease of small, immature dogs seen most commonly in Cairn Terriers, West Highland White Terriers, Manchester Terriers, Miniature Pinschers, and Poodles. Spontaneous degeneration of the femoral head and neck (Figure 15.73) is followed by collapse of the coxofemoral joint and osteoarthritis.

Etiology

The cause of Perthes disease is unknown, although in the Manchester Terrier, a multifactorial inheritance pattern with a high degree of heritability has been identified.

Pathophysiology

A major part of the blood supply to the capital epiphysis of the femur becomes compromised, and the ischemic portion becomes necrotic. Necrosis of subchondral bone leads to collapse and deformation of the femoral head under normal weight bearing.

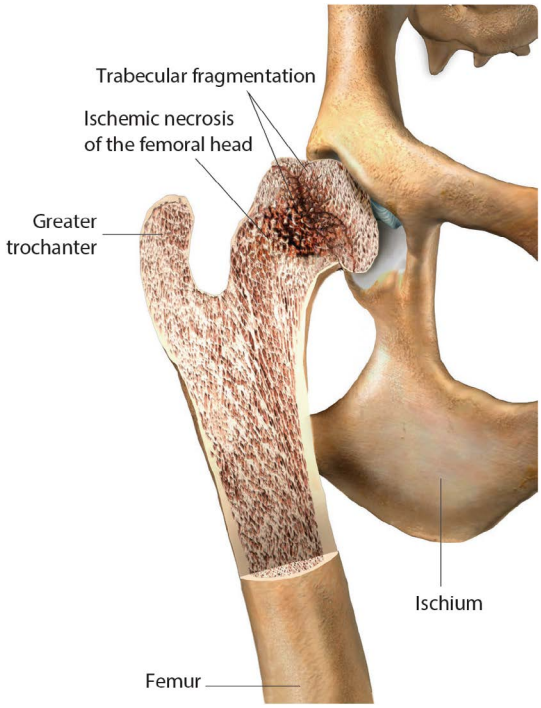


FIGURE 15.73 Illustration of Legg–Calvé–Perthes disease depicting collapse of the femoral head and neck areas.

Clinical Presentation

Perthes disease is usually unilateral and associated with thigh muscle atrophy and pain in the hip.

Differential Diagnosis

Luxating patella, coxofemoral luxation, capital physeal fracture.

Diagnosis

Diagnosis is confirmed by radiographic findings that include radiolucent areas of the proximal femoral epiphysis (Figure 15.74), epiphyseal deformity, thickening of the femoral neck, and increased width of the hip joint space.

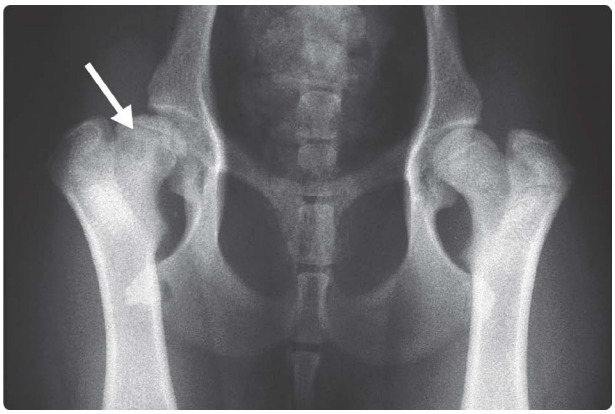


FIGURE 15.74 Unilateral Perthes disease in a 6-month-old female Fox Terrier presented for right hindlimb lameness. This radiograph shows lysis of the femoral head (arrow).

Management

Pathology is usually advanced by the time dogs are presented with clinical signs. The surgical procedure of femoral head and neck ostectomy is recommended as a salvage procedure. Micro total hip prosthesis may be available for clients interested in this option. Total hip arthroplasty is also considered a salvage procedure.

BONE CYSTS

Definition/Overview

Simple bone cysts are benign bone lesions occurring only in large breed dogs. The distal radius and/or ulna is affected most often.

Etiology

The etiology is unknown but may involve intramedullary metaphyseal hemorrhage or local disturbance of bone growth.

Pathophysiology

Lesions occur in metaphyses and adjacent diaphyses of long bones. They are lined by thin membranes and contain serosanguineous fluid.

Clinical Presentation

Affected dogs either have no clinical signs referable to the lesion or have an associated lameness. Pain, swelling, and joint stiffness may be evident in the area of the bone cyst, and the cyst may predispose to a pathologic fracture.

Differential Diagnosis

Atypical bone neoplasia, fibrous dysplasia of bone, aneurysmal bone cyst.

Diagnosis

Radiographically, bone cysts appear as radiolucent defects with cortical thinning (Figures 15.75 and 15.76). Periosteal reaction is absent, and the lesion may consist of several chambers. Fine needle aspiration biopsy and cytologic examination may prove diagnostic.

Management

Drainage, curettage, autogenous grafting, and drilling with multiple holes have all been used to treat bone cysts. Left untreated, bone cysts have the potential for inciting a pathologic fracture.



FIGURE 15.75 A lateral radiograph showing an aneurysmal bone cyst in the distal tibia of a mature male Sheltie. This is a rare neoplasm and has produced bony lysis with minimal cortical or periosteal reaction. The bone has expanded with a thin cortex, and a pathologic fracture may ensue. (*Courtesy of S. Newell.*)



FIGURE 15.76 The same dog as **Figure 15.75** on cranial-caudal projection. (*Courtesy of S. Newell.*)

SECONDARY HYPERTROPHIC OSTEOPATHY

Definition/Overview

Hypertrophic osteopathy (pulmonary osteoarthropathy, hypertrophic pulmonary osteoarthropathy, hypertrophic pulmonary osteopathy) is a secondary pathologic disease frequently associated with some form of pulmonary disease and characterized by bilateral symmetrical swellings in the distal extremities of all four limbs. It is a disease of older dogs, and the majority of bones in the limb may show a diffuse periosteal reaction. Bone changes usually begin distally and spread proximally.

Etiology

The cause is unknown, and the disease is not restricted to primary thoracic neoplasia.

Pathophysiology

This disease involves increased blood flow to the distal extremities, then overgrowth of connective tissue and subsequent osteoneogenesis. It is proposed that a neural reflex originating in the thorax affects connective tissue and periosteum of the limbs.

Clinical Presentation

Diseased patients are stiff and reluctant to move. Limbs are often painful, warm, and swollen (**Figure 15.77**). Primary thoracic disease may manifest with cough, abnormal lung sounds, dyspnea, or cardiac displacement.

Differential Diagnosis

Osteomyelitis, metastatic neoplasia.

Diagnosis

Radiographic examination reveals early involvement of the metacarpal and metatarsal bones (**Figure 15.78**), with subsequent progression of periosteal reaction recognized in more proximal long bones and joints. Radiographic studies should include films of the thoracic and abdominal cavities to rule out pulmonary or abdominal (e.g., bladder rhabdomyosarcoma or liver adenocarcinoma) disease. Skeletal recognition of hypertrophic osteopathy signals other disease processes; therefore, interrogative diagnostics should follow if hypertrophic osteopathy is suspected.

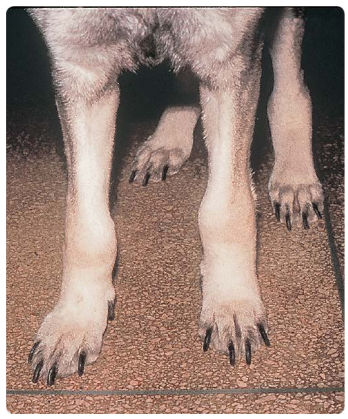


FIGURE 15.77 This 11-year-old female spayed German Shepherd Dog has hypertrophic osteopathy as a result of renal carcinoma metastasizing to its chest. Note the distal appendageal swellings. (*Courtesy of M. Schaer.*)

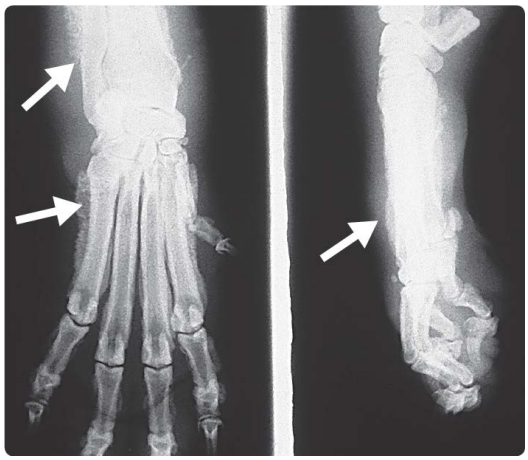


FIGURE 15.78 Hypertrophic osteopathy was diagnosed in this 11-year-old female spayed German Shepherd Dog. All four distal extremities were involved. The radiograph shows the periosteal proliferation involving the distal foreleg (arrows). (*Courtesy of M. Schaer.*)

Management

Clinical signs typically resolve within 1–2 weeks of successful treatment for the primary cause, although resolution of the bony lesions may take months. Relief of lameness may be gained with intrathoracic vagotomy on the ipsilateral side to the bony lesion(s).

MULTIPLE CARTILAGINOUS EXOSTOSES

Definition/Overview

Multiple cartilaginous exostoses (osteochondromatosis, diaphyseal aclasis, hereditary multiple exostoses), reported in both dogs and cats, is a disease manifestation of endochondral ossification where partially ossified protrusions arise from the cortical surfaces of bones. The vertebrae, ribs, and long bones are most frequently affected in dogs.

Etiology

The condition may be inherited as an autosomal dominant trait in dogs. Differentiation to cartilage and bone of chondrocytes displaced from the metaphyseal growth plate is believed to be the cause, and growth of the exostoses usually ceases with skeletal maturation. In the cat, feline leukemia virus has been associated with osteochondromas. Transformation of cartilaginous exostoses into osteosarcoma and chondrosarcoma has been reported.

Pathophysiology

Protuberances consist of cancellous bone covered by a surface of hyaline cartilage; they arise in the metaphyseal region of bones by endochondral ossification. As growth continues, exostoses may finally become located in the diaphysis.

Clinical Presentation

Clinical signs may include paresis due to spinal cord compression or pain from exostoses touching adjacent tissue. Superficial exostoses may be palpated.

Differential Diagnosis

Neoplasia, fracture callus.

Diagnosis

Radiographs reveal bony masses with a smooth, thin shell arising from the cortical surfaces of the appendicular or axial skeleton (Figures 15.79 and 15.80a–d). The expanding exostoses may lead to skeletal deformation. Periodic radiographic evaluation is advised, with the consideration that chronic lesions may transform to bone neoplasia.

Management

The extent of the lesion dictates treatment, and surgical excision may be indicated if the lesion interferes with function.



FIGURE 15.79 Cartilaginous exostoses observed on the medial aspect of the distal radial metaphysis.

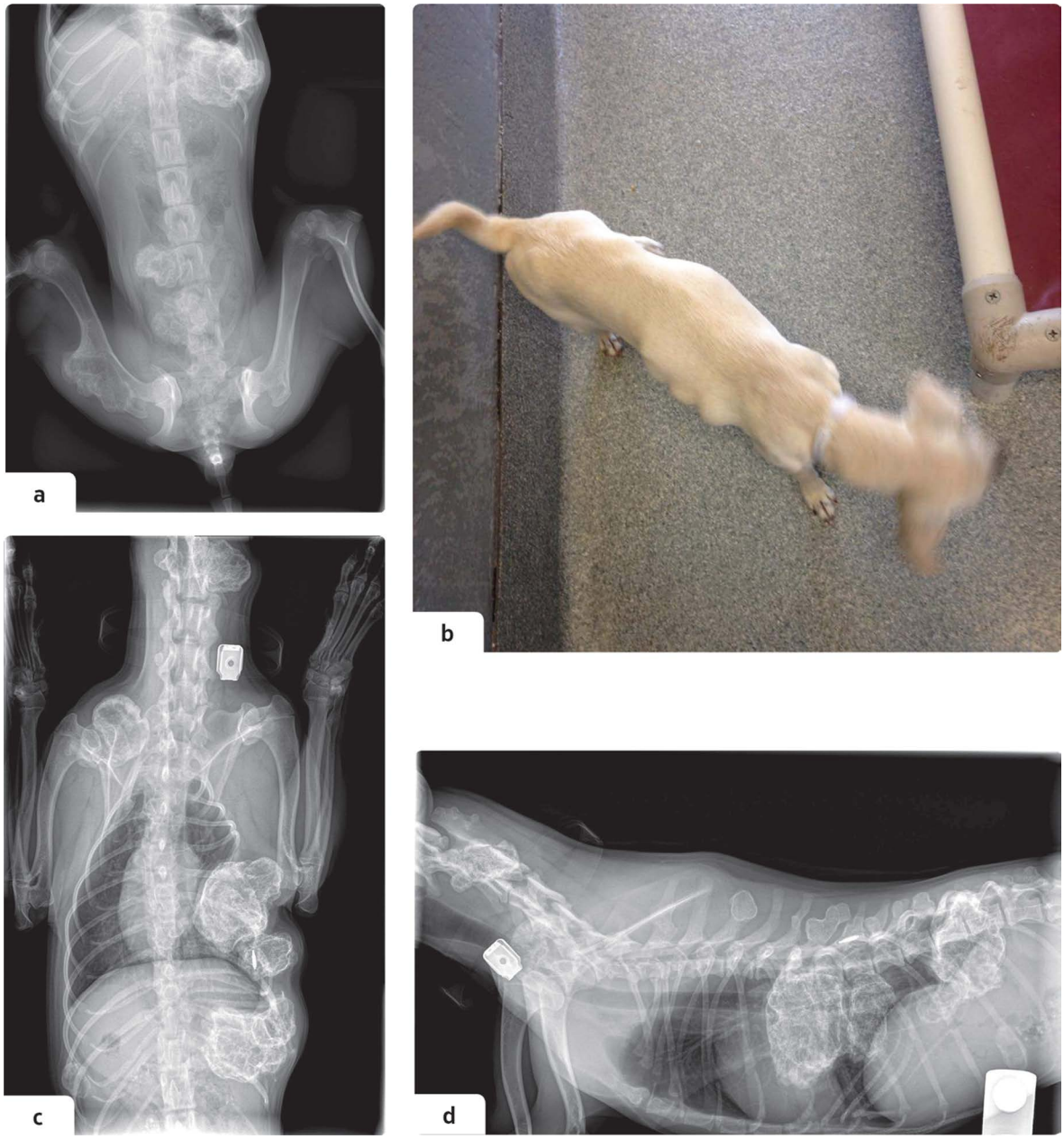


FIGURE 15.80 (a–d) These images depict a young mixed-breed dog with diffuse cartilaginous exostoses showing the external masses and their radiographic appearance at various costochondral sites. (*Courtesy of H. Campbell and A. Alvarez.*)

TOXICITY AND TRAUMA

LEAD POISONING

Definition/Overview

Skeletal signs are usually absent with lead poisoning, but in some affected young dogs, radiography reveals "lead lines" in the bones.

Etiology

Plumbism is a disease caused by the ingestion of lead-containing materials, mainly paint.

Pathophysiology

Lead toxicity may result in gastrointestinal, neurologic, and hematologic abnormalities. Radiographic "lead lines" result from accumulation of thick, mineralized trabeculae at the metaphyseal sites because of impaired osteoclastic activity.

Clinical Presentation

Gastrointestinal signs of vomiting, diarrhea, anorexia, and abdominal pain tend to predominate over central nervous system (CNS) signs of lethargy, hysteria, seizures, and blindness.



FIGURE 15.81 "Lead lines" seen in the metaphysis of an immature dog. (*Courtesy of B.R. Jones.*)

Differential Diagnosis

Hypervitaminosis D, hyperphosphatemia, bismuth toxicity.

Diagnosis

Radiographically, dense sclerotic "lead lines" may be seen in the metaphysis of long bones of immature dogs (Figure 15.81). They are most apparent in the distal radius and ulna. Chronic toxicity of vitamin D, phosphorus, or bismuth can cause a similar radiographic lesion.

Management

Skeletal signs may persist following treatment for toxicity.

TRAUMATIC LUXATIONS

Definition/Overview

Hip—craniodorsal displacement of the femoral head is the most common presentation. This injury causes significant trauma in a normal hip. Dogs with mild dysplasia are at risk with even minor traumatic incidents. Caudoventral luxations occur more frequently in small-breed dogs with low-intensity traumatic events such as slipping on floors with limb abduction. It is important to differentiate direction of luxation as treatment recommendations are different. Closed reductions are potentially effective in dogs with no underlying hip dysplasia,

Elbow—requires significant force to cause elbow luxation in dogs without underlying elbow disease process and may accompany periarticular fractures. Luxations that result in damage to annular ligament separating the radial head from the ulna are less likely to resolve with closed reduction and conservative management.

Etiology

Craniodorsal luxation is likely secondary to increased force directed along the weight-bearing access, resulting in failure of the round ligament of the femoral head and subsequent luxation. In contrast, a caudoventral luxation is thought to be secondary to an excessive abducting force resulting in failure of the ventral acetabular ligament with or without rupture of the round ligament of the femoral head.

Elbow luxation most commonly is the result of a medially or laterally applied force to the forelimb during weight bearing.

Pathophysiology

Regardless of direction of luxation, traumatic luxation will result in reduced or altered range of motion of the joint. Depending on relative location of displaced bone, there may or may not be crepitus present during range of motion. Pain on manipulation is often, but not always, present during examination.

Clinical Presentation

Hip

Dogs with craniodorsal luxation typically present with a non or partially weight-bearing lameness. The affected limb is often observed to be held in slight abduction with external rotation of the limb. Manipulation of the affected joint is typically noted to have reduced range of motion in extension and possible bony conflict with extension. Palpation of the local anatomic landmarks reveals dorsal displacement of the greater trochanter, resulting in alignment of ischial tuberosity, greater trochanter, and wing of the ilium. Caudoventral luxations are more likely to be non-weight bearing. The limb is most often held in a flexed position with possible adduction and internal rotation.

Differential Diagnosis

Periarticular fracture, neoplasia.

Diagnosis

The diagnosis is usually highly suspected following history and physical examination. Definitive diagnosis

usually requires radiographic imaging (Figure 15.82a–d). Additionally, imaging also helps to determine if any periarticular comorbidities are present, and in the case of hip luxation, the presence of underlying hip dysplasia greatly affect the prognosis and recommended course of treatment.

Management

Traumatic luxation of the hip can be managed with closed or open reduction. Closed reduction is recommended; up to 50% of closed reductions do not reluxate and can recover without surgical intervention.

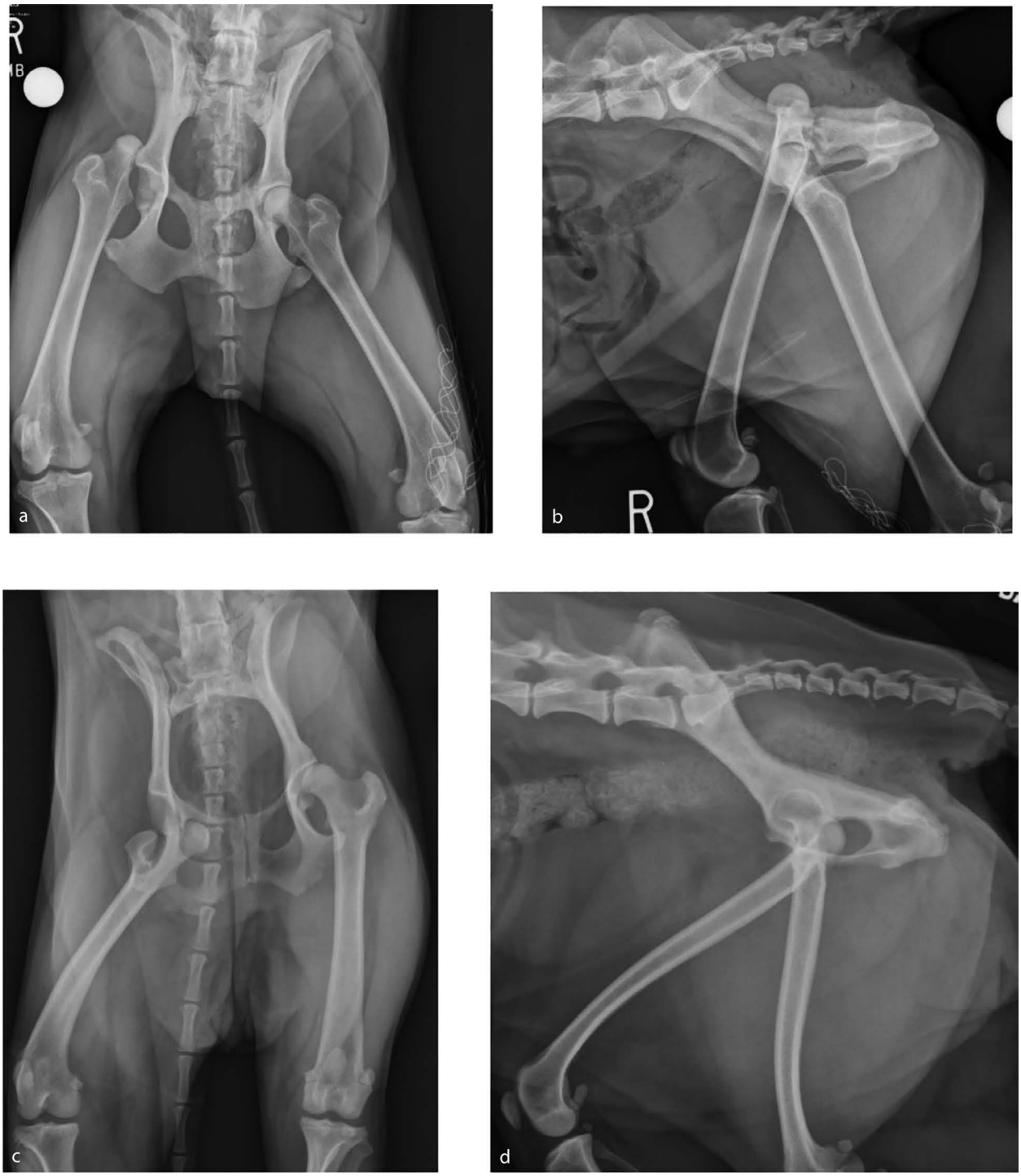


FIGURE 15.82 (a, b) Orthogonal projections of a traumatic craniodorsal luxation in a dog. In this dog, the femoral ligament remained intact. Luxation resulted from a slab fracture of the ventral femoral head. Careful examination of the image shows flattening of the ventral femoral head and a small bone fragment within the acetabular region on the ventrodorsal projection. **(c, d)** Orthogonal projections of a caudoventral luxation in a Cavalier King Charles' Spaniel that occurred following a slip in the house.

Open surgical reduction is accomplished with a toggle and suture technique to recreate the ligament of the head of the femur and imbrication of the joint capsule. If left untreated and managed conservatively, some smaller dogs and cats will have fair function as they form a false arthrosis dorsal to the acetabulum. However, most will have muscle atrophy, chronic pain, and reduced range of motion (ROM) to the hindlimb.

Correction of traumatic elbow luxations via either open or closed reduction is recommended, as these patients do not respond favorably to conservative management. The elbow is inherently stable, if closed reduction is successful, with continued treatment of immobilization for 4–6 weeks followed by gradual reintroduction of range of motion.

COLLATERAL LIGAMENT RUPTURE/INJURY

Definition/Overview

Collateral ligaments play an important role in joint stability for most hinged-type joints. Partial injuries such as partial ligament rupture or stretching of the ligament may not result in joint instability such that nonsurgical interventions may be effective. The tarsus, stifle, and phalanges are more often affected (Figure 15.83a–c).

Etiology

Collateral ligamentous disruption is generally secondary to a medial/lateral force with a fixed distal limb (i.e., weight bearing). The ligamentous injury can be midsubstance or occur as a result of an avulsion with or without a bone segment accompanying the detached ligament.



FIGURE 15.83 Radiographic images for a dog with suspected collateral ligament injury. **(a, b)** Standard radiographic imaging with only mild-to-moderate stifle effusion. Dog was limping following a traumatic event. PE revealed a positive cranial drawer. However, the stifle appeared more lax than usual. **(c)** A lateral stress view was requested revealing lateral collateral incompetence.



FIGURE 15.84 (a–c) Orthogonal radiographic projections of the tarsus in a dog following a road traffic accident. A severe shearing injury was sustained medially. Medial instability was apparent on examination and manipulation of the tarsus. Radiographic images were taken to document extent of injury. Stressed views at the time of presentation can aid in assessment of stability following intervention—surgical or conservative management—in serial assessments during recovery.

Pathophysiology

Ligamentous injury can occur at the bone ligament interface (origin or insertion) or can be within the ligament substance. If the injury occurs at the bone interface, resulting in a sufficiently large bone fragment (avulsion) included with the ligament, there is a better chance for bone-to-bone healing with intervention. Midsubstance tears rarely heal, and successful healing with coaptation alone has a very low chance for successful resolution. In cases such as Figure 15.84a–c with extensive soft tissue injury, sufficient fibrous healing may occur periarticularly to provide sufficient stability to the joint. In these cases, a significant loss of range of motion can be expected. Isolated collateral ligament injury in the absence of other regional soft tissue injury is unlikely to heal, and, in many cases, primary ligament repair via surgical intervention is not possible. Prosthetic ligament repair is typically performed.

Clinical Presentation

Most collateral ligament injuries occur with a traumatic event and may have other more serious comorbidities that require immediate care. Collateral ligament injuries can often initially be managed with coaptation while other injuries are addressed first.

Collateral ligament injury is suspected after a thorough orthopedic examination. Collateral ligament injury may accompany joint luxations; however, it often presents without joint luxation. In acute cases, patients are often non-weight bearing. Some patients with isolated collateral ligament injury may be willing to attempt weight bearing but often are unable to support their weight. During weight bearing, the limb may be observed to angulate in an abnormal manner at the joint.

Differential Diagnosis

Periarticular fracture.

Diagnosis

Physical exam findings, radiographic confirmation with additional stress views challenging stability of suspected collateral ligament injury.

Management

For large avulsion segments, the bone component can be reattached with cross pins and a tension band or with a cortical screw. Prosthetic ligament repair can be performed for most collateral ligaments from the tarsus/carpus and proximal. Prosthetic ligament repair is usually accomplished with large-gauge monofilament suture (nylon, Prolene, or similar) or braided suture (ultra-high-molecular-weight polyethylene or similar). Suture material may be attached to bone via anchors or through bone tunnels.

In some cases, collateral ligament injury accompanies other sever joint injuries such that arthrodesis may be the best option for continued comfortable limb use long term.

Regardless of the technique used to re-establish primary joint stability, secondary support will be needed via splint or cast immobilization or in some cases with transarticular external fixation. For tarsal instability with extensive soft tissue injury, no difference in clinical outcome was shown regardless of the technique chosen. All three (coaptation, prosthetic ligament reconstruction, or arthrodesis) options resulted in similar frequency of complications and similar ultimate limb use and client satisfaction.

Coaptation is initially indicated for phalangeal injuries and tarsal injuries with significant soft tissue wounds. The stifle joint can initially be coapted but will require reconstruction for optimal return to function.

Anatomic reconstruction, partial or pantarsal arthrodesis is effective for persistent tarsal instability. Phalangeal injuries are typically treated with conservative management.

ADVANCED DIAGNOSTIC TECHNIQUES

Increasingly sophisticated tests for the diagnosis of musculoskeletal disorders have become available over recent years. Patient history and physical examination continue to be the mainstay; however, arthroscopy, CT, and MRI are becoming more integrated into our diagnostic offerings. In addition, nuclear scintigraphy, ultrasonography, and gait analysis are diagnostics for special interests.

Magnetic Resonance Imaging

MRI offers excellent contrast and resolution, providing the ability to differentiate between adjacent joint structures.

Indications

Any soft tissue structure that can be placed within the magnetic field. Common uses include:

- CNS diseases of the brain and spinal cord; peripheral nerve root diseases
- Orthopedic conditions of tendons, ligaments, joint capsule, connective tissue, and bone marrow
- Nasal, oral, and auditory diseases

Contraindication

Cases precluding general anesthesia.

Advantages

- Helpful in early disease detection
- Assists in chemotherapy and radiation therapy planning
- Noninvasive
- Higher contrast makes MR image quality superior to that of reconstructed CT images
- Chemically maps body tissues
- Excellent detection of tissue hemorrhage and edema
- Allows image acquisition in any anatomic plane
- Paramagnetic contrast medium is very safe
- Allows detection of discospondylitis before radiographic detection
- More accurate detection of tumor invasion to adjacent structures
- Absence of ionizing radiation
- High sensitivity in detecting abnormal bone marrow

Disadvantages

- Highly motion sensitive
- Resolution inferior to that of CT images
- Cannot image body areas containing metal
- Limited availability
- Costly to purchase and maintain

Computed Tomography

The newest CT technology is spiral or helical scanning. In CT, the patient continuously moves through a gantry on a motorized couch, while the x-ray tube rotates continually during the patient transit. This gives a volumetric representation of the resulting pixels that allows for 3D reconstruction. Multiple slices (1–64) are taken per rotation. The technique is very fast, requiring approximately 10 seconds to do an entire canine thorax.

Indications

- Any body part can be assessed, provided it can fit within the gantry.
- Skull and CNS lesions are most often assessed in veterinary patients.

Contraindications

Relative contraindication: The patient could not be anesthetized for CT; therefore, instead of general anesthesia,

CT is performed under sedation. Often CT imaging can be accomplished with sedation, and for severely affected animals (moribund), sedation may not be needed to obtain diagnostic imaging.

Advantages

- Excellent resolution (down to 0.1 mm diameter) and detail and speed of image acquisition
- Excellent image contrast, with 2,000 shades of gray
- Any areas of mineral and gas are detectable, where they are unseen in conventional radiographs
- Noninvasive

Disadvantages

- General anesthesia may be required for some studies
- Limited availability
- Larger doses of ionizing radiation compared to conventional radiography
- Limited gantry size
- Expense

Arthroscopy

Arthroscopy has revolutionized orthopedic surgery since its veterinary acceptance in the 1970s. In the equine species, arthroscopy has replaced many arthrotomies. A characteristic value of arthroscopy is that this procedure can simultaneously serve as both a diagnostic and therapeutic. The technique is implemented as an adjunct to a thorough orthopedic and radiographic examination.

Advantages

- Is routinely available at surgical referral centers
- Offers a minimally invasive technique, with few complications
- Provides a detailed view and magnification of intra-articular structures and lesions

Disadvantages

- Requires a substantial financial investment and long learning curve.
- Has more limited application in the smaller breeds.
- While associated with a low frequency of complications, the most common is perhaps iatrogenic cartilage damage associated with instrument insertion and manipulation.

RECOMMENDED FURTHER READINGS

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CHAPTER 16

Hematologic Disorders

Katie M. Boes, Claire M. Cannon, and Julien R.S. Dandrieux

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INTRODUCTION

Blood disorders occur commonly in dogs and cats, often secondary to systemic disease or injury. History, physical examination, and laboratory diagnostic tests, including a complete blood count (CBC), are crucial for recognition and complete characterization of these disorders. Once a baseline is obtained, further workup can be planned to include imaging, sampling of abnormal organs, and bone marrow evaluation as indicated.

ERYTHROCYTE DISORDERS (NONNEOPLASTIC)

GENERAL APPROACH TO ANEMIA

Definition/Overview

Anemia is one of the most frequent hematologic abnormalities encountered in practice. It is not a disease but rather the reflection of a disease state.

Etiology

The three general causes of anemia are erythrocyte loss (hemorrhage), lysis (hemolysis), and decreased production in the bone marrow (atrophy, hypoplasia, or aplasia). Anemia is classified as preregenerative, regenerative, or post-regenerative. **Figure 16.1** lists the main causes of anemia.

Pathophysiology

A decreased red blood cell (RBC) mass leads to insufficient oxygen delivery to vital organs and subsequent decreased aerobic metabolism, energy production, and tissue function. Cellular and tissue injury can occur with more severe or prolonged anemia.

Clinical Presentation and Physical Examination Findings

Common historical signs of anemia include lethargy, depression, weakness, exercise intolerance, pica, and hyporexia. Recumbency, seizures, syncope, and coma may occur with severe anemia.

Pale mucous membranes are a common physical examination finding (**Figure 16.2a, b**). Pallor can be due to hypoperfusion, hypoxemia, or anemia. Animals with hypoperfusion have typically no or only mild decrease in their packed cell volume (PCV) and have an increased capillary refill time (CRT). In contrast, cats and dogs that develop pallor secondary to anemia have a moderate-to-severe reduction in their PCV and are typically hyperkinetic (normal-to-decreased CRT and hyperkinetic pulses). A PCV should always be measured in the pale animal, but the CRT cannot always be evaluated due to the lack of contrast with pallor. If pallor is present, thorough examination for evidence of petechiae, ecchymosis, or bleeding is indicated.

With moderate-to-severe anemia, heart murmur, tachycardia, tachypnea, and dyspnea may be appreciated. Icterus (**Figure 16.3**) may occur with hemolytic anemia or internal hemorrhage, whereas intravascular hemolytic anemia can cause hemolysis (**Figure 16.4**) and hemoglobinuria in addition to icterus (see also Chapter 2.8). Hemorrhage into the thoracic and abdominal cavities may cause dyspnea and abdominal enlargement, respectively. Occasionally, anemia may be discovered during routine blood evaluation in an apparently clinically normal animal. Sedentary animals, especially cats, often have a moderate anemia that goes unnoticed for long periods of time. Splenomegaly and hepatomegaly frequently occur due to increased extravascular hemolysis or extramedullary hematopoiesis. Lymph nodes should be carefully palpated as lymphadenomegaly can suggest underlying diseases such as infectious or neoplastic processes. The

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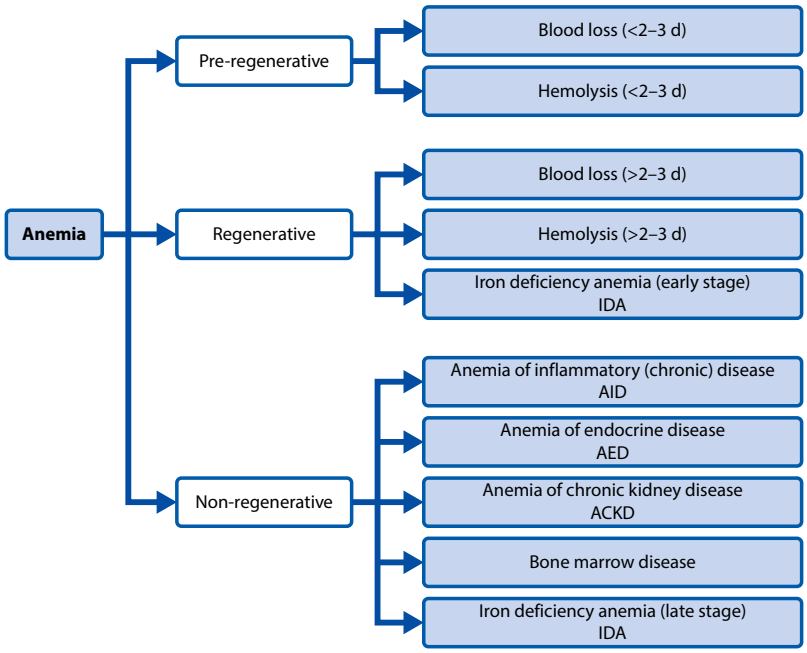


FIGURE 16.1 Classification of anemias.

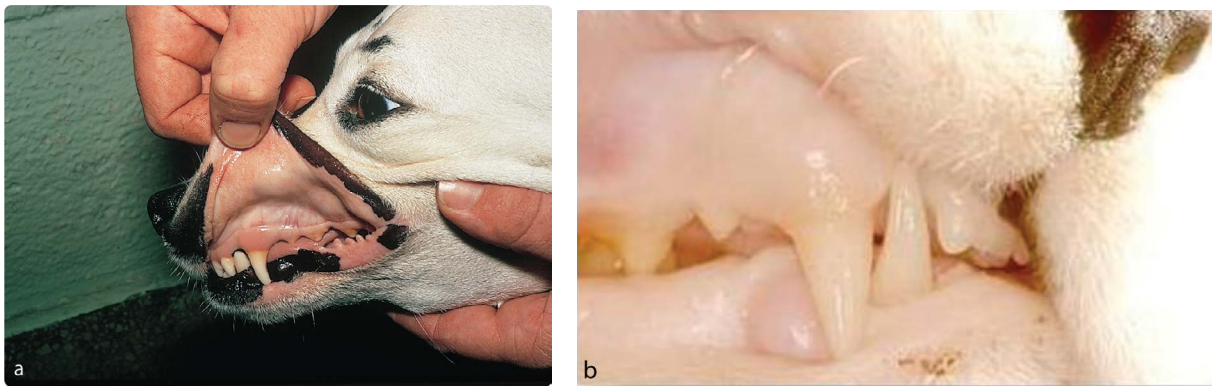


FIGURE 16.2 Marked pallor in a dog **(a)** and cat **(b)**. (*Courtesy of M. Schaer.*)



FIGURE 16.3 Icterus demonstrated by yellow skin discoloration. (*Courtesy of J. Thompson.*)

animal should also be evaluated for trauma or surgery and sites of blood loss. A fundic exam is helpful as a first screen for an underlying infectious disease.

Clinical signs depend on the severity of the anemia and the onset of anemia. An animal with slow progressive anemia will develop compensatory mechanisms (see ahead given in the text), and obvious clinical signs will only develop with moderate-to-severe anemia. In comparison, an animal with acute hemolysis will develop marked clinical signs with a comparatively mild anemia.

History

If not previously obtained, a complete history is required in addition to a thorough physical examination. Table 16.1 lists some of the pertinent questions, and Table 16.2 lists the drugs and toxins that have been reported as a cause of anemia in dogs and cats. The clinician also needs to obtain information about concurrent disease and duration of disease.

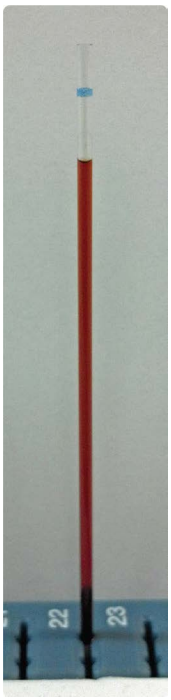


FIGURE 16.4 Red plasma and PCV of 0.14 L/L (14%) in an animal with intravascular hemolysis. The pink supernate characterizes hemolysis.

Differential Diagnosis

Refer to each specific disease.

Diagnosis

Diagnosis include laboratory testing (starting with a CBC), including infectious agent testing according to the animal history, diagnostic imaging, and sampling for cytology or histology as indicated. When this is insufficient to reach a diagnosis, bone marrow sampling may be required. In the emergency setting, the clinician should ideally take the samples prior treating and at a minimum an ethylenediaminetetraacetic acid (EDTA) sample for PCV/total protein (TP)/hematology/polymerase chain reaction (PCR)/Coombs as indicated and serum for biochemistry and serology. A citrate sample is also indicated if a hemostasis problem is suspected.

Complete Blood Count

Anemia is identified by a decreased PCV, hematocrit (Hct), RBC count, or hemoglobin (Hgb) concentration. The PCV is the most accurate and least expensive method of documenting anemia. It is performed by centrifuging a microhematocrit tube filled with anticoagulated whole blood for 5 minutes at 12,000–15,000 g and then measuring the RBC volume as a percentage of the total blood volume. See Table 16.3 for causes of erroneous PCV.

The plasma of the spun microhematocrit tube should be evaluated for lipemia, hemolysis, or icterus, since this may help identify the cause of the anemia, disease states, or potential biochemical interferences (Figure 16.4). The plasma protein or total solid concentration should be determined by refractometer.

The Hct may be calculated from the mean cell volume (MCV) and RBC by a hematology analyzer (see Table 16.3 for equations and artifacts), or it may be measured by conductivity by some blood gas instruments. The Hct is similar to the PCV, except the PCV is typically higher by 1–3 percentage units due to trapped plasma between RBCs in the microhematocrit tube.

Hgb concentration is typically determined using a spectrophotometer by the cyanmethemoglobin method or a cyanide-free method.

TABLE 16.1 Specific questions to ask owners of a pet with anemia

Questions	Reasons
Bloody or dark tarry stools?	Intestinal bleeding (e.g., ulcerated mass) Potential for iron deficiency
Change in urine coloration?	Either due to bilirubinuria, hematuria, or hemoglobinuria (intravascular hemolysis)
Fleas noted?	Severe flea infestation can be a cause of anemia
Ticks noted?	Possible tick-borne disease such as ehrlichiosis (bone marrow) or babesiosis (hemolysis)
Worming status?	Severe hookworm infestation may cause anemia, especially in young animals
Any current treatment or possible access to toxins?	See Table 16.2 for some of the drugs and toxins reported as cause for anemia in dogs and cats
FeLV/FIV status?	Retroviral infection can lead to anemia through different mechanisms
Dog fight (Pitbull), kennels (Greyhound)	*Babesia gibsoni* may be transmitted by bites from Pitbulls
Female pet used for reproduction or pet has received a blood transfusion	Requirements for crossmatching if blood transfusion is likely to be required

TABLE 16.2 Examples of common drugs and toxins that can cause anemia in dogs and cats (this is not an exhaustive list, as any drug has the potential to trigger an idiosyncratic reaction)

Drug*	Species
Acetaminophen/paracetamol†	C > D
Nonsteroidal anti-inflammatories (NSAID)	C, D
Benzocaine	C
Chemotherapeutic agents	C, D
Chloramphenicol	C, D
Gold salts	C, D
Griseofulvin	C, D
Methimazole	C
Methionine	C
Methylene blue†	C > D
Metronidazole	D
Penicillins and cephalosporins	D > C
Phenobarbital	D
Phenothiazines	C, D
Propylthiouracil	C
Propylene glycol	C
Sulfa derivatives	D > C
Zinc	C, D

* Different mechanisms can lead to anemia (e.g., thrombocytopenia, IMHA, bone marrow suppression).

† Drug is not recommended for cats.

The RBC count is usually performed by an automated cell counter or, less commonly, by a hemocytometer.

The mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) are calculated RBC indices (Table 16.3 for equations and artifacts) that help classify the type of anemia as normochromic (normal MCH and MCHC) or hypochromic (decreased MCH and MCHC). When these values are discrepant, MCHC is the preferred index for interpretation.

MCV may be determined directly by automated cell counters or calculated (Table 16.3). MCV reflects RBC size and may be categorized as macrocytic (increased MCV), microcytic (decreased MCV), or normocytic (normal MCV). An increased MCV may occur with RBC regeneration, feline leukemia virus (FeLV) infection, or breed variation (Toy and Miniature Poodle dogs). Decreased MCVs are observed with iron deficiency, liver disease, portosystemic shunts, breed variation (Akita and Shiba dogs), or young animals.

Blood smear evaluation of RBCs involves qualification of changes in size (anisocytosis), shape (poikilocytosis), and color (chromasia). The presence of abnormal red cells (e.g., nucleated precursors, basophilic stippling, infectious parasites, and Heinz bodies) or red cell arrangement (e.g., agglutination and rouleaux) should be noted.

Reticulocyte Counts

Reticulocytes are young RBCs that contain more ribonucleic acid (RNA) and less Hgb than mature RBCs. Most reticulocytes develop into mature RBCs in the bone marrow and are subsequently released into peripheral circulation. However, low numbers of reticulocytes are present in blood under normal hematologic conditions. Increased numbers of reticulocytes in blood (reticulocytosis) are seen with tissue hypoxia, and the presence or absence of reticulocytosis classifies the anemia as regenerative or nonregenerative, respectively. Once initiated in the bone marrow, regeneration may take at least 3 days before reticulocytes appear in circulation. For this reason, a preregenerative anemia can be seen during the first 3 days after the development of acute anemia. If the animal is stable, a repeat reticulocyte count 3 days after the first one can be used to confirm that an anemia is nonregenerative.

Reticulocyte counts may be determined by automated hematology analyzers or by manual methods. For manual reticulocyte count quantification, equal volumes of blood and 0.5% new methylene blue stain are incubated together for 15–20 minutes at room temperature. Then, a routine blood smear is made and allowed to dry. The numbers of aggregated (dogs and cats) and punctate (cats) forms per 1,000 erythrocytes are counted to determine the reticulocyte percentage (retic%) (Figures 16.5 and 16.6). The absolute reticulocyte count (retic#) is the more accurate reflection of RBC regeneration and is calculated from the retic% and RBC count (Table 16.3).

Dogs normally have 0%–1% reticulocytes (0–80,000/μL) in blood. In normal cats, aggregated reticulocytes range from 0% to 0.4% (0–30,000/μL), and punctate reticulocytes are <5% (<500,000/μL). Aggregated reticulocytes represent the most active or recent form of regeneration in the dog and cat and are identified as polychromatophils in Romanowsky-stained smears. Punctate reticulocytes in cats do not stain as polychromatophilic cells, and they represent past regeneration that occurred in the prior 2–4 weeks.

Note that the absolute reticulocyte count is the best method to identify regeneration. In the absence of a reticulocyte count, increased polychromasia on a Romanowsky-stained blood smear is the only RBC morphology that is specific for regeneration. Within the monolayer, dogs normally have 0–1 polychromatophils/100× objective field, and cats have no to rare polychromatophils/100× objective field. Greater numbers reflect regeneration.

When the RBC count is not available, the PCV may be used to calculate the corrected reticulocyte percentage (Table 16.3). A corrected reticulocyte percentage (CRP) value >1% indicates increased RBC regeneration.

Some hematology analyzers also provide reticulocyte indices, which characterize the size and hemoglobin content of reticulocytes. Causes for abnormal reticulocyte

TABLE 16.3 Hematologic parameter abnormalities

Parameter and method	Increased patient result	Decreased patient result
Packed cell volume (PCV) Directly measured	– Dehydration – Excitement (epinephrine) – Breed (Greyhound, Whippet) – Chronic hypoxia – Neoplasia – Artifact: Inadequate mixing or centrifugation	– Anemia – Overhydration – Artifact: Excessive EDTA, in vitro hemolysis, inadequate mixing
Hematocrit (Hct) Hct (%) = MCV (fL) × RBC ($x10^6$/μL) ÷ 10	– See increased PCV (except artifact) – Artifact: Falsely increased MCV or RBC, inadequate mixing	– See decreased PCV (except artifact) – Artifact: Excessive EDTA, falsely decreased MCV or RBC, in vitro hemolysis, inadequate mixing
Hemoglobin (Hgb) Directly measured	– See increased PCV (except artifact) – Artifact: Excessive Heinz bodies, hemolysis, lipemia, some gammopathies	– See decreased PCV (except artifact)
Red blood cell concentration (RBC) Directly measured	– See increased PCV (except artifact) – Artifact: Inadequate mixing, marked thrombocytosis	– See decreased PCV (except artifact) – Artifact: Clotted sample, in vitro hemolysis, inadequate mixing, RBC agglutination
Mean cell volume (MCV) Directly measured	– Reticulocytosis – Breed (some Poodles) – FeLV – Folate/cobalamin deficiency – Artifact: Hypernatremia, RBC agglutination, sample storage	– Young animals using adult RIs – Breed (Asian dog breeds) – Iron deficiency – Portosystemic shunt – Artifact: Excess EDTA, hyponatremia
Mean corpuscular hemoglobin (MCH) MCH (pg) = Hgb (g/dL) × 10 ÷ RBC ($x10^6$/μL)	– See increased MCV (except artifact) – Artifact: Falsely increased Hgb, falsely decreased RBC	– See decreased MCV (except artifact) – Artifact: Falsely decreased Hgb, falsely increased RBC
Mean corpuscular hemoglobin concentration (MCHC) MCHC (g/dL) = Hgb (g/dL) × 100 ÷ Hct (%)	– Artifact: Falsely increased Hgb, falsely decreased Hct	– Reticulocytosis – Iron deficiency – Portosystemic shunt – Lead poisoning – Artifact: Falsely decreased Hgb, falsely increased Hct
Absolute reticulocyte count (retic#) Retic# ($x10^3$/μL) = Retic% (%) × RBC ($x10^6$/μL) × 10	– Marrow erythroid hyperplasia – Artifact: Babesiosis, inadequate mixing, leukemia	– Marrow erythroid atrophy – Artifact: Clotted sample, in vitro hemolysis, inadequate mixing, reticulocyte agglutination
Corrected reticulocyte percentage (CRP) Dog: CRP (%) = Retic% (%) × Patient's Hct (%) ÷ 45% Cat: CRP (%) = Retic% (%) × Patient's Hct (%) ÷ 35%	– See increased retic#	– See decreased retic#

Retic%, percent reticulocyte count; RI, reference interval.

hemoglobin content (CHr) and reticulocyte mean corpuscular volume (rMCV) are similar to those of abnormal MCHC and MCV, respectively. In particular, low CHr and rMCV may detect iron deficiency earlier than erythrocyte indices.

Biochemical Profiles

Biochemical profiles may reveal disease that can affect the ability to regenerate erythrocytes, especially diseases of the liver and kidney. Other changes can be suggestive of endocrine disease, and a discrepancy in urea increase compared to creatinine can suggest gastrointestinal blood loss. A low albumin and total protein are more likely with blood loss than hemolysis in an animal with normal liver function. Icterus can develop secondary to hemolysis, especially in dogs, and can also be present with internal bleeding resorption.

Fecal Examination and Urinalysis

These tests are performed to determine sources of blood loss in the gastrointestinal (GI) tract or urinary tract, respectively.

Fecal occult blood test consists of smearing feces on a test pad to detect bleeding that is not apparent grossly. The animal should ideally not be fed red meat for 3 days prior to testing to reduce the risk of a false-positive result. The sample should be run 2–3 days after application to reduce the risk of false-positive result from

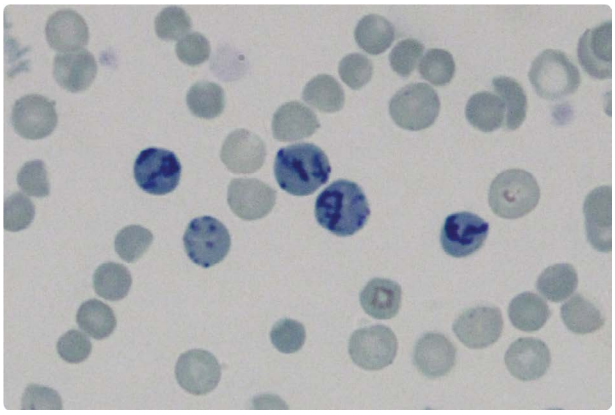


FIGURE 16.5 New methylene blue–stained blood smear from a dog, showing five aggregated reticulocytes.

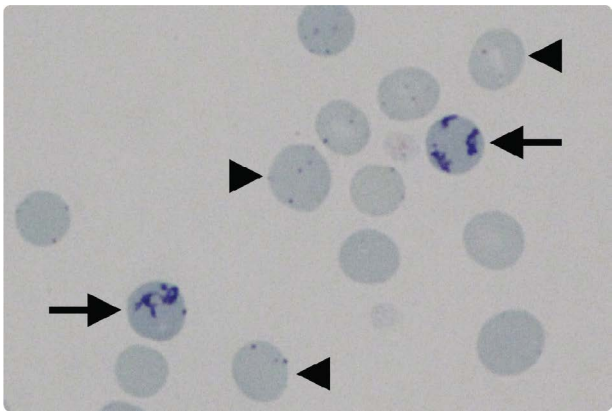


FIGURE 16.6 Feline aggregated (arrows) and punctate (arrowheads) reticulocytes demonstrated by new methylene blue stain.

plant-derived peroxidases. Vitamin C supplementation can falsely decrease the result.

Dipstick can be used to detect microscopic hematuria and confirm ongoing hematuria. Comparison of a free catch and cystocentesis urine sample can be useful to differentiate significant hematuria proximal or caudal to the bladder neck (e.g., distal urethra or uterine pathology).

Laboratory Testing for Infectious Etiologies

The clinician needs to be aware of the travel history of the pet and potential infectious agents that are relevant in their region. Testing modalities include direct visualization (e.g., *Babesia* on a smear), serology (e.g., FIV antibody test to identify viral exposure), and antigenic testing (e.g., FeLV antigen test). See Chapter 11.

Diagnostic Imaging

Diagnostic imaging is often required in the workup of the anemic animal. It can be especially useful to assess the origin of bleeding in the absence of obvious source. In the emergency setting, this includes abdominal and thoracic-focused assessment with sonography for trauma, triage, and tracking (AFAST and TFAST).

Similarly, imaging is useful to rule out triggers for hemolysis (e.g., abdominal radiographs to exclude a foreign body containing zinc) or in an animal with suspected associative immune-mediated hemolytic anemia (e.g., neoplasia with secondary immune-mediated hemolytic anemia [IMHA]).

Endoscopy

Endoscopy might be indicated to further assess and sample sources of GI, respiratory, or urinary bleeding. See specific diseases for more information.

Cytology and Histopathology

If abnormalities are detected during the workup that are potentially relevant as a cause for the anemia, sampling should be considered to reach a final diagnosis, help with prognosis, and guide treatment. Platelet count and coagulation profile should be considered in an anemic animal prior to sampling if a primary or secondary hemostasis disorder is suspected.

Sampling of enlarged organs (e.g., lymphadenomegaly, splenomegaly, and hepatomegaly) may reveal primary pathology (e.g., bleeding tumor) or secondary pathology (e.g., extramedullary hematopoiesis, reactive lymphoid hyperplasia).

Bone Marrow Evaluation

Bone marrow evaluation (Table 16.4) is best performed when both aspirate and core biopsies are taken together, since each provides different information. Results must always be compared with a recent CBC (within 24 hours) to determine the current status of regeneration. Indications for bone marrow evaluation include persistent cytopenia(s) of unknown etiology, diagnosing leukemia, and infectious myelitis. The procedure is typically performed if the disease etiology has not been identified with previous workup, including sampling of abnormalities such as lymphadenopathy, diagnostic imaging, and laboratory testing (e.g., tick-borne disease). This is a sterile procedure, and usually, sedation with or without local anesthesia (ilium, sternum) or general anesthesia (humeral sampling) is recommended as pain is expected.

Sites frequently used in dogs include the dorsal ilium, humerus (best for obese animals), and femur (small dogs or puppies). Aspirate from the sternum has also been described and is used in some institutions routinely for monitoring purposes. Sites frequently used in cats include the humerus, femur, and dorsal ilium by transilial or perpendicular approach (Figures 16.7–16.9). Specialized needles are preferred for the collection process, and the procedures are well established.

Classifying the General Cause of Anemia

The previous tests help classify the cause of anemia as hemorrhage, hemolysis, or decreased RBC production (Table 16.5).

TABLE 16.4 Bone marrow aspiration and core biopsy procedures for the dog and cat

Aspiration biopsy	Core biopsy
Equipment – Illinois sternal disposable needle, 15–18 G, 2.5–5 cm (1–2 inches) long (Cardinal Health, Dublin, OH) Procedure – Pass the needle with its stylet a few millimeters into the bone until it is firmly embedded – Place a 12 mL syringe coated with 5% EDTA solution onto the biopsy needle and collect 1–2 mL of bloody material – Place the marrow material into a plastic Petri dish and pick up the glistening particles with a pipette – Gently express this material out of the tube onto a glass slide – Make a squash preparation by laying a second slide on the first and pulling them horizontally apart	Equipment – Jamshidi aspiration/biopsy disposable needle, 11–13 G, 5–10 cm (2–4 inches) long (Cardinal Health, Dublin, OH) Procedure – Pass the needle with stylet through the skin and subcutaneous tissues – Remove the stylet while advancing the needle 0.5–1.5 cm into the bone, depending on the size of the animal – Twist the instrument sharply to cut the sample and withdraw the needle slowly – Remove the core sample and roll it onto a glass slide for cytologic examination; following this, place sample in 10% buffered formalin for histologic fixation

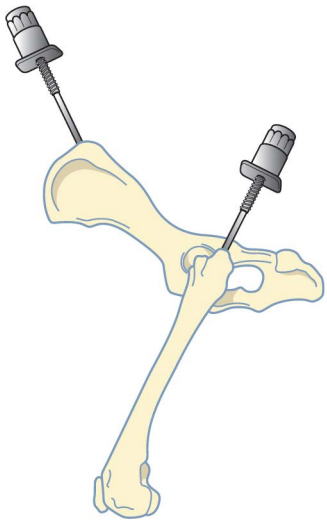


FIGURE 16.7 Bone marrow sites for aspiration and core biopsy using the dorsal crest of the ilium and the proximal femur. The parallel approach to the ilium is best for aspiration biopsy in medium- or large-sized breeds having an easily palpable crest protuberance.

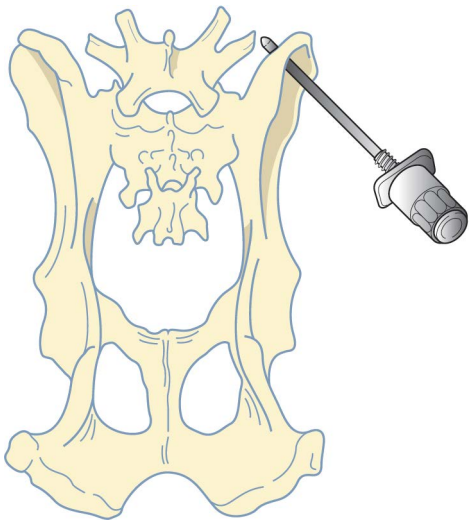


FIGURE 16.8 Bone marrow site for the transilial approach for core biopsy in a cat or small dog.

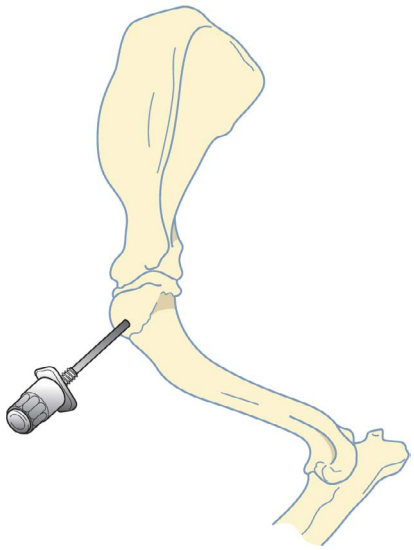


FIGURE 16.9 Bone marrow site for aspiration and core biopsy using the anterior lateral side of the proximal humerus. This site is especially helpful in obese animals.

Historical and physical support for hemorrhage includes a history of trauma or surgery or the observation of bleeding wounds, petechiae, ecchymoses, heavy external or intestinal parasitism, epistaxis, hemoptysis, melena, hematochezia, hemorrhagic effusions, or hematuria. Hemorrhage typically causes regenerative anemia, but nonregenerative anemia may occur with peracute hemorrhage prior to the release of reticulocytes from the bone marrow (preregenerative anemia, first 3 days), or with chronic external blood loss leading to iron deficiency. Proportionate decreases in albumin and globulin concentrations, termed *panhypoproteinemia*, support hemorrhage as the cause of anemia, since proteins are also lost with extravasation of whole blood. An increased serum urea nitrogen concentration relative to creatinine concentration can occur with excessive intestinal absorption of protein due to gastric or small intestinal hemorrhage.

External bleeding such as melena or hematuria might be obvious for the owner but can also easily be missed. For example, hematuria might only be noticed when the pet urinates in snow or might not be macroscopically

TABLE 16.5 Indicators of general categories of anemia

	Blood loss	Hemolysis	Decreased production
Clinical	Hemorrhage (internal or external), petechiae, ecchymosis, trauma	Icteric plasma and mucous membranes	Petechiae (if also decreased platelet production)
CBC	Reticulocytosis; increased polychromasia, decreased plasma proteins	Reticulocytosis, increased polychromasia, increased MCHC, red plasma	No reticulocytosis, no polychromasia, other cytopenias
Chemistry	Increased BUN versus creatinine (GI bleeding), panhypoproteinemia, hyperbilirubinemia (internal hemorrhage)	Hyperbilirubinemia	
Urinalysis	Hematuria (if urine loss is the cause), bilirubinuria (internal hemorrhage)	Golden-orange urine, pigmenturia without hematuria, bilirubinuria	

apparent as the amount of blood loss is too small. Long-term external bleeding will lead to iron deficiency with the typical nonregenerative, microcytic, hypochromic anemia. However, in the early stage, the anemia will be strongly regenerative, and for this reason, the primary cause might be missed. Changes in hematological indices over time can be useful in these cases to identify the primary cause.

Excessive destruction of mature RBCs results in regenerative anemia unless the hemolysis is peracute and, therefore, preregenerative. Support for hemolysis as the cause of anemia includes yellow plasma or mucous membranes (icterus), red plasma (hemolysis), and hemoglobin in the urine (hemoglobinuria). Since icterus may occur with other disease processes (e.g., liver disease or cholestasis), it is not pathognomonic for hemolysis. Panhypoproteinemia is not an expected finding of hemolysis.

Decreased RBC production causes nonregenerative anemia. Therefore, reticulocyte counts are typically within normal limits or decreased. Icterus or hemolysis does not typically occur, but both can occasionally be seen with precursor immune-mediated anemia or if there is concurrent liver or cholestatic disease. Nonregenerative anemia is not directly linked with panhypoproteinemia. The main causes of nonregenerative anemia include anemia of endocrine disease, anemia of inflammatory or chronic disease, anemia of chronic kidney disease (CKD), bone marrow disease, and late-stage iron-deficiency anemia.

The severity of the anemia can also allude to the cause, as marked anemia is typically seen with hemolysis or with bone marrow disorders. Although it can also be seen in animals with CKD due to a lack of erythropoietin production, this is only expected in animals with advanced disease (see ahead given in the text). For this reason, further investigation is required in an animal with marked anemia and early-stage kidney disease.

The combination of the severity of the anemia and clinical signs is also useful to categorize the type of anemia. A dog or a cat with moderate-to-severe anemia without clinical signs, such as tachycardia, tachypnea, change in appetite, or lethargy, is likely to have chronic anemia. Signs will be more pronounced in an animal with acute anemia or with decompensation of end-stage chronic anemia.

Management

Principles of Transfusion Therapy

Blood transfusion depends on the etiology, severity, and chronicity of the anemia. Whole blood contains both red blood cells and clotting factors. Whole blood can be centrifuged and separated into packed RBCs (pRBCs, RBCs without plasma) that can be stored up to 5 weeks at –4°C and fresh frozen plasma (FFP) that can be stored for at least a year at –20°C. Less readily available products include platelet-rich plasma or platelet concentrates.

A patient that is anemic secondary to significant blood loss will benefit from whole blood transfusion to replenish RBCs and plasma that have been lost (hypovolemic anemia). If not available, the animal will benefit from pRBC to improve the oxygen-carrier capacity and fluid therapy as required.

If coagulopathy is causing blood loss and anemia, then FFP or whole blood should be given to correct the underlying problem, if warranted (see Chapter 17). If the amount of blood loss is significant, whole blood transfusion or pRBC will also be needed.

If the origin of the anemia is hemolysis or bone marrow disorder (isovolemic anemia), then pRBC is the product of choice. Although pRBC might also be beneficial in marked anemia of renal disease, treatment of the primary cause (erythropoietin deficiency) is likely to be more useful long term with iron supplementation (see Chapter 13).

Whole blood should not be used to replenish platelets in a thrombocytopenic animal, but platelet products should be used, if available. Animals with significant bleeding will need RBCs as required until the platelet count has improved. Similarly, albumin cannot be significantly replenished with blood products.

Rapid decreases in RBC mass can cause more severe clinical signs and patient outcomes, since physiologic compensation mechanisms are more easily overwhelmed. However, slow daily decreases in PCV of 0.01–0.03 L/L (1%–3%) may not cause clinical signs. Generally, replacement therapy in chronic anemia may not be warranted until the PCV drops below 0.20–0.25 L/L (20%–25%), since compensatory mechanisms begin to fail at lower RBC masses. When the PCV reaches 0.12–0.15 L/L

(12%–15%), transfusion therapy is usually strongly recommended, especially if sedation or anesthesia is required for workup (e.g., bone marrow sampling).

There is not a single trigger to determine when a specific animal requires a transfusion, and the clinician needs to take an educated guess accounting for the breed normal hematocrit (e.g., Greyhounds have a higher normal PCV and might require a transfusion earlier than other breeds), the clinical signs (lethargy, tachycardia) at rest, hyperlactatemia, and other signs.

Pretransfusion testing should be performed to ensure efficacy of treatment and patient safety. The clinician should consider running these tests in advance if the animal is likely to require a transfusion urgently to save time if not cost prohibitive. Pretransfusion compatibility testing includes blood typing and cross-matching. Blood typing detects RBC antigens, while cross-matching detects the presence of anti-RBC antibodies in plasma or serum.

Dogs do not have naturally occurring RBC alloantibodies. Therefore, dogs develop alloimmune RBC antibodies when they are exposed to foreign RBCs during pregnancy, parturition, or blood transfusion. At least 12 dog erythrocyte antigens (DEAs) have been identified, but DEAs 1.1, 1.2, 4, 7, and Dal are most likely to induce alloantibody formation. Blood typing is not essential prior to a nonparous patient's first blood transfusion, but administering DEA 1.1-positive blood to a DEA 1.1-negative dog will reduce the blood donor pool if subsequent blood transfusions are needed. Cross-matching is also not essential for a transfusion in a naïve dog but is recommended if repeated transfusion is required after 4 days from the first one, as alloantibodies develop in this time frame.

Cats have three major RBC types: Type A, type B, and type AB. Type A is the most prevalent blood type in the United States, with type B cats more commonly identified in Europe and Australia; type AB cats are rare. Exotic breeds of cats, including Abyssinians, Birmans, Persians, Himalayans, and Rexes, have an increased prevalence of type B blood. RBC alloantibodies occur naturally in cats except in type AB cats, which do not produce A or B alloantibodies. At a minimum, all cats should be blood typed prior to their first blood transfusion to ensure they receive appropriate type A or type B blood. However, only typing for A and B antigens carries a slight risk of not identifying other natural occurring alloantibodies, such as the Mik antigen. If blood typing is not available, a cross-match should be performed. Similar to dogs, cross-matching should be performed if blood is administered 4 or more days after the first transfusion.

During cross-match testing, incompatibility between patient and donor manifests itself as hemolysis and/or agglutination in either the major or minor cross-matches (Table 16.6). If the donor autocontrol displays either hemolysis or agglutination, it is best not to use it. If the donor autocontrol displays these changes, the major and minor cross-match results will be difficult, if not impossible, to interpret. A major cross-match incompatibility indicates that the donor's blood may not be used. However, incompatibility in the minor cross-match may not prevent use of the donor's packed RBCs if a better match cannot be found. The decision is up to the clinician, and the blood transfusion should be carefully monitored.

TABLE 16.6 Standard cross-matching procedures used to detect transfusion incompatibility

- Collect from each patient and donor, 1 tube for serum (red top) and 1 tube for cells (purple top)
- Wash cells 3 times in 0.9% saline
- Add 4.8 mL saline to 0.2 mL RBCs to make a 4% cell suspension
- Red cells and serum mixtures
  - *Major cross-match:* Donor RBCs (0.1 mL or 2 drops) + patient serum (0.1 mL or 2 drops)
  - *Minor cross-match:* Patient RBCs (0.1 mL or 2 drops) + donor serum (0.1 mL or 2 drops)
  - *Donor control:* Donor cells (0.1 mL or 2 drops) + donor serum (0.1 mL or 2 drops)
  - *Patient control:* Patient cells (0.1 ml or 2 drops) + patient serum (0.1 ml or 2 drops)
- Incubate each mixture in a glass tube for 15 minutes at 37°C (98.6°F) to evaluate compatibility; additional incubations at room temperature and 4°C (39.2°F) may be performed to identify cold agglutinins and hemolysins
- Centrifuge tubes at 280 g for 1 minute
- Examine the supernatant for hemolysis in all cross-matches, including autocontrols; report the presence of hemolysis relative to autocontrols
- Examine cell suspension for gross and microscopic agglutination in all cross-matches, including autocontrols (agglutination is defined as the collection of three or more RBCs), report the presence of agglutination relative to autocontrols

Blood Transfusion

The goal of transfusion therapy is to provide the anemic patient with sufficient oxygen-carrying particles (RBCs) to alleviate clinical signs of hypoxia but with as little product as necessary so as to reduce the likelihood of transfusion reactions and volume overload. Smaller dosages may be needed in chronic anemias due to the presence of physiologic compensation and internal blood loss anemia, since hemorrhaged RBCs will reenter the circulation (approximately 50% over 24 hours). Discussion on fluid type, rate, and monitoring for resuscitation of severe hemorrhage is discussed in depth in Chapter 23. In these cases, the patient should be monitored for hypocalcemia and hypomagnesemia secondary to citrate anticoagulant administration.

In general, the optimal component for normovolemic patients (e.g., normovolemic blood loss anemia, hemolysis, bone marrow disorder) is packed RBCs with the aim to increase the oxygen-carrying capacity. Hypovolemic blood loss anemia is best treated with packed RBCs and fluids (e.g., crystalloid or colloid solutions) in separate lines and into different veins or alternatively whole blood transfusion. Product availability often dictates which component will be administered.

The blood product is typically administrated via a peripheral or jugular vein, although intraosseous access

can be used in neonates. Initial dosages are typically 6–10 mL packed RBCs/kg or 10–20 mL whole blood/kg. Dosage as low as 5 mL/kg/day might be needed in animals with heart disease. Animals with preexisting heart disease, that are normovolemic but transfused with whole blood, should be carefully monitored for fluid overload, especially cats.

Appropriate filters and administration sets must be used to retain clotted blood or debris. The blood does not need to be warmed prior to administration. For the first 30 minutes, the initial rate of administration should be kept slow (e.g., up to 0.5 mL/kg/h) in order to observe any incompatibility reactions (see ahead given in the text). After initial transfusion, normovolemic patients can receive rates of 10–20 mL/kg/h, but hypovolemic patients with acute anemia may require higher rates depending on the individual needs. Slow transfusion rates are recommended for patients with cardiac disease, but any transfusion should be given within 4–6 hours of initiating treatment. The blood product should be considered contaminated after this time frame. An estimate is that 2.2 mL/kg of whole blood will increase the recipient hematocrit by about 1%.

Transfusion reactions can be divided in acute (within the first 48 hours) and delayed as well as immunological versus nonimmunological. Examples of nonimmunological reaction include fever, citrate intoxication (with high transfusion rate or significant liver impairment), fluid overload, and disease transmission. Immune-mediated hemolysis can be acute (within minutes) with signs such as tremor, fever, or vomiting. Delayed hemolysis is characterized by rapid decline of the RBCs with concurrent hemoglobinemia and hyperbilirubinemia starting a few days after the transfusion. It can be difficult to differentiate between ongoing immune-mediated destruction of the animal's own red cells versus a delayed transfusion reaction. A common complication in people is a transfusion-related acute lung injury (TRALI) that seems to be infrequent in dogs (3.7% of cases in one study).

In view of the potential life-threatening complications and rapid onset, it is important to closely monitor animals receiving blood products prior and during transfusion. An example of protocol is to acquire a baseline prior transfusion on a monitoring sheet (body temperature, heart rate, respiratory rate, and blood pressure). The transfusion is started at a slow rate, and any signs of vomiting, pruritus, or change in the baseline are monitored every 5–10 minutes for the first 30 minutes. If the transfusion is tolerated, the rate can be increased to the desired flow, and monitoring continues every 30 minutes thereafter. The transfusion should be discontinued if severe signs are noted (e.g., urticaria, vomiting, diarrhea, or collapse). If the animal develops a fever, the transfusion should be stopped, and the animal monitored for 15–30 minutes prior to deciding to continue the transfusion at the same or a lower rate. Overall efficacy of the blood transfusion is assessed by measuring the Hct, PCV, or Hgb prior to and after the administration of whole blood or packed RBCs If not initially hemolyzed, transfused RBCs have a half-life of approximately 21–35 days but shorter if there is ongoing destruction.

Xenotransfusion

Xenotransfusion from dogs to cats has been reported. Although, the literature on the subject is sparse, there is one recent large case series of 49 cats receiving xenotransfusion. No severe acute adverse reaction has been reported in different studies, but delayed hemolytic transfusion reaction within 2 days was noted in 64% of cats (25 out of 39 cats) surviving the first 24 hours in the largest study. Reasons to consider xenotransfusion include lack of adequate feline blood products, life-threatening emergencies, and financial constraints. For this reason, despite the low risk of severe acute adverse reaction, a delayed hemolytic transfusion is likely. Xenotransfusion might be successful if the anemia is expected to become regenerative timely and can be quickly controlled (e.g., such as acute blood loss during surgery or after trauma).

REGENERATIVE ANEMIA

Regenerative anemia is anemia with increased numbers of reticulocytes in the blood. It identifies the cause of the anemia as RBC loss from blood vessels or RBC destruction. Depending on the severity of hemorrhage or hemolysis, the regenerative response may be mild to strong. In some cases, the anemia may occur so rapidly that the animal may have too little time to mount a regenerative response by the time the condition is recognized. A period of 2–3 days is necessary for RBC maturation once the stimulation from hypoxia has occurred. Therefore, anemia due to hemorrhage or hemolysis may appear nonregenerative during this preregenerative phase. In a stable animal with mild-to-moderate anemia, sequential CBCs over 3 days can help differentiate preregenerative anemia from nonregenerative anemia.

ACUTE BLOOD LOSS

Definition/Overview

Whole blood is lost from the blood vessels. Hemorrhage may be internal (e.g., abdominal, thoracic, or pericardial cavities) or external (e.g., GI tract, urinary tract, respiratory tract, or open wounds).

Etiology

Common causes of blood loss include trauma, surgery, intracavitary bleeding lesion (mass, organ rupture such as spleen), external and internal parasitism, gastric ulcers, tumors of the GI and urinary systems, and phlebotomy (Table 16.7). Repeat phlebotomy can be a significant cause of blood loss in hospitalized small dogs and cats.

TABLE 16.7 Common causes of blood loss

- Trauma
- Surgery
- External and internal parasitism
- Gastric or intestinal ulcers
- Tumors of gastrointestinal and urinary systems
- Splenic rupture
- Coagulation abnormalities
- Thrombocytopenia
- Iatrogenic (repeat phlebotomy in a small dog or cat)

Pathophysiology

Large volumes of blood must be lost before appreciable changes occur in the number of erythrocytes or PCV. The immediate loss of blood results in little or no change to the PCV, owing to the concurrent and proportional loss of RBCs and plasma. To increase blood volume and pressure, the body redistributes fluid from the extravascular space to the intravascular space over the course of several hours to days. This results in a lowered PCV and plasma protein concentration. Physiologic alterations to acute blood loss include preservation of perfusion of the brain, heart, and viscera by restricting blood flow to less essential tissues (e.g., skin). Table 16.8 lists differences in findings that can help the clinician to differentiate an animal with blood loss versus hemolysis (immune mediated or not).

Clinical Presentation

Animals with acute blood loss (>20% of normal blood volume) will present with abnormal perfusion that can be assessed with mucous membrane (MM) color, CRT, heart rate, and pulse quality. This is the result of several hemodynamic mechanisms directing blood away from less essential tissue to preserve the perfusion of important organs such as the brain and heart. An animal with mild hypovolemia will have normal/pink MM, normal CRT (<1s), mild tachycardia with increased pulse amplitude. If hypovolemia progresses, the animal will develop pale pink MM with a normal CRT and decreased pulse amplitude. With severe hypovolemia and decompensated shock, the MM become white or muddy, the CRT is prolonged to not measurable, and the pulse amplitude is severely decreased. Such animals develop hypotension and might also be profoundly lethargic with cold extremities and skin and be hyperlactemic. Blood losses of >50% normal blood volume cause shock and death within hours.

Differential Diagnosis

Bleeding secondary to disorders of primary (marked thrombocytopenia) or secondary hemostasis, hemolytic conditions.

Diagnosis

Physical examination for external wounds, obvious parasites load, including rectal examination for melena. TFAST and AFAST to assess a source of bleeding. As mentioned before, a PCV/TP and CBC are recommended to assess the animal including platelet count but will be normal in an acute setting. Serial measurements of PCV/TP will be helpful to confirm a decrease with time and fluid therapy.

Other diagnostic tests include buccal mucosal bleeding time and coagulation testing to rule out hemostasis disorders. If no obvious cause is determined, further considerations include thorough abdominal and thoracic

TABLE 16.8 Changes in findings between blood loss, immune-mediated hemolysis, and nonimmune-mediated hemolysis

	Blood loss	Hemolysis (immune-mediated)	Hemolysis (not immune-mediated)
Source of bleeding	Often evident†	None	None
Icterus	Rare‡	Often	Often
Hepatomegaly/splenomegaly	Rare	Often	Often
Plasma or serum protein concentration	Normal to low	Normal to high	Normal to high
PCV	Normal to low§	Low	Low
Hemoglobinemia/Hemoglobinuria	No	Often / Often	Yes / Yes
Autoagglutination	No	Possible	Possible*
Spherocytosis	No	Likely	Rare*
Direct Coombs test	Negative	Likely positive	Rarely positive*
RBC changes	Signs of regeneration	See Table 16.3	See Table 16.3

* Hemolysis secondary to an infectious process can have an immune-mediated component, and for this reason, infectious diseases need to be ruled out from history and specific testing. No autoagglutination or spherocytosis would be expected from oxidant-induced hemolysis.

† If the bleeding is in the gastrointestinal tract or urinary tract and in small amount, detection can be difficult.

‡ Icterus is possible with significant internal bleeding; however, the source is likely to be evident from physical examination and diagnostic imaging.

§ PCV will be normal with an acute blood loss until fluid shift has occurred.

imaging, urinalysis for hematuria, fecal floatation, and fecal occult blood. If present and safe (adequate hemostasis), sampling of body cavity fluid or abnormal findings for cytology is indicated. Blood sampled from a cavity will not clot as platelets have been consumed; therefore, a sample can be placed in a tube without additive for a few minutes to confirm the absence of clotting and ensure that the spleen or the liver was not inadvertently sampled during the procedure.

If there is a strong suspicion for significant GI bleeding, endoscopy can be used to assess the stomach and proximal duodenum as well as distal ileum. However, the lesion can be out of reach in which case capsule endoscopy (such as ALICAM®) or explorative laparotomy might be indicated if there is strong evidence of GI bleeding. Limitation to the use of an endocapsule include failure to enter the duodenum before the battery dies and inability to obtain biopsies. In rare cases, significant bleeding from the respiratory tract is ingested by the animal, and thoracic imaging +/– bronchoscopy will be required to achieve a diagnosis.

Management

See Chapter 21 for treatment of hypovolemic shock and blood transfusion. Blood products should be considered when acute hemorrhage causes the PCV to drop to 0.2–0.25 L/L (20%–25%) in the dog or cat during stabilization.

HEMOLYTIC ANEMIA

Hemolytic anemia is most commonly a result of immune-mediated destruction, RBC parasites, oxidant-induced injury, or mechanical fragmentation (micro-angiopathy). Blood smear evaluation has a critical role in differentiating the causes of hemolysis (Table 16.9) and, therefore, the appropriate disease treatment. Other differences between blood loss versus hemolytic process are listed in Table 16.8.

PRIMARY (NONASSOCIATIVE OR IDIOPATHIC) IMMUNE-MEDIATED HEMOLYTIC ANEMIA

Definition/Overview

IMHA is antibody- and complement-mediated RBC destruction. It is subclassified into primary or nonassociative IMHA and secondary or associative IMHA. Both terminologies will be used synonymously for the remainder of this section. The nonassociative form is characterized by a dysregulated immune system that produces antibodies against unaltered RBC surface antigens in the absence of an identifiable cause (truly idiopathic or unrecognized trigger). Associative or secondary IMHA may occur as a sequela to infection, drugs, or neoplasms that typically alter RBC surface antigens. In some instances, it is impossible to determine if the comorbidity is the cause for the IMHA (secondary) or coincidental; therefore, the term associative has been suggested. Associative or primary IMHA is the most common form of IMHA in dogs. Although previous reports in cats suggested that feline IMHA was more frequently associative, especially with concurrent FeLV infection, more recent studies suggest that primary IMHA is more common in cats as well.

Etiology

The etiology of nonassociative IMHA is unknown, but regulatory T-lymphocyte dysfunction, defects in central or peripheral tolerance, cross-reactivity with self- and foreign antigens, and exposure of hidden antigens have been implicated. It may be associated with systemic lupus erythematosus (SLE) or other autoimmune disease.

TABLE 16.9 Potential erythrocyte abnormalities with main causes of hemolysis

Abnormality	Immune-mediated	Infectious	Oxidant-induced	Micro-angiopathy
Ghost cells	✔	✔	✔	
Agglutination	✔	✔		
Spherocytes*	✔	✔		
RBC parasites		✔		
Heinz bodies†			✔	
Eccentrocytes			✔	
Methemoglobinemia			✔	
Schistocytes				✔
Acanthocytes				✔
Keratocytes				✔

* Spherocytes are difficult to identify in cats since their red cells normally lack central pallor.

† Up to 15% of feline RBCs may normally contain Heinz bodies. In addition to oxidative toxicosis, increased Heinz bodies in cats may occur with hyperthyroidism, diabetes mellitus, and lymphoma.

Pathophysiology

Antibodies of the IgG subclass are most commonly implicated in canine IMHA, but IgM antibodies and complement may also contribute to disease. The variable fragment of the antibody binds the RBC surface antigen, marking it for removal by the monocyte–macrophage system or activating the classical complement pathway. Splenic macrophages, and to a lesser degree hepatic macrophage (Kupffer cells), bind the constant fragment of the RBC-bound antibody. The macrophages either completely phagocytize the RBC and remove it from circulation or only phagocytize a part of the RBC membrane. Completely phagocytized RBCs are digested, and the hemoglobin is converted to bilirubin, which results in clinical icterus and hyperbilirubinemia. The partially phagocytized RBC remains in circulation but with an abnormal RBC morphology (spherocyte). Therefore, spherocytes on a blood smear indicate RBC lysis by macrophages (extravascular hemolysis). Activation of the classical complement pathway can lead to membrane attack complex formation and subsequent RBC lysis within the blood vessel (intravascular hemolysis). The lysed RBC releases its intracellular contents into the plasma, which results in hemoglobinemia and subsequent hemoglobinuria if the haptoglobin savage system is overwhelmed. The lysed RBC membranes can be visualized on a blood smear as ghost cells. In vivo agglutination of RBCs occurs when IgM or high titers of IgG molecules cause bridging of RBCs.

Common causes of death in canine IMHA are tissue hypoxia due to anemia, and thromboembolic disease, including disseminated intravascular coagulation (DIC) and pulmonary thromboembolism.

Clinical Presentation

Primary IMHA may occur in dogs of any signalment, but young adult to middle-aged dogs, females, and several breeds (American Cocker Spaniel, Bichon Frise, Collie, English Springer Spaniel, Finnish Spitz, Miniature Pinscher, Miniature Schnauzer, Old English Sheepdog, and Poodle) have an increased risk of disease. In dogs, the mean age is 5–6 years, with a reported range of 1–13 years. In feline IMHA, cats less than 6-year-old are overrepresented. Although males have been reported to be more frequently represented, this was not the case in a larger study with inclusion of a control group.

Clinical signs vary with the severity and duration of onset of the anemia but often include lethargy, depression, weakness, and anorexia. Collapse, vomiting, diarrhea, tachypnea, and polydipsia are less common. Multisystemic hemorrhages may occur secondary to DIC, whereas pigmenturia may occur with intravascular hemolysis.

Pale mucous membranes are the most common physical examination finding, but patients may also exhibit tachycardia, tachypnea, icterus, and fever. A systolic heart murmur may occur from increased turbulences due to low red blood cell content. Due to extravascular phagocytosis, splenomegaly and/or hepatomegaly may



FIGURE 16.10 Cold agglutinin disease demonstrating necrotic ear tips. (*Courtesy of J. Thompson.*)

be detected. If the patient's autoantibodies are primarily active below normal core body temperatures (cold agglutinins), then clinical signs may be most prominent at the cooler extremities, particularly necrosis of the tail, ear tips, nose, and nail bed (Figure 16.10).

Differential Diagnosis

Other causes of hemolysis, including infectious hemolytic anemia, oxidant-induced hemolytic anemia, congenital erythrocyte defects, hypophosphatemia, envenomation, mechanical fragmentation, and hemophagocytic histiocytic sarcoma. Hemorrhage.

Diagnosis

CBC often reveals severe to moderate (0.05–0.3 L/L [5%–30%]) anemia with evidence of regeneration (reticulocytosis and polychromasia) and support for regeneration (increased MCV, decreased MCHC, anisocytosis, nucleated RBCs in circulation [metarubricytosis, rubricytosis, or normoblastemia], Howell–Jolly bodies, basophilic stippling, and siderocytes). Identification of agglutination or spherocytes confirms an immune-mediated etiology for the anemia (Figures 16.11–16.13);

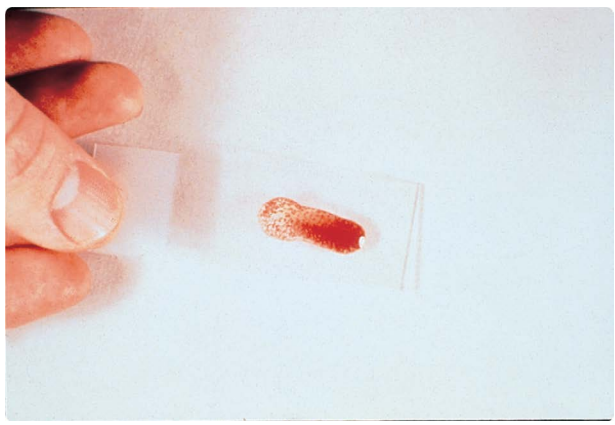


FIGURE 16.11 Gross appearance of macroscopic agglutination. (*Courtesy of J. Thompson.*)

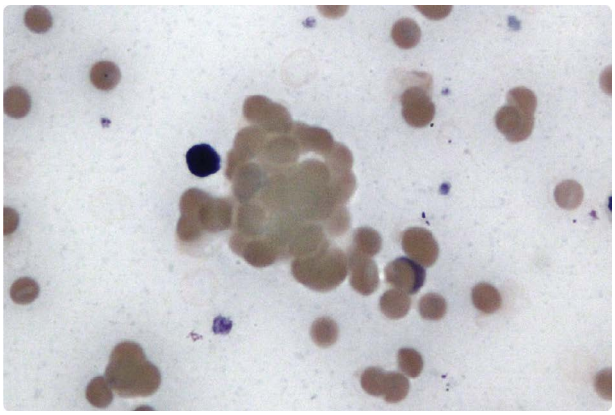


FIGURE 16.12 Microscopic RBC agglutination on a Romanowsky-stained blood smear.

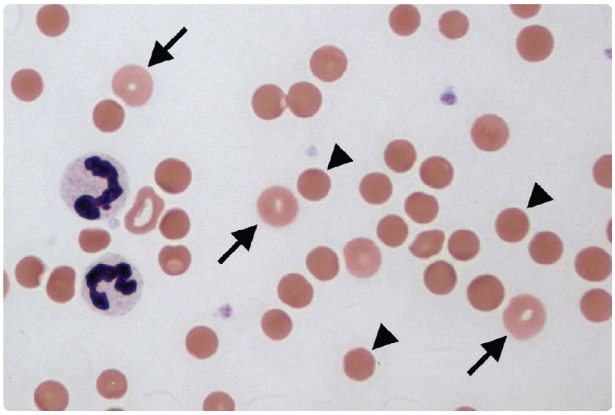


FIGURE 16.13 Compared with normal RBCs (arrows), spherocytes (arrowheads) are more eosinophilic, appear smaller, and lack central pallor.



FIGURE 16.14 Rouleaux formation in a wet mount of blood before the addition of saline to dilute or reduce cell adherence. (*Courtesy of J. Thompson*.)



FIGURE 16.15 Wet mount of blood demonstrating tight red cell clusters following addition of saline, indicating true agglutination. (*Courtesy of J. Thompson*.)

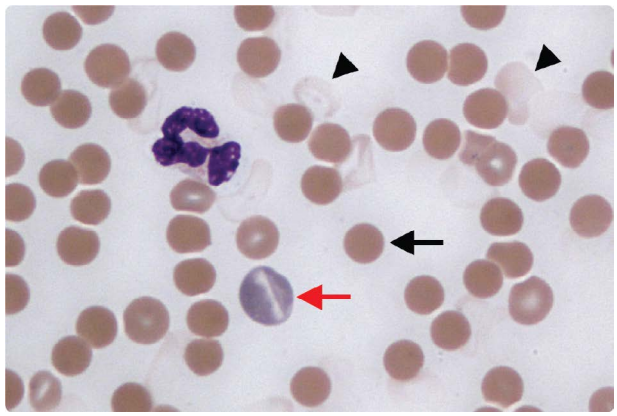


FIGURE 16.16 Blood smear from a dog with immune-mediated hemolytic anemia shows spherocytes (black arrow), ghost cells (arrowheads), and one polychromatophil (red arrow).

however, agglutination can be seen with some infectious etiologies, and spherocytes are difficult to appreciate in cats, since their RBCs normally lack central pallor. The saline test is helpful in distinguishing agglutination from rouleaux. A drop of physiologic saline is mixed with a drop of blood and then examined as a wet mount. The dilution will reduce rouleau formation, but agglutinated RBCs remain in tight clusters (Figures 16.14 and 16.15). Ghost cells may be seen with intravascular hemolysis (Figure 16.16). The leukogram is often inflammatory and is characterized by moderate-to-marked neutrophilia with increased band neutrophils (left shift), variable lymphocyte counts, and monocytosis. Neutrophil toxicity is usually absent or mild. Despite the marked neutrophilia, there is no active infectious trigger in nonassociative IMHA, hence antibiotic treatment is not required. Neutrophils may contain hemosiderin, and monocytes may exhibit erythrophagocytosis. Thrombocytopenia is present in 25%–70% of dogs with IMHA and may be due to concurrent immune-mediated platelet destruction (Evans syndrome) or DIC. Although many cats are not regenerative at presentation, regeneration will occur in a large proportion within 5 days. Cats also have frequently a lymphocytosis at presentation. Cats with nonassociative anemia have been reported to have higher albumin and lymphocyte count than cats with associative anemia.

However, this is of limited use clinically as there is a large overlap between both populations.

Serum biochemistry findings may include hyperbilirubinemia due to enhanced RBC destruction, and elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities with hypoxic liver injury. Alkaline phosphatase (ALP) activity may be increased with cholestasis and, in the dog, stress.

Urine may be golden or orange due to bilirubinuria or red due to hemoglobinuria (intravascular hemolysis). Proteinuria may be attributed to hemoglobinuria or renal injury secondary to immune complex deposition, hypoxia, or hemoglobin nephropathy. Cylindruria may present as Hgb or granular casts.

A direct antiglobulin test or Coombs test identifies antibody and complement on the surface of RBCs and is used to diagnose IMHA in the absence of spherocytosis and agglutination. The Coombs test may be positive in up to 75% of animals with IMHA. For this test, the patient's washed RBCs are combined with antiglobulin reagent. This reagent contains species-specific antibodies that bind complement and the Fc portion of the patient's antibodies. When the patient's complement and antibodies are bound to the patient's RBCs, the antiglobulin reagent creates antibody bridges and induces RBC agglutination. Agglutination, when observed, is diagnostic for the presence of antibody-coated erythrocytes. A positive Coombs test may also occur with secondary hemolytic anemias, lymphoproliferative disorders, and immune-mediated thrombocytopenia. False-negative results may occur with the recent use of corticosteroids or low levels of antibody present on the red cell surface. Flow cytometry is another valuable tool to detect the presence of antibody on the surface of erythrocytes.

Figure 16.17 describes an approach to determine if an animal is likely to have immune-mediated hemolysis. After confirming the anemia, the first step is to assess the animal for signs of RBC immune-mediated destruction, and the second step is to determine if there are signs of hemolysis.

Once an IMHA is suspected or confirmed, then additional tests such as diagnostic imaging and testing for blood-borne infectious agents should be pursued to rule out causes of associative IMHA that are relevant for the animal. In the absence of other relevant causes, a diagnostic of nonassociative IMHA is reached.

Management

Specific recommendations for IMHA treatment remain challenging, as there is a paucity of well-designed studies to compare treatment options as recently reviewed (recommended further reading: ACVIM statements). Treatment considerations for nonassociative IMHA

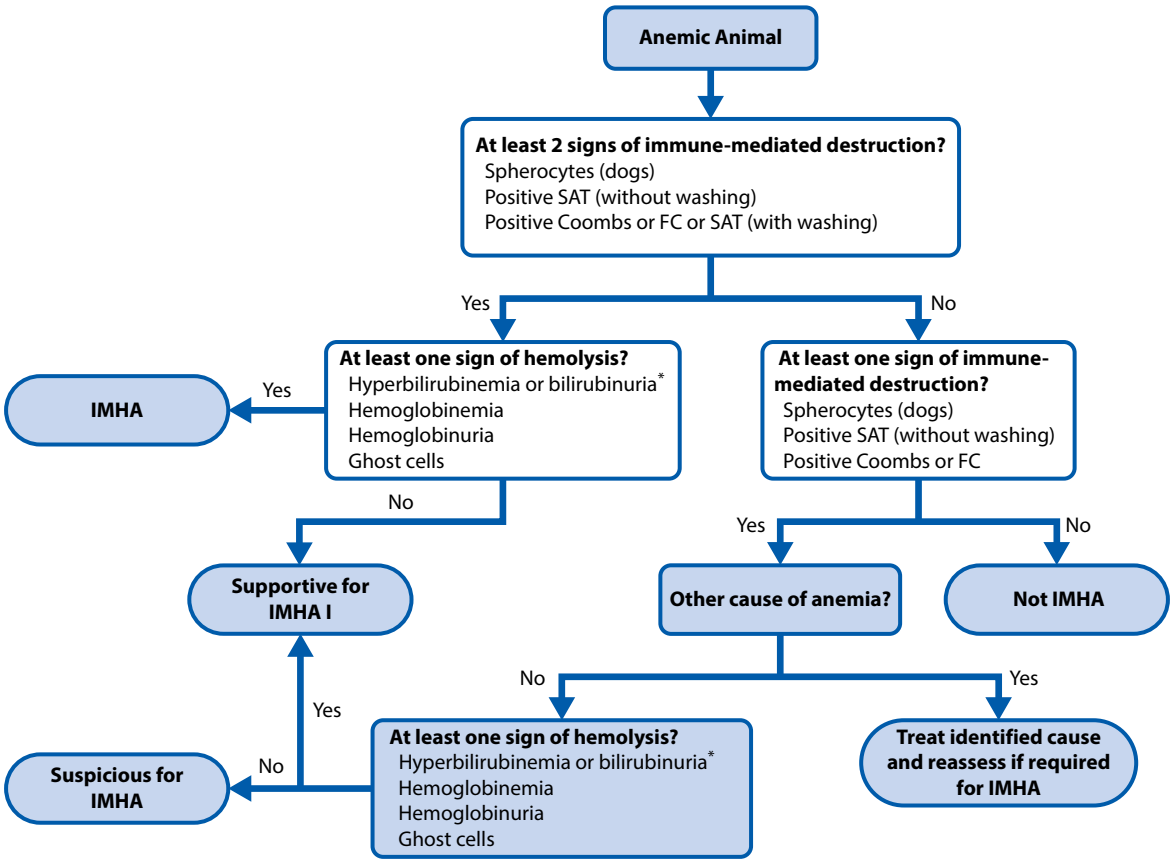


FIGURE 16.17 Flow chart to determine the likelihood of an animal to have primary or secondary IMHA. FC, flow cytometry; SAT, saline-agglutination test. *In the absence of hepatic or posthepatic cause. Clinically, icterus confirms the presence of hyperbilirubinemia.

include blood transfusion (as required), immunosuppression, and thromboprophylaxis, as thromboembolism is a frequent complicating factor.

Steroids are the mainstay treatment of IMHA as they are cheap, have a rapid onset of action, and several mechanisms of action such as inhibition of phagocytes, decreased complement and antibody bindings to the erythrocytes, and suppression of Ig production (over a few weeks). Severity of clinical signs and presence of negative prognostic factors such as intravascular hemolysis, increased bilirubin or urea might warrant more aggressive treatment. The use of some modalities is limited by the cost and availability (e.g., intravenous immunoglobulins [IVIG], plasmapheresis). For this reason, the clinician needs to make treatment decisions according to the animal, comorbidities, financial and emotional status of the owners without a fit-all answer.

An example of a decision tree to start immunosuppressant treatment is outlined in Figure 16.18. The owners need to be warned that the treatment will last for several months (typically >4–6 months) with a reduction of steroid side effects during tapering. Considerations for a second-line immunosuppressant include severe or life-threatening disease, no response to prednisolone monotherapy within 1–2 weeks, expected marked steroids side effects (dogs >25 kg or known side effects from previous treatment), and relapse early with steroids tapering. Common drugs, dosages, and monitoring are summarized in Table 16.10.

Starting dose for oral prednisone or prednisolone is 2 mg/kg pertuzumab day for 1–2 weeks. There is evidence that large dogs have increased prednisolone plasma concentration at the same dosage as small dogs. Consequently, side effects are worse without increased immunosuppression, and life quality of the animal can become unacceptable for owners (e.g., incontinent dog too weak to go outside to urinate), leading to euthanasia due to side effects rather than lack of control of the IMHA. For this reason, the recommendation for large dogs is to dose by body surface rather than weight (40–50 mg/m^2 q.24 h.). Parenterally administered dexamethasone (0.1–0.2 mg/kg IV q.12 h.) can be used initially if the patient is unable to receive oral medications.

If the initial dosage of prednisolone is higher than 2 mg/kg/day, the clinician should aim to reduce it to less than 2 mg/kg/day 1–2 weeks after starting treatment. If the disease is not controlled after this time, then the addition of a second-line immunosuppressant should be considered.

There is currently no clear evidence to help the clinician choose the best second-line treatment, and several options are available (Table 16.10). Azathioprine and cyclosporine have been used historically as second-line treatment and more recently mycophenolate mofetil (MMF), whereas only little information is available for leflunomide. Cyclosporine has the advantage of not being bone marrow suppressive. In cats, chlorambucil is used instead of azathioprine. The use of cyclophosphamide is not recommended, as there is evidence suggesting a worse prognosis with it.

Cyclosporine is a very potent immunosuppressant. Microemulsified cyclosporine is recommended, and the clinician needs to be aware that compounded cyclosporine might be differently absorbed than commercial

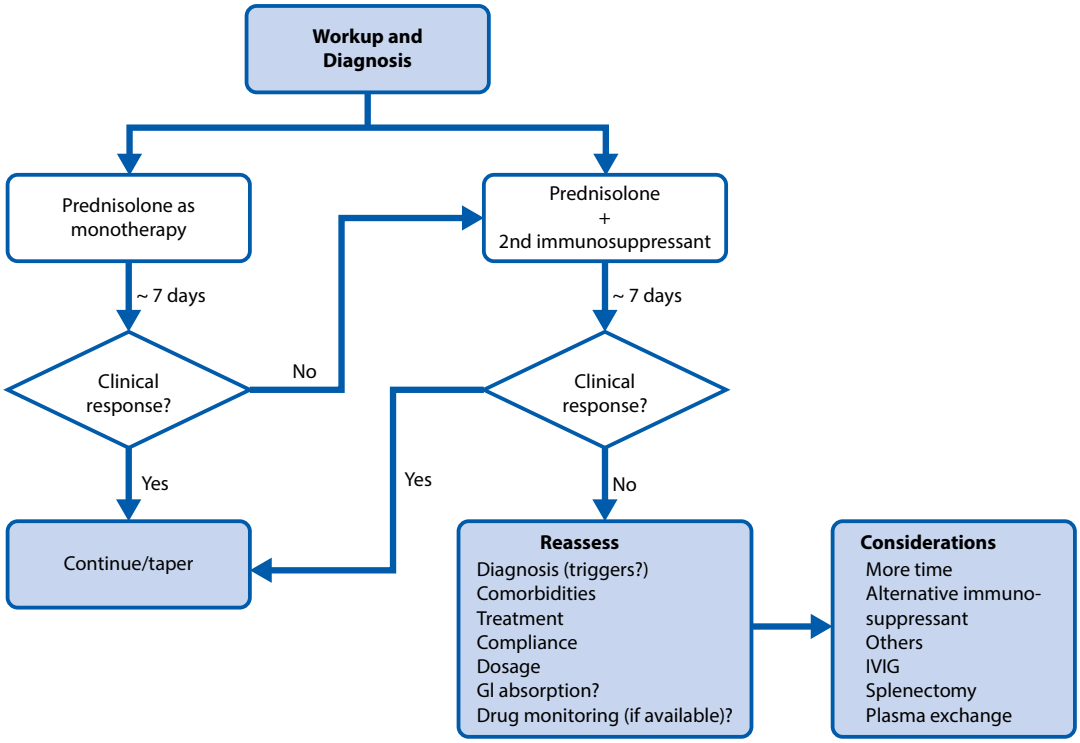


FIGURE 16.18 Decision tree for treatment of dogs diagnosed with nonassociative (primary) IMHA. GI, gastrointestinal; IVIG, intravenous immunoglobulin.

TABLE 16.10 Immunosuppressant dosages, common adverse effects, and suggested monitoring

Drug	Dog	Cat	Adverse effects	Monitoring suggestion*
Prednisolone	<25 kg: 2 mg/kg q.24 h. >25 kg: 40–50 mg/m^2 q.24 h.[2†]	2 mg/kg q.24 h.	– PU/PD, polyphagia, panting, (D) urinary incontinence, muscle loss and weakness, lethargy, diabetes	– CBC, biochemistry every month for 3 months, then every 2–3 months – Cats: Every month for the first 3 months
Cyclosporine	10 mg/kg p.o. q.24 h. (or divided q.12 h.)	3–4 mg/kg p.o. q.12 h. 5–7 mg/kg p.o. q. 24 h.	– Nausea, anorexia, vomiting, diarrhea – Gingival hyperplasia	– CBC, biochemistry every month for 3 months, then every 3–6 months – Consider therapeutic drug monitoring
Azathioprine	2 mg/kg p.o. q.24 h. for 2 weeks, then q.48 h.	Not recommended	– Nausea, anorexia, vomiting, diarrhea – *Less frequently:* Hepatotoxicity, myelosuppression	– CBC, ALT/ALP every 2 weeks for the first 8 weeks, every 1–3 months after
Chlorambucil	2–4 mg/m^2 p.o. q.24 h.	1.5–4 mg/m^2 p.o. q.24 h. or 15 mg/m^2 p.o. q.24 h. for 4 days every 3 weeks or 20 mg/m^2 p.o. every 2 weeks	– Vomiting, diarrhea – Anemia, leukopenia, thrombocytopenia – Neurotoxicity – Fanconi syndrome (C)	– Repeat CBC after 1 month, thereafter every 2–3 months – Biochemistry and urinalysis (inc. UPC every 3 months)
Mycophenolate mofetil	8–12 mg/kg p.o. q.12 h.	10 mg/kg p.o. q.12 h.	– Diarrhea (dose related), hyporexia	– GI side effects – CBC every 2 weeks for the first 4 weeks, every 2–3 months until discontinued
Leflunomide	2 mg/kg p.o. q.24 h.	2 mg/kg p.o. q.24 h. for 48 hours, then 2 mg/kg p.o. q.48 h.	– Diarrhea, inappetence, lethargy, unexplained hemorrhage, thrombocytopenia	– CBC, ALT/ALP every month for 3 months, then every 2–3 months – Consider TDM

* A baseline is recommended including CBC, biochemistry, and urinalysis. Urine protein-to-creatinine ratio is also recommended in cats treated with chlorambucil. Cats develop diabetes secondary to steroid treatment usually within the first 3 months of treatment.

† The author typically uses 40 mg/m^2 in dogs ≥5 kg. For example, a 40 kg dog (1.18 m^2) will receive 50 mg daily rather than 80 mg. Cats have poor hepatic methylation, and for this reason, prednisolone rather than prednisone should be used to achieve a more reliable effect.

Azathioprine: Hepatotoxicity usually develops in first 2–4 weeks, more common in GSD. Myelosuppression can occur much later in the treatment.

Mycophenolate: Hepatotoxicity reported in people but not dogs. As not commonly used, consider monitoring liver enzymes.

TDM, therapeutic drug monitoring.

cyclosporine. Therapeutic drug monitoring (TDM) is available for cyclosporine. Pharmacokinetic monitoring consists in measuring cyclosporine trough concentration (i.e., prior next dose), whereas pharmacodynamic monitoring consists in measuring inhibition of IL-2 transcription (i.e., direct effect of cyclosporine, currently only available for dogs). Pharmacokinetic or pharmacodynamic monitoring can be performed after a week of treatment and should be considered in dogs not responding to treatment, where drug interaction might affect cyclosporine pharmacokinetics (i.e., concurrent treatment with ketoconazole), or excessive immunosuppression is suspected due to secondary infections. Specific targets should be discussed with the laboratory. Cyclosporine side effects include vomiting, gingival hyperplasia, hair loss, and papilloma-like skin lesions. The gastrointestinal signs might be controlled by giving the treatment with food or freezing the capsules prior treatment.

Azathioprine is a thiopurine that inhibits purine synthesis with a complex metabolism involving the enzyme thiopurine methyltransferase (TPMT). Cats are at high risk of myelotoxicity due to low TPMT activity, and for this reason, the drug is not recommended in this species. As the drug can cause bone marrow toxicity, it is ideally avoided if the animal is neutropenic (<2,000/µL) or thrombocytopenic (<80,000/µL); however, it might be used if the cause for the bicytopenia or pancytopenia is immune mediated. Although side effects of azathioprine therapy are infrequent, they may include GI signs, hepatotoxicosis, and bone marrow toxicosis. It might also be linked to acute pancreatitis. The tablet should not be split, and the owner should handle with gloves. Chlorambucil is an alkylating agent that can be used instead of azathioprine in cats. Variable dosages have been reported (Table 16.10), and the animal needs to be monitored for immunosuppression.

MMF, as azathioprine, is also a purine inhibitor. For this reason, both drugs should not be used concurrently. The main side effect is delayed, dose-related GI signs.

There is very little information on the use of leflunomide, a pyrimidine inhibitor, and dosage frequency in cats is less than in dogs. Some rare cases of unexplained hemorrhage have been reported in dogs with the use of this drug.

If an animal requires more than two immunosuppressive drugs to control the disease, there is a high risk of secondary infection, especially if cyclosporine is one of the immunosuppressant used.

IVIG has also been used in dogs with nonassociative IMHA. The literature available does not suggest that IVIG is superior to other immunosuppressive treatment but supports quick onset of action and faster response. Other therapies, such as plasmapheresis, is likely to play a more important role in the future for severe IMHA, but there is limited information and accessibility currently.

Thromboembolism has been recognized as an important cause of morbidity and mortality in dogs with IMHA. This is particularly relevant for dogs with autoagglutination, intravascular hemolysis, and treated with high-dose prednisolone or IVIG. As thrombosis in IMHA is mostly venous (lungs, spleen, and portal vein), thromboprophylaxis with anticoagulants or anticoagulants and platelets inhibition is favored over platelet inhibition alone. Thromboprophylaxis is recommended in all dogs with IMHA except if marked thrombocytopenia is present. An arbitrary cut-off of platelets less than 30,000 x10^9/L has been suggested, which is likely to reflect destructive rather than consumptive thrombocytopenia. Recommended dosages are listed in Table 16.11, and the reader is referred to the CURATIVE and ACVIM statements for more in-depth reading. Options include unfractionated heparin or low-molecular-weight heparin (dalteparin or enoxaparin) with individual dose adjustment using anti-Xa assay. The latter is a limitation as the assay is not widely available. An alternative is to use rivaroxaban, an oral Xa inhibitor. Options for antiplatelet drugs include clopidogrel and aspirin. There is some evidence that suggest that clopidogrel is more efficacious. Thromboprophylaxis should be administered for at least 2 weeks (highest risk of thromboembolism event) but ideally until the dog is in remission.

Splenectomy has been reported as treatment for relapsing or refractory IMHA; however, there is limited information and no studies with a control population. If this treatment is considered, the clinician should exclude a vector-borne disease as much as possible, and treatment adjusted prior surgery (especially antithrombotic treatment). Cats seem to be less prone to develop thrombi than dogs.

Treatment Response Monitoring and Tapering Regime

Treatment response is characterized by increase in the PCV, normalization of the bilirubin, and resolution of the autoagglutination and spherocytosis if present. If this is achieved 2 weeks after starting treatment and the PCV is ideally ≥30%, then slow reduction of the prednisolone (up to 25%) can start. It will take time for some of the abnormalities noted at diagnosis to resolve (for example small number of spherocytes remains), but the overall picture needs to suggest treatment response. If the animal is treated with an additional immunosuppressant, more rapid reduction of the steroid can be considered (25%–50%).

The authors taper prednisolone every 2–3 weeks until the dosage is <1 mg/kg q.24 h., and every 4–6 weeks thereafter. If the animal receives a second-line immunosuppressant, alternate tapering with prednisolone can be considered once the prednisolone dosage is <1 mg/kg q.24 h. if the second-line treatment is tolerated and affordable until then. Some clinicians prefer to stop prednisolone first and then the second-line treatment 4–8 weeks later without tapering.

It is important to note that dogs may remain mildly anemic, despite control of the disease, until complete weaning of prednisolone. For this reason, a mild anemia without evidence of hemolysis should not be interpreted as a lack of response. At a minimum, PCV should be monitored prior to each reduction and 1–2 weeks after.

If there is a relapse during tapering, prednisolone should be restarted (if stopped) or increased to the last effective dose. If the animal was treated with prednisolone alone, a second-line immunosuppressant should be considered. The animal should be reassessed for possible triggers and if none is found tapering as previously described but with longer intervals between tapers once the disease is controlled again. If there is a third relapse, long-term immunosuppressive treatment might be required.

Prognosis

In general, there is guarded to poor prognosis for long-term survival in dogs. While 50%–88% of dogs with IMHA are discharged from the hospital, most die or are

TABLE 16.11 Thromboprophylaxis treatment available in dogs

Drug	Route	Dosage	Mechanism of action
Unfractionated heparin	IV SC	100 U/kg bolus, then 900 U/kg/24 h. 150–300 U/kg q.6 h.	Anticoagulant
Dalteparin	SC	150–175 U/kg q.8 h.	Anticoagulant
Enoxaparin	SC	0.8–1/0 mg/kg q.6–8 h.	Anticoagulant
Rivaroxaban	p.o.	1–2 mg/kg q.24 h.	Anticoagulant
Clopidogrel	p.o.	1.1–4.0 mg/kg q.24 h.	Antiplatelet
Aspirin	p.o.	1–2 mg/kg q.24 h.	Antiplatelet

euthanized within the subsequent 2 months. Negative prognostic indicators are the presence of severe disease (liver, kidney), thrombocytopenia, SLE, intravascular hemolysis, RBC agglutination, prolonged coagulation times (PT and aPTT), increased band neutrophils (left shift), marked leukocytosis, and increased urea and bilirubin.

Primary feline IMHA has a better prognosis with 24%–32% mortality rate, and relapse occurs in 16%–19% of cases. Negative prognostic factors include higher bilirubinemia and age, and positive prognostic factors are higher lymphocyte count and globulin concentration. In the largest study, 59.3% of cats with nonassociative IMHA were still alive at 6 months compared to 25.8% of cats with associative IMHA.

DRUG-INDUCED IMMUNE HEMOLYTIC ANEMIA

Definition/Overview

Red cell destruction is secondary to an adverse or idiosyncratic drug reaction.

Etiology

Substances known to induce immune hemolytic anemia include levamisole, carprofen, cephalosporin antibiotics, griseofulvin, propylthiouracil, and methimazole.

Pathophysiology

Drug-induced immune hemolytic anemia (DIIHA) may be drug dependent or drug independent. Drug-dependent IHA occurs only in the presence of the inciting drug. In these cases, the immune reaction is directed at the drug, which is bound to RBC surface antigens. Drug-independent IHA may occur in the absence of the inciting drug and is likely secondary to immune system stimulation.

Clinical Presentation

See nonassociative IMHA.

Differential Diagnosis

See nonassociative IMHA.

Diagnosis

Diagnosis is based on a history of administering a drug known to induce IMHA, the presence of laboratory findings consistent with IMHA, and the absence of other causes of associative IMHA (e.g., erythrocytic parasites). Rechallenging is not recommended because of the potential for morbidity and mortality.

Management

Drugs known to cause associative IMHA should be discontinued. Immunosuppressive and supportive therapy as described for nonassociative IMHA.

ALLOIMMUNE HEMOLYSIS

Definition/Overview

Alloimmune hemolysis is immune-mediated destruction of RBCs that express foreign antigens. The most common forms of alloimmune hemolysis in small animal medicine are hemolytic transfusion reactions and neonatal isoerythrolysis (NI).

Etiology

See principles of transfusion medicine.

Pathophysiology

In dogs, sensitization occurs at least 4 days after initial antigen exposure. A major hemolytic transfusion reaction occurs when a blood recipient receives a blood product containing a DEA to which the recipient has been sensitized, causing hemolysis of the donated RBCs. NI rarely occurs in dogs but most commonly involves a DEA 1.1-positive puppy ingesting colostrum that contains DEA 1.1-antibodies from a previously sensitized DEA 1.1-negative bitch.

Since RBC alloantibodies occur naturally in cats, transfusion reactions may occur on the initial exposure to blood. The naturally occurring anti-B antibodies in type A cats are weak hemolysins and agglutinins, reducing the donated RBC half-life to 2.1 days. However, type B cats produce anti-A antibodies that are strong hemolysins and agglutinins, which can induce severe and life-threatening hemolytic transfusion reactions. NI is most commonly seen in kittens, wherein type A or type AB kittens ingest colostrum that contains type A antibodies from a type B queen.

Clinical Presentation

See nonassociative IMHA, except for the additional historical findings of receiving a blood transfusion or nursing from the dam. Clinical signs can occur within minutes to days of receiving a blood product or hours to days after ingesting colostrum. In NI, puppies and kittens are born healthy and nurse normally, then become pale and weak within 1–2 days after birth; reluctance to nurse, failure to thrive, dyspnea, hemoglobinuria, icterus, tail tip necrosis, and death may also occur.

Differential Diagnosis

See primary IMHA.

Diagnosis

The blood product recipient's temperature, heart rate, respiratory rate, blood pressure, and PCV should be monitored during the transfusion for signs of an adverse reaction. Evidence of hemolytic transfusion reaction includes hemolyzed plasma and red urine. Blood typing and cross-matching, if not already performed, can help confirm a hemolytic transfusion reaction. Clinical signs of nonhemolytic transfusion reactions, such as

vomiting, diarrhea, abdominal pain, or facial swelling, should also be monitored.

NI should be suspected in pale, icteric 1- to 2-day-old kittens and puppies. For a definitive diagnosis of NI, the dam's serum or colostrum can be cross-matched against the sire's or neonate's washed RBCs or by blood typing the queen and tom or kitten.

Management

Blood transfusion reactions can be avoided or reduced by blood typing and cross-matching prior to blood product administration. Starting the transfusion at a slower rate can help lessen the severity of the reaction if a reaction were to occur. The blood transfusion may be stopped once clinical signs of a reaction have been identified, or the transfusion may be slowed if the reaction is mild.

If NI is identified, puppies and kittens should not be allowed to nurse from their dam and should be fed a milk replacement formula. Blood typing queens and toms prior to breeding can prevent disease.

HEMOPLASMOSIS

See also Chapter 21.

Definition/Overview

Hemotropic mycoplasmosis (hemoplasmosis, formerly hemobartonellosis) is an infectious hemolytic disease of mammals caused by small, pleomorphic bacteria that parasitize the surface of RBCs. Acute hemolytic anemia is most common in cats, whereas dogs typically require immunosuppression, splenectomy, or splenic pathology to manifest clinical signs of disease.

Etiology

Carrier animals are the source of infection. The hemoplasmas of feline erythrocytes are *Mycoplasma haemofelis*, *Candidatus Mycoplasma haemominutum*, and *Candidatus Mycoplasma turicensis*. Dogs may be infected by *Mycoplasma haemocanis* or *Candidatus Mycoplasma haematoparvum*. See Chapter 21.

Pathophysiology

Hemoplasmas cause hemolysis by inducing secondary IMHA, the "innocent bystander effect," and direct RBC lysis.

Clinical Presentation

Clinical signs include those generally observed with hemolytic anemia (see primary IMHA and Chapter 21). Canine hemoplasmosis and the small form of feline hemoplasmosis are often not associated with clinical disease unless other conditions exist.

Differential Diagnosis

Similar differential diagnoses to primary IMHA.

Diagnosis

CBC, biochemical, and urinalysis abnormalities are almost identical to primary IMHA, except that *Mycoplasma* organisms may be observed on the surface of RBCs or in the background of the smear if there is a delay between sample collection and blood smear preparation. However, bacteremia is cyclical during the acute phase, so absence of visible organisms does not rule out infection. Organisms are rare or inapparent during preparasitemic, recovery, and carrier phases. Blood films should be well stained without precipitate to minimize any confusion in identifying the parasite. Cats often have coccoid or ring shapes, whereas dogs mostly have linear chain forms (**Figure 16.19a** and **b**). Polymerase chain reaction (PCR)–based tests are more sensitive than blood smear review. A PCR that is species specific is more useful as infections with *Candidatus M. haemominutum* or *Candidatus M. turicensis* should not be a cause for marked anemia without concurrent diseases. A positive Coombs test may be observed. Bacterial consumption of glucose in a blood sample may cause in-vitro hypoglycemia with heavy bacterial loads. Splenomegaly is often noted in cats.

Management

See Chapter 21.

Prognosis

See Chapter 21.

BABESIOSIS

See also Chapter 21.

Definition/Overview

Babesiosis is a tick-borne protozoal disease affecting erythrocytes of dogs (*Babesia canis*, *Babesia gibsoni*). There are three subspecies of *B. canis*, *B. canis vogeli* endemic in Africa, Asia, Australia, Europe, and North and South America, whereas *Babesia canis canis* is endemic in Europe and Africa and *Babesia canis rossi* only in Africa. More recently, *Babesia vulpes* has been reported in European and in North America, mostly as a coinfection. *Babesia conradae* has been detected in dogs from southern California. *Babesia felis* has not been reported in North American cats but is reported in Africa and southern Asia.

Etiology

Ixodid ticks are the major vectors of *Babesia* spp., although there have been cases of infection through blood transfusion and transplacental transmission. Sporozoites are transmitted through the tick's saliva during a blood meal, but the parasite needs to feed for at least 2 days before transmission occurs. Infection is also thought to occur through dog fighting.

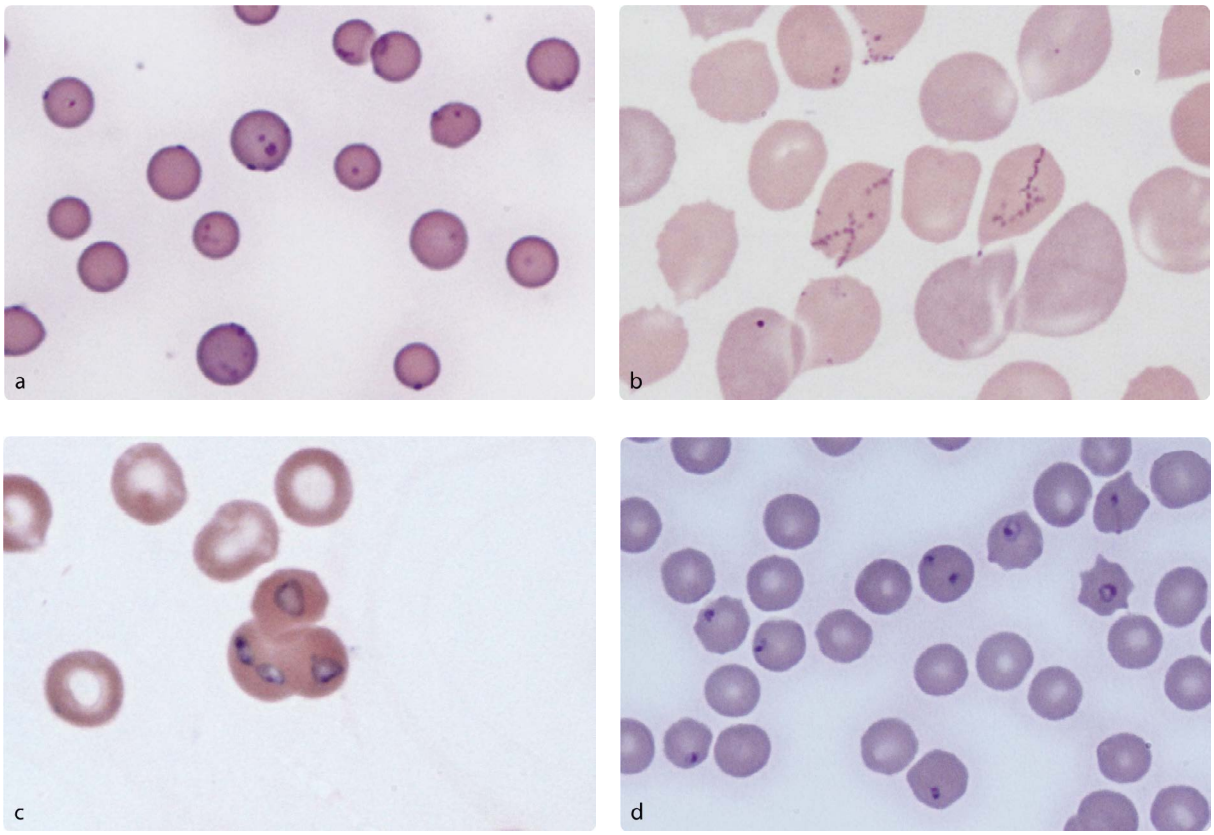


FIGURE 16.19 Erythrocytes parasites in cats and dogs. **(a)** Blood smear from cat with coccoid and ring forms of *M. haemofelis*. **(b)** *M. haemocanis* forms chains on the surface of dog erythrocytes. **(c)** Singular or paired tear-drop-shaped organisms of *B. canis* in three agglutinated erythrocytes. **(d)** Blood smear with multiple organisms from a cat infected with *C. felis*. (*Courtesy of N. Weinstein*.)

Pathophysiology

Babesia organisms become engulfed by erythrocytes, in which the parasites multiply to merozoites capable of infecting other erythrocytes. The incubation period is 10–12 days. Hosts are usually able to mount an effective immune response at this stage. If not, infected animals may develop a severe hemolytic anemia, hypotensive shock, and multiple organ dysfunction syndrome. Direct RBC lysis and secondary IMHA contribute to anemia. Thrombocytopenia might occur secondary to destruction or consumption. Animals may relapse following therapy, and affected dogs often remain carriers.

Clinical Presentation

See Chapter 21.

Differential Diagnosis

See nonassociative IMHA.

Diagnosis

CBC, biochemical, and urinalysis abnormalities are almost identical to primary IMHA, including anemia and thrombocytopenia, except that *Babesia* organisms may be observed within RBCs as clear, teardrop-shaped organisms, sometimes in pairs. *B. canis* is often large (Figure 16.19c), while *B. gibsoni* is much smaller. An indirect fluorescent antibody (IFA) serum test is available, which, when titers are high, indicates current infection. The most sensitive and specific test for genus, species, and subspecies is the PCR-based assay. Concurrent infections with *Ehrlichia canis* and hemotropic *Mycoplasma* spp. may occur. A Coombs test may be positive, as in IMHA. In severe cases, DIC may be present.

Management

See Chapter 21.

Prognosis

See Chapter 21.

CYTAUXZOONOSIS

Definition/Overview

Cytauxzoonosis, caused by *Cytauxzoon felis*, is a highly fatal protozoal disease of wild and domestic cats in the southern United States and mid-Atlantic states. It is a tick-borne disease whose natural reservoir host is the bobcat and possibly Florida panthers.

Etiology

C. felis is transmitted by *Dermacentor variabilis* and *Amblyomma americanum* ticks. The organism is a piroplasm hemoparasite of the family Theileriidae.

Pathophysiology

Macrophages infected with schizonts, a large membrane-bound structure containing numerous merozoites, line and occlude blood vessels throughout the body. This leads to tissue ischemia and hypoxia, hemorrhage, organ dysfunction, and DIC. Schizonts release merozoites, which infect erythrocytes and cause hemolysis. Infection may also cause bone marrow suppression and decreased RBC production.

Clinical Presentation

See Chapter 21.

Differential Diagnosis

Other infectious agents, neoplasia, organ failure, DIC.

Diagnosis

Cytology can be diagnostic, and commercial PCR is also available. Diagnosis is generally made postmortem by histologic identification of large schizonts in macrophages lining the sinusoids and veins of many tissues. Terminally, blood films may contain small (1–2 mm in diameter) ring or "safety pin" structures within erythrocytes (**Figure 16.19d**).

Management

See Chapter 21.

Prognosis

See Chapter 21.

OXIDANT-INDUCED HEMOLYTIC ANEMIA

Definition/Overview

Irreversible damage occurs to erythrocytes when the normal protective antioxidant mechanisms are exceeded, resulting in the formation of methemoglobin, Heinz bodies, and/or eccentrocytes.

Etiology

Oxidative agents that cause precipitation of Hgb and fusion of RBC membranes produce Heinz bodies and eccentrocytes, respectively. Causes of oxidant-induced hemolytic anemia include onions, garlic, Chinese chives, zinc (e.g., pennies, toys, zippers, galvanized wire, and zinc phosphide rodenticides), acetaminophen (paracetamol), methylene blue (in old urinary antiseptics), vitamin K3, methionine, topical benzocaine, propofol, mothball ingestion, propylene glycol, and skunk spray. Heinz body formation in cats has also been associated with diabetic ketoacidosis, hyperthyroidism, and lymphoma.

Pathophysiology

Accelerated red cell destruction involves intravascular fragmentation and extravascular phagocytosis by the spleen. Feline RBCs are predisposed to oxidant damage because of their Hgb structure. Oxidation of iron converts hemoglobin with Fe^{2+} to methemoglobin with Fe^{3+}, which cannot bind and transport oxygen.

Clinical Presentation

Clinical signs are similar to those with acute primary IMHA.

Differential Diagnosis

Similar differential diagnoses to primary IMHA.

Diagnosis

Diagnosis is made by the observation of methemoglobinemia and hemolytic anemia (regenerative anemia, icterus, hemolysis, hemoglobinuria, and/or ghost cells) with many Heinz bodies and/or eccentrocytes on a blood smear. On Romanowsky-stained blood smears, Heinz bodies are large, pale-staining areas in erythrocytes, or blunt projections from the membrane surface (**Figure 16.20**); there is only one Heinz body per RBC. On new methylene blue–stained wet mounts or dried blood smears, Heinz bodies are dark blue spots within RBCs (**Figure 16.21**). Eccentrocytes are RBCs with densely packed Hgb on one side of the cell and a thin colorless portion, or hemighost, on the opposite side (**Figure 16.22**). When the hemighost fragments off from the RBC, the remaining RBC is termed a *pyknocyte*. At moderate-to-higher concentrations, methemoglobinemia results in chocolate brown mucous membranes and blood. With zinc toxicosis, abdominal radiographs may reveal the ingestion of a metal object.

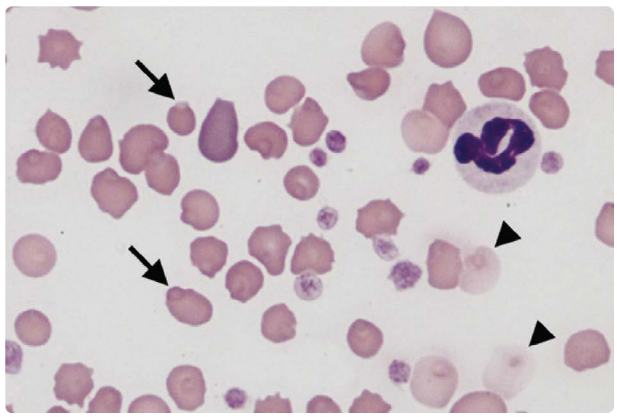


FIGURE 16.20 Heinz bodies in intact erythrocytes (arrows) and ghost cells (arrowheads) in a cat with oxidant-induced hemolytic anemia.

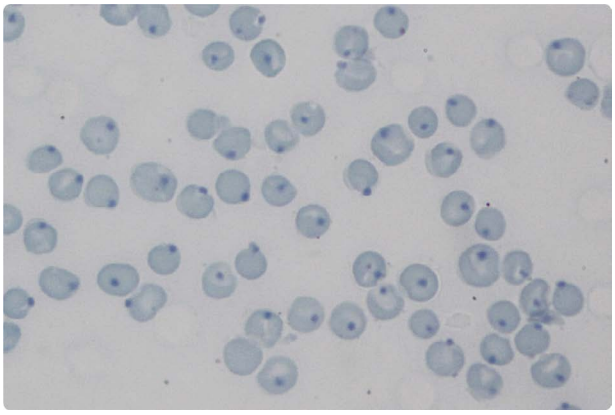


FIGURE 16.21 Heinz bodies are basophilic round structures with new methylene blue stain.

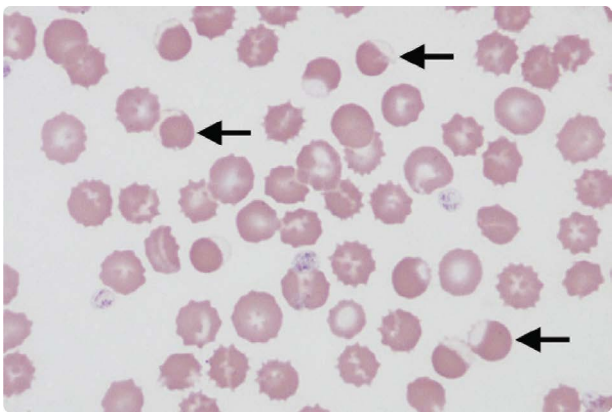


FIGURE 16.22 Eccentrocytes (arrows) in a dog receiving a continuous rate infusion of propofol.

Management

Treatment primarily involves removal of the source of oxidant. Emetics can be used if recent ingestion has occurred or endoscopic/surgical removal of a zinc foreign body. Blood transfusions or other forms of supportive care should be given as indicated. Acetylcysteine (Mucomyst®) (140 mg/kg of a 5% solution diluted with saline IV initially, then give 70 mg/kg [of a 5% solution] q.4–6 h. for 3–5 treatments) should be given to treat acetaminophen-induced toxicity.

MICROANGIOPATHIC HEMOLYTIC ANEMIA

Definition/Overview

Microangiopathic hemolytic anemia is due to mechanical fragmentation of normal RBCs in an abnormal vasculature system.

Etiology

Diseases that cause intravascular deposition of fibrin, turbulent blood flow, or abnormal blood vessel morphology can cause mechanical fragmentation of normal RBCs.

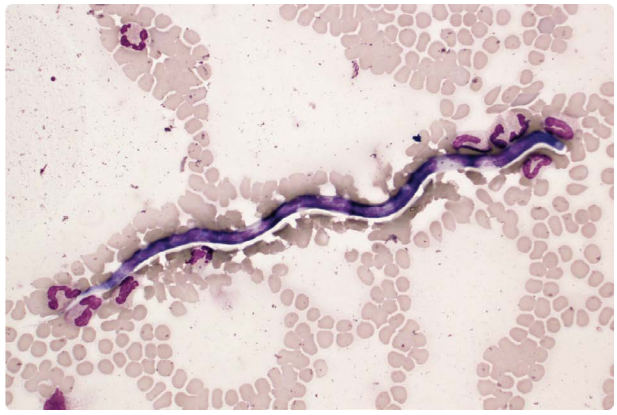


FIGURE 16.23 Microfilaria in a dog with *D. immitis* infection.

These diseases include DIC, vasculitis, hemangiosarcoma, heart valvular defects, dirofilariasis (Figure 16.23), splenic disease, hepatic disease, glomerulonephritis, myelofibrosis, and intravascular lymphoma.

Pathophysiology

Fibrin strands or abnormal rheologic forces cause shearing or lysis or RBCs. The RBC fragments, including schistocytes, acanthocytes, and keratocytes, are removed from circulation by the monocyte–macrophage system.

Differential Diagnosis

Blood loss, IMHA, oxidant-induced hemolysis, infectious hemolytic anemia, liver disease, disorders of lipid metabolism.

Clinical Presentation

The clinical presentation varies depending on the cause of the RBC fragmentation.

Diagnosis

Microangiopathic hemolytic anemia is typically a regenerative anemia with evidence of RBC fragmentation on blood smear evaluation (e.g., schistocytes, acanthocytes, keratocytes) (Figure 16.24). The degree of anemia is typically mild but may be moderate to rarely severe. Marrow erythropoiesis may be able to compensate for the degree of hemolysis, so RBC regeneration and/or anemia may not be present. Diagnosis of the underlying disease may include CBC with blood smear evaluation, heartworm antigen test, serum biochemical and urine analysis, coagulation panel, abdominal and thoracic imaging, and bone marrow biopsy.

Management

Management is directed at resolving the underlying cause of the microangiopathy.

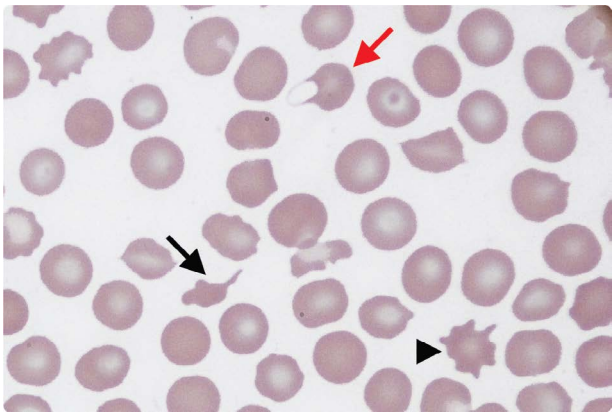


FIGURE 16.24 This dog with disseminated intravascular coagulation has circulating schistocytes (black arrow), acanthocytes (arrowhead), and keratocytes (red arrow).

PYRUVATE KINASE DEFICIENCY

Definition/Overview

Pyruvate kinase (PK) deficiency is a congenital deficiency in glycolytic enzymes. The condition has been documented in dogs (Basenji, Beagle, West Highland White Terrier, Cairn Terrier, American Eskimo Dog, Miniature Poodle, Chihuahua, and Pug) and cats (Abyssinian, Somali, Bengal, Maine Coon, and Domestic Shorthair cats).

Etiology

PK deficiency is an autosomal recessive trait due to a variety of mutations in the erythrocyte PK gene.

Pathophysiology

PK is an enzyme in the glycolytic pathway that is necessary for the anaerobic production of adenosine triphosphate (ATP). Therefore, energy metabolism is markedly impaired in PK-deficient RBCs, leading to shortened RBC life spans and hemolytic anemia. Persistent anemia causes increased intestinal absorption of iron and subsequent hepatic (hemosiderosis, hemochromatosis, cirrhosis, and failure) and bone marrow (myelofibrosis and osteosclerosis) injury.

Clinical Presentation

Heterozygotes show no clinical signs. Homozygotes often present in their youth with pale mucous membranes, exercise intolerance, tachycardia, and splenomegaly. Cats may not present until they are at an advanced age or with intermittent hemolytic anemia.

Differential Diagnosis

Phosphofructokinase deficiency, IMHA, oxidant-induced hemolysis, mycoplasmosis, and babesiosis.

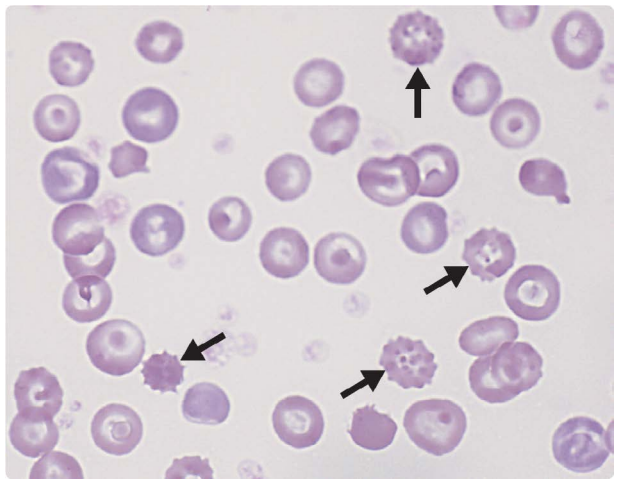


FIGURE 16.25 Pyruvate kinase deficiency in a dog showing polychromasia and several echinocytes (arrows).

Diagnosis

Diagnosis is suggested by the presence of hemolytic anemia with an intense reticulocytosis (15%–50%) and frequent nucleated red cells in a young dog (Figure 16.25). Splenectomy results in marked poikilocytosis with schistocytes and acanthocytes. Dogs may also show biochemical signs of liver injury or failure, as well as hematologic evidence of marrow failure (e.g., neutropenia and thrombocytopenia). PCR-based tests are available for the Basenji, West Highland White Terrier, Beagle, Dachshund, Toy Eskimo, and Cairn Terrier dog breeds, as well as Abyssinian and Somali cats. Definitive diagnosis for other breeds requires PK isoenzyme characterization.

Management

There is no specific treatment.

Prognosis

Dogs usually die between 1 and 5 years of age.

PHOSPHOFRUCTOKINASE DEFICIENCY

Definition/Overview

Phosphofructokinase (PFK) deficiency is a congenital deficiency in glycolytic enzymes. It has been identified in English Springer Spaniels, American Cocker Spaniels, Whippets, Wachtelhund, and mixed-breed dogs.

Etiology

A nonsense mutation of the muscle-type PFK gene leads to truncation of M-type PFK enzyme, which is structurally unstable and rapidly degrades.

Pathophysiology

Decreased PFK in RBCs leads to decreased glycolysis and anaerobic ATP generation, as well as decreased

concentrations of 2,3-diphosphoglycerate (2,3-DPG). Energy metabolism is impaired in PFK-deficient RBCs, leading to a shortened RBC life span and hemolytic anemia. The 2,3-DPG deficiency causes an increase in intracellular pH, and RBCs are especially fragile under alkaline conditions, such as hyperventilation-induced alkalemia.

Clinical Presentation

Heterozygote dogs show no clinical signs. Homozygote dogs have persistent compensated hemolytic anemia with sporadic episodes of intravascular hemolysis. Animals between episodes of hemolytic crises appear clinically normal or may have a decreased muscle mass; Hct is typically 30%–45%. Clinical signs during hemolytic crises include lethargy, pale or icteric mucous membranes, hemoglobinemia, hemoglobinuria, hepatosplenomegaly, and fever. Persistent reticulocytosis (10%–30%) and metarubricytosis are often noted (Figure 16.26).

Differential Diagnosis

PK deficiency, IMHA, oxidant-induced hemolysis, mycoplasmosis, and babesiosis.

Diagnosis

A PCR-based test differentiates normal, heterozygote, and homozygote animals of any age. Homozygotes can also be identified after 3 months of age by measuring erythrocyte PFK activity.

Management

Management is directed at avoiding situations that could lead to hyperventilation, such as excessive exercise, excitement, or high temperatures.

Prognosis

Dogs may have a normal life span if properly managed.

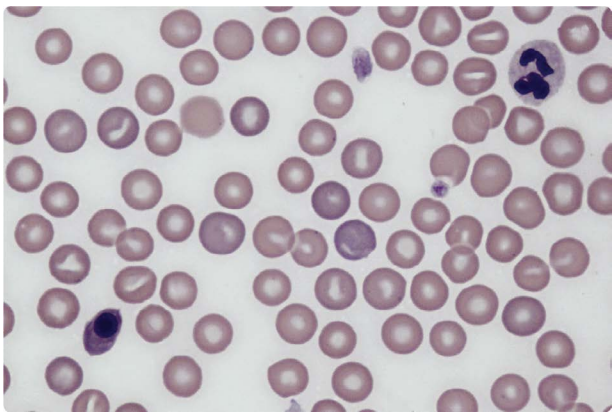


FIGURE 16.26 Polychromasia and metarubricytosis in a dog with phosphofructokinase deficiency. (*Courtesy of H. Tvedten.*)

OTHER CAUSES OF HEMOLYTIC ANEMIA

Other rare congenital hemolytic anemias have been documented. Feline erythropoietic porphyria has been reported in a family of Siamese cats that had hemolytic anemia, photosensitivity, and renal disease. A hereditary nonspherocytic hemolytic anemia has been identified in three related Beagles that exhibited persistent regenerative mild anemia (Hct, 30%–39%). Idiopathic hemolytic anemia has been documented in 13 Abyssinian and five Somali cats with regenerative moderate to marked anemias (Hct, 5%–25%).

Uncommon to rare causes of acquired hemolytic anemia include snake envenomation, hypophosphatemia, hemophagocytic histiocytic sarcoma, L-sorbose intoxication, and hypo-osmolality. Hematologic changes also noted with snakebites include spherocyte formation, echinocytosis, and coagulation abnormalities. Marked hypophosphatemia, typically ≤1.0–1.5 mg/dL, may cause intracellular ATP depletion, loss of RBC membrane integrity, and subsequent hemolysis. Severe hypophosphatemia has been associated with insulin administration in dogs and cats with diabetes mellitus, feline idiopathic hepatic lipidosis, and enteral alimentation in dogs and cats.

Hemophagocytic histiocytic sarcoma is a malignant proliferation of macrophages that exhibit marked erythrophagocytic activity. The neoplasm occurs with high incidence in Bernese Mountain Dogs, Golden Retrievers, Rottweilers, and Labrador Retrievers; it is rare in cats. Affected animals often present with Coombs-negative regenerative anemia, thrombocytopenia, hypoalbuminemia, hypocholesterolemia, and diffuse splenomegaly. Oral ingestion of L-sorbose, a sugar substitute, by dogs may cause intravascular hemolytic anemia secondary to glycolysis inhibition and decreased production of ATP within erythrocytes. Dogs with inherited high Na-K-ATPase activity in their RBCs (e.g., Japanese Akitas and Japanese Shibas) are resistant to hemolysis. Hypo-osmolar hemolysis may occur with rapid IV infusion of hypotonic fluids.

NONREGENERATIVE ANEMIA

A poorly regenerative or nonregenerative anemia is generally due to decreased RBC production in the bone marrow. Causes of regenerative anemia (hemorrhage and hemolysis) appear initially nonregenerative since the bone marrow requires at least 3–4 days to undergo erythroid hyperplasia and release greater numbers of reticulocytes. The main causes of nonregenerative include anemia of inflammatory or chronic disease (AID), anemia of endocrine disease (AED), anemia of renal disease (ARD), bone marrow disease (including precursor immune-mediated anemia, [PIMA]), and end-stage iron-deficiency anemia (IDA). A mild chronic nonregenerative anemia is more likely to be secondary to AID, AED, or ARD. ARD, IDA, or bone marrow disease are the likely differentials with moderate-to-severe chronic nonregenerative anemia. As mentioned earlier,

IDA will progress over time with a highly regenerative anemia early in the process, progressing to a poorly regenerative anemia with ongoing iron loss, and finally to the typical microcytic hypochromic nonregenerative anemia in end-stage disease.

SELECTIVE ERYTHROID ATROPHY, HYPOPLASIA, OR APLASIA

Atrophy is a reduction in the size of an organ or tissue, whereas hypoplasia and aplasia result from defective growth. Selective erythroid atrophy, hypoplasia, or aplasia is decreased or absent RBC production in the bone marrow without decreased production of other hematopoietic cells. Therefore, neutropenia and thrombocytopenia due to decreased production are not present.

ANEMIA OF INFLAMMATORY OR CHRONIC DISEASE

Definition/Overview

Anemia of inflammatory disease (AID) is the most frequent cause of nonregenerative anemia and is seen with chronic diseases. The anemia is usually mild to moderate in severity (i.e., typically PCV > 20%). Once recognized, it is of little clinical significance.

Etiology

Almost any inflammatory or chronic disorder can initiate AID, including infectious diseases, immune-mediated diseases (not targeting red cells), toxicities, and neoplasms.

Pathophysiology

The mechanism may involve decreased erythropoiesis, relatively reduced iron availability through sequestration in macrophages, and decreased RBC survival. This type of anemia is inflammatory in origin and studies have shown that cytokines, such as tumor necrosis factor (TNF), interferon-gamma, and interleukin (IL)-1, inhibit erythropoietin synthesis and decrease the responsiveness of progenitor cells to growth factors.

Clinical Presentation

Affected animals may present with prolonged anorexia, weight loss, and weakness. Other clinical signs reflect the actual source of inflammation or organ systems affected.

Differential Diagnosis

AED, ARD, IDA, bone marrow disease, preregenerative anemia.

Diagnosis

Laboratory findings often indicate a mild-to-moderate, normocytic, normochromic, nonregenerative anemia with or without an inflammatory leukogram in the face of an identifiable underlying disease. The MCV may be normal to slightly decreased. A serum iron profile may show low serum iron, low total iron-binding capacity, and increased serum ferritin, but there may be considerable overlap within the normal reference interval. The bone marrow has variable cellularity, with a normal to increased myeloid-to-erythroid ratio and normal-to-increased iron stores.

Management

Treatment is directed at the underlying disease and not the anemia. Iron supplementation does not effectively reverse this form of anemia.

ANEMIA OF CHRONIC KIDNEY DISEASE

See also Chapter 13.

Definition/Overview

The peritubular interstitial cells in the renal cortex produce erythropoietin (EPO) at a rate inversely proportional to the oxygen content (and therefore RBC mass) of blood. The anemia of chronic kidney disease (ACKD) is progressive and also mild to start with. It can become severe in advanced stages.

Etiology

Decreased EPO production is the major cause of ACKD, with minor contributions from decreased marrow responsiveness to EPO, poor nutrition, and decreased RBC survival. Concurrent GI hemorrhage caused by uremia may contribute to anemia.

Pathophysiology

Inadequate EPO and reduced response to EPO lead to decreased erythropoiesis. Uremic toxins may damage RBCs and decrease the RBC life span.

Clinical Presentation

See Chapter 13 for CKD and the International Renal Interest Society (IRIS), IRIS website for further discussion of presentation, staging, and treatment of CKD (http://www.iris-kidney.com/index.html).

If anemia is present in an animal with early CKD (IRIS stage 1 and 2), the cause of anemia is unlikely to be decreased EPO production, and the clinician should look for another cause.

Differential Diagnosis

AID, AED, GI blood loss, chronic liver disease, and IDA.

Diagnosis

See Chapter 13 for diagnosis of CKD. The major hematologic abnormality is normocytic, normochromic,

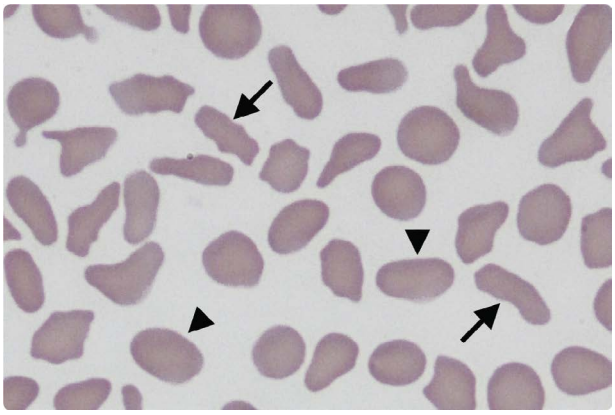


FIGURE 16.27 Burr cells (arrows) and ovalocytes (arrowheads) are elongate erythrocytes with and without ruffled borders, respectively.

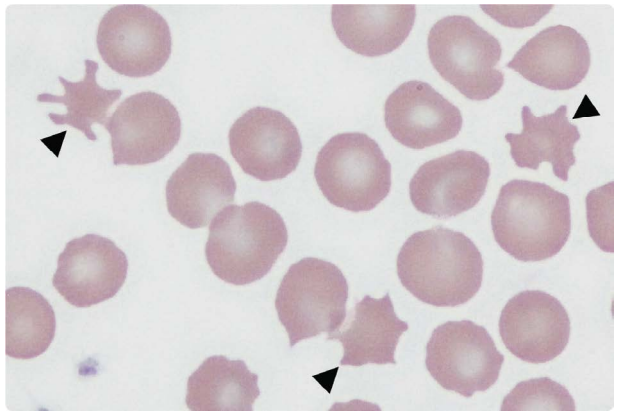


FIGURE 16.28 Three acanthocytes (arrowheads) with multiple irregularly shaped cytoplasmic projections.

nonregenerative anemia. Abnormal RBCs called burr cells (**Figure 16.27**) are associated with chronic kidney disease.

Management

See Chapter 21.

ANEMIA OF LIVER DISEASE

See also Chapter 10.

Definition/Overview

Decreased liver functional mass may influence red cell production, survival, or loss.

Etiology

Chronic-onset liver failure or portosystemic shunts may cause a significantly decreased liver functional mass. The liver produces the plasma iron transport protein, transferrin, and a small percentage of EPO. Clinical signs are usually primarily due to liver disease rather than anemia.

Pathophysiology

Mechanisms for nonregenerative anemia may include AID, decreased RBC life span due to defective protein and lipid metabolism, iron sequestration due to decreased production of transferrin, and EPO deficiency. Iron sequestration may cause microcytosis. Concurrent blood loss secondary to decreased liver production of clotting factors may contribute to the anemia.

Clinical Presentation

See Chapter 10.

Differential Diagnosis

Chronic kidney disease, nonhepatic AID, neoplasia, iron deficiency.

Diagnosis

The anemia is typically mild to moderate, normocytic, and normochromic; microcytosis is occasionally noted. Blood smears often reveal acanthocytes (**Figure 16.28**) or budding fragmentation. See Chapter 10.

Management

Treatment is directed at the underlying liver disease and not anemia.

ANEMIA OF ENDOCRINE DISORDERS

See also Chapter 12.

Definition/Overview

Hypothyroidism and hypoadrenocorticism may cause mild-to-moderate nonregenerative anemia in dogs. Anemia due to hyperestrogenism is discussed elsewhere (see generalized marrow atrophy, hypoplasia, or aplasia). The anemia is usually mild and not the cause for the clinical signs, except if significant GI bleeding occurs secondary to hypoadrenocorticism (regenerative to poorly regenerative anemia).

Etiology

Anemia is secondary to hypothyroidism or hypoadrenocorticism.

Pathophysiology

In hypothyroidism, low levels of thyroid hormone cause a decreased metabolic rate and thus reduced oxygen requirement by the tissues. This decreases EPO production and then erythropoiesis. Glucocorticoids have a stimulatory effect on erythropoiesis; therefore, glucocorticoid deficiency is expected to reduce erythropoiesis. GI hemorrhage due to glucocorticoid deficiency may contribute to anemia.

Clinical Presentation

See Chapter 12. The clinician should remember that dogs with only glucocorticoid deficiency (atypical Addison's) will present with chronic GI signs and lethargy but will not have the typical electrolytes abnormalities.

Differential Diagnosis

For nonregenerative anemia, AID, ACKD, IDA. See Chapter 11 for differential diagnoses for the patient's presentation.

Diagnosis

See Chapter 12.

Management

See Chapter 12. Except for severe GI bleeding requiring blood treatment, the degree of anemia is generally mild and expected to resolve with control of the primary disease.



FIGURE 16.29 Typical appearance of melena: Tarry black feces after digestion of blood. (*Courtesy of J. Dandrieux.*)

IRON-DEFICIENCY ANEMIA

Definition/Overview

Iron-deficiency anemia (IDA) occurs most commonly with chronic external blood loss and rarely with inadequate dietary iron intake and is due to deficient Hgb synthesis. After a preregenerative phase that is typically not noticed clinically except if the bleeding is important, the animal will develop first a strongly regenerative anemia. With ongoing iron loss, the anemia will progress to poorly regenerative anemia and finally to a nonregenerative anemia. End-stage IDA is characterized by nonregenerative, microcytic, and hypochromic anemia.

Etiology

Etiologies include chronic GI hemorrhage (neoplasia, intestinal parasites, or ulcerative diseases), chronic cutaneous blood loss (fleas, ticks, or bleeding tumors), urinary loss, and repeated phlebotomy (small animals hospitalized, blood donor animals). The owner might notice melena, black tarry feces, if the bleeding is important (**Figure 16.29**).

Pathophysiology

Hemoglobin synthesis is dependent on iron availability, and RBC maturation is dependent on adequate intracytoplasmic concentrations of hemoglobin. During times of iron deficiency, RBCs undergo additional mitoses to form smaller cells (microcytes) in an attempt to reach optimal intracytoplasmic concentrations of hemoglobin. With continued iron unavailability, the microcytes are no longer able to obtain optimal intracytoplasmic hemoglobin concentrations, thereby forming hypochromic cells. RBCs formed during times of iron deficiency are more fragile and less deformable and, therefore, lyse easily in circulation. This leads to decreased RBC life spans and the formation of keratocytes, acanthocytes, and schistocytes.

Clinical Presentation

Clinical signs of IDA are nonspecific and include insidious fatigue and exercise intolerance that develop over weeks to months. Owners may report pica as the animal licks or chews at unusual substances to try to compensate for the iron loss. Physical examination may reveal a systolic murmur, gallop rhythm, pale mucous membranes, and bounding pulses. Melena or hematochezia might be present, whereas heavy parasitism is less common. However, if there is an ongoing small amount of blood loss, it might be unnoticed.

Differential Diagnosis

Internal blood loss, hemolysis (especially early in the disease), AID, AED, ACKD, and bone marrow disease.

Diagnosis

Diagnosis is based on history and the presence of a microcytic, hypochromic anemia that is nonregenerative or poorly regenerative for the degree of anemia. However, the anemia will be strongly regenerative to start with without typical hematological changes until the iron storage has decreased sufficiently. For this reason, monitoring trends in MCV, MCHC, and reticulocytes count is very valuable to diagnose IDA. The MCV usually decreases prior to the MCHC, and so the MCHC may be within normal limits at the time of presentation. Erythrocytes in blood smears may appear

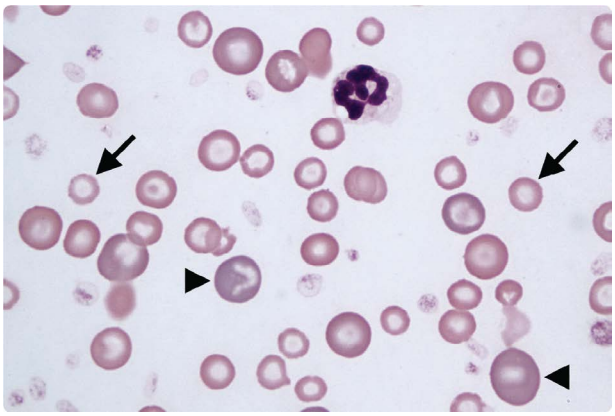


FIGURE 16.30 Iron-deficient erythrocytes are small with increased central pallor (arrows). Regeneration is present in early stages of iron-deficiency anemia (arrowheads).

small (microcytes) with increased central pallor (hypochromasia) (Figure 16.30). Microcytes and hypochromasia are observed in blood prior to changes in the MCV and MCHC, since the latter represent average cell values. Poikilocytosis may be prominent in the form of schistocytes, acanthocytes, keratocytes, codocytes, and elliptocytes (Figure 16.31). Thrombocytosis occurs in 50% of canine cases. Iron profiles have a decreased serum iron level (in cats <10.7 µmol/L [60 µg/dL]; in dogs <14.3 µmol/L [80 µg/dL]), normal-to-increased level of transferrin (measured as total iron-binding capacity), and decreased serum ferritin concentration. Percent saturation of transferrin in iron deficient animals is often <19% (normal is about 33%). Bone marrow examination shows decreased iron stores in the dog and marked erythroid proliferation. Absence of bone marrow iron stores is a normal finding in the cat.

Other changes suggestive of GI blood loss is a disproportionate increase in urea compared to creatinine due to the digestion of a high protein meal (the blood). A urinalysis is also recommended, if the source of external blood loss is not evident to rule out hematuria.

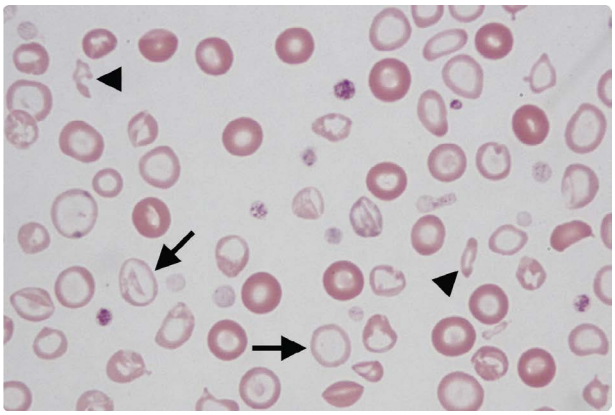


FIGURE 16.31 Late-stage iron-deficiency anemia with marked hypochromasia (arrows) and no polychromatophils. Iron-deficient erythrocytes are fragile and prone to fragmentation (arrowheads).

Management

Treatment involves correction of the inciting cause for the blood loss and iron supplementation either orally or parenterally. Parenteral supplementation is often preferred to start with as absorption is more reliable.

Ferrous sulfate is given orally at a rate of 100–300 mg ferrous sulfate (not elemental iron) in dogs and 50–100 mg in cats orally in divided doses. The main adverse effect with nontoxic dose is mild GI upset. This can be reduced by dividing the dose over the day or giving the iron with food, although the latter might reduce absorption. Antiacid may reduce iron absorption, and ferrous sulfate will decrease absorption of fluoroquinolone and thyroxine. Care in dosing is important as overdoses can be life-threatening.

Iron dextran is given IM (not IV or SC). Pain at injection site can be noted and rarely anaphylaxis. A drug interaction with reduced efficacy of mycophenolate mofetil is possible. In dogs, 50–300 mg IM (10–20 mg/kg, maximum 300 mg) is recommended with ongoing oral supplementation or repeat IM injections after a month. A dose of 50 mg (~10 mg/kg) IM is used in cats that can be repeated monthly. Therapy is continued for several weeks to months until the PCV and MCV return to normal.

The pet should be monitored for an anaphylactic reaction for 15–20 minutes after administration.

PRECURSOR-TARGETED IMMUNE-MEDIATED ANEMIA

Definition/Overview

Precursor targeted immune-mediated anemia (PIMA, nonregenerative immune-mediated hemolytic anemia) is characterized by immune-mediated destruction of erythroid precursors within the bone marrow, resulting in moderate-to-marked anemia without reticulocytosis. The bone marrow may reveal a near complete absence of erythroid precursors (pure red cell aplasia [PRCA]) or erythroid hyperplasia with maturation arrest (ineffective erythropoiesis) depending on the stage of maturation that is targeted.

Etiology

Similar to the more common regenerative IMHA, PIMA may be nonassociative or associative. Nonassociative PIMA is more common in dogs. Potential causes of associative PRCA include vaccination of dogs with a modified live parvovirus vaccine and FeLV infection in cats. Administration of recombinant human EPO may induce the development of anti-EPO antibodies, leading to an absence of EPO.

Pathophysiology

Immune-mediated destruction of erythroid cells may occur at any level of maturation. If hemolysis is directed at erythroid stem cells, there is PRCA. If hemolysis is directed at later erythroid precursors, there is marked

proliferation of stages prior to the targeted developmental stage and near absence of those after. This is termed "maturation arrest," and is indicative of either ineffective erythropoiesis or an early marrow response to anemia (preregenerative anemia). Therefore, preregenerative anemia should be ruled out prior to diagnosing ineffective erythropoiesis. Since mature RBCs in blood are not the target of immune destruction, RBCs in blood survive for their expected circulating lifespans (approximately 3 months in the dog and 2 months in the cat) prior to physiologic removal by splenic macrophages. This results in a gradual reduction in the PCV over weeks to months and allows for the development of physiologic compensation. PCV at time of admission is typically moderately to markedly decreased. Transport and utilization of oxygen and anaerobic metabolism are optimized, often resulting in mild clinical signs relative to the severity of anemia. Some dogs have evidence of bone marrow and peripheral destruction (presence of spherocytes, agglutination, or positive Coombs test).

Clinical Presentation

History and physical examination findings are similar to those seen in animals with regenerative nonassociative IMHA, except that chronic onset is more common, red plasma and urine are not expected, and icterus is less frequent.

Differential Diagnosis

Iron-deficiency anemia, drug toxicosis, other bone marrow diseases.

Diagnosis

Hematologic findings include moderate-to-severe normocytic, normochromic, nonregenerative anemia (Hct, 5%–26%). Spherocytes and agglutination are present in 15%–54% and 0%–5% of cases, respectively. Mature and band neutrophils are often increased, but neutrophils may be within the reference interval or decreased. Platelets may be increased, decreased, or within the reference interval. A direct Coombs test is often positive. Bone marrow findings are dependent on the RBC stage that is being destroyed and may reveal erythroid atrophy (including pure red cell aplasia) or erythroid hyperplasia with maturation arrest (ineffective erythropoiesis). Increased numbers of lymphocytes and plasma cells are common and may compose up to 60% and 33% of the total marrow cells, respectively. Serum ALT activity is commonly increased due to hypoxia-induced liver injury, but the total serum bilirubin concentration is only increased in less than 25% of cases. Concurrent immune-mediated disorders, such as polyarthritis, positive antinuclear antibody titers, and the presence of anti-megakaryocyte antibodies, support immune-mediated etiology.

Management

See regenerative nonassociative IMHA. Although less frequent, there is also a risk of thromboembolism.

Prognosis

More than 70% of dogs and cats are expected to recover. However, response to treatment takes typically longer than for a peripheral IMHA (take weeks to months). It is not unusual that animals are euthanized due to the need of costly transfusion until regeneration occurs. In a large study of 66 dogs, the presence of myelofibrosis did not impact on survival, although the study might have been underpowered. In any case, presence of myelofibrosis should not be a reason to preclude treatment.

FOLATE OR COBALAMIN DEFICIENCY

Definition/Overview

Folate (vitamin B9) and cobalamin (vitamin B12) are acquired through the diet and intestinally absorbed. Both are needed for DNA synthesis. Unlike most other tissues, bone marrow is particularly susceptible to the inhibition of DNA synthesis, as hematopoietic cells are constantly produced.

Etiology

Folate deficiency has been experimentally produced in cats fed a folate-deficient diet. However, dogs are highly resistant to folate deficiency. Congenital cobalamin deficiency (Imerslund-Gräsbeck syndrome, IGS) is an autosomal recessive trait in Giant Schnauzer dogs due to a cobalamin receptor complex defect. The genetic defect has also been documented in a Beagle, Border Collie, and in Australian Shepherd Dogs. Drug-induced folate deficiency is associated with anticonvulsants (phenobarbital, primidone), sulfonamides (sulfasalazine, trimethoprim–sulfadiazine), and antineoplastic agents by impairing its absorption or production. Serum folate and/or cobalamin levels may be decreased in dogs and cats with various GI and hepatic diseases and/or exocrine pancreatic insufficiency, but this very rarely results in anemia. Breeds reported with an increased frequency of hypocobalaminemia in the United Kingdom and North America include Chinese Shar-Pei and German Shepherd Dogs, whereas Staffordshire Bull Terriers were only reported in the United Kingdom.

Pathophysiology

Folate and cobalamin are required for DNA synthesis. Deficiencies in folate and/or cobalamin impair hematopoiesis, especially erythrocyte and neutrophil production. Nonregenerative anemia with erythroid dysplasia is typical of folate deficiency; concurrent neutropenia and myeloid dysplasia often occur. Cobalamin is also a cofactor for methylmalonyl coenzyme A. Reduced activity of this enzyme causes accumulation of methylmalonic acid (MMA), which is excreted in the urine and may indirectly impair urea cycle function.

Clinical Presentation

Patients of appropriate breeds with IGS are often presented at less than a year of age for lethargy, inappetence,

neurological signs, or failure to thrive. The signs are due to the systemic effect of folate and cobalamin deficiency rather than the anemia

Differential Diagnosis

Myelodysplastic syndrome, drug-induced dysplasias.

Diagnosis

Erythrocyte changes with congenital cobalamin deficiency include normocytic, normochromic anemia (Hct, 21%–36%), anisocytosis, poikilocytes, and nucleated erythrocytes with fully hemoglobinized cytoplasm and immature nuclei (erythroid dysplasia; megaloblasts). Neutropenia with hypersegmented neutrophils is frequently present, but neutrophilia may occur. Platelet concentrations are typically normal, and giant platelets may be present. The megaloblastic anemia described in people is not seen in dogs. In bone marrow, both erythroid hypoplasia and hyperplasia have been documented, but erythroid and myeloid dysplasia is a consistent finding. Specific tests include measurement of serum folate and cobalamin concentrations, as well as urine MMA concentrations.

Management

Dogs with congenital cobalamin deficiency have been successfully treated with parenteral or oral cobalamin supplementation. Protocols have not been rigorously validated and are guidelines only. Dogs with IGS require life-long supplementation. If an underlying cause is found, supplementation is required until the primary disease is controlled. Parenteral supplementation consists of injection of 250–1,000 µg SC weekly for 4–6 weeks before reassessing vitamin B12 concentration to ensure adequate supplementation. Alternatively, oral supplementation with 250 µg in cats and 250–1,000 µg in dogs daily for 12 weeks with recheck of cobalamin concentration can be used.

Prognosis

Dogs with congenital cobalamin deficiency have a good prognosis for recovery.

OTHER CAUSES OF SELECTIVE ERYTHROID HYPOPLASIA OR APLASIA

Dyserythropoiesis in English Springer Spaniels is characterized by microcytic normochromic nonregenerative anemia with polymyopathy, megaesophagus, and cardiomegaly.

GENERALIZED MARROW ATROPHY, HYPOPLASIA, OR APLASIA

Generalized marrow atrophy, hypoplasia, or aplasia results in decreased production of all hematopoietic lineages that arise from bone marrow. The typical finding is nonregenerative anemia with neutropenia and/or thrombocytopenia. Bicytopenia indicates that two cell lines are affected and pancytopenia all three cell lines. Blood lymphocyte concentrations should not be used to document bicytopenia or pancytopenia, since secondary lymphoid tissue is the primary site for lymphocyte production in adult dogs and cats. Blood monocyte, eosinophil, or basophil concentrations should also not be used, since these cells are normally present in low concentrations in peripheral blood, and it is difficult to reliably document decreased blood concentrations of these cells.

APLASTIC ANEMIA

Definition/Overview

The marrow consists of adipose and is nearly void of all nonlymphoid hematopoietic cells. Contradictory to the name, aplastic anemia is commonly acquired (atrophy) versus failed development of the bone marrow (aplasia), and it commonly causes bicytopenia (including red blood cells) or pancytopenia.

Etiology

A variety of etiologies have been implicated, including infectious agents (e.g., canine parvovirus, feline panleukopenia virus, canine distemper virus [CDV], *E. canis*, FeLV, and feline immunodeficiency virus [FIV]), drugs (e.g., trimethoprim–sulfadiazine, antineoplastic drugs, estradiol, phenylbutazone, fenbendazole, quinidine, cephalosporins, and griseofulvin), hyperestrogenism (e.g., Sertoli cell and granulosa cell tumors), whole body irradiation, and nonassociative immune-mediated stem cell destruction.

Pathophysiology

Stem cells or progenitor cells are targeted and destroyed, leading to decreased production of all hematopoietic precursors (granulocytic, erythroid, and megakaryocytic) with subsequent pancytopenia.

Clinical Presentation

The clinical presentation is partially dependent on the cause of aplastic anemia. Specifically, animals with hyperestrogenism may exhibit alopecia, feminization, or cryptorchidism. Clinical signs attributable to cytopenias include those associated with anemia (e.g., lethargy, weakness, pale mucous membranes), neutropenia (e.g., fever, infection, sepsis), and thrombocytopenia (e.g., petechial hemorrhages, epistaxis).

Differential Diagnosis

Nonassociative myelofibrosis, myelophthisic neoplasia, infectious myelitis, FeLV infection.

Diagnosis

Minimal diagnostics include CBC, bone marrow aspirate, and core biopsies. The diagnosis of aplastic anemia is based on the presence of nonregenerative anemia with concurrent marked hematopoietic atrophy/hypoplasia/aplasia in the bone marrow, which is nearly replaced with adipose tissue. The nonregenerative anemia is often accompanied by neutropenia and/or thrombocytopenia, but isolated anemia less commonly occurs. The cytopenias are often moderate to severe. In CDV infections, erythrocytes or leukocytes may contain one or more pale blue spots in the cytoplasm when stained with methanolic Romanowsky-type stains. However, these inclusions stain a deep purple color with an aqueous Romanowsky stain such as Diff-Quik® (Figure 16.32a–d). Other diagnostics should be directed at finding the underlying cause for aplastic anemia and include historical inquires of drug, radiation, or toxin exposure, testing for specific infectious agents, and evaluation for estrogen-secreting neoplasms.

Management

Specific treatment is directed at the underlying cause of the aplastic anemia, and includes cessation of myelotoxic drug administration, toxin removal, antiviral therapy, doxycycline administration for chronic *E. canis* infection, and surgical removal of estrogen-secreting neoplasms. Immune suppression may be attempted for nonassociative aplastic anemia. Supportive therapy may include blood transfusions for anemia or DIC, broad-spectrum antibiotics for neutropenia-induced bacterial infections, and bone marrow stimulants. Supportive treatment is likely to be required for an extended period of time.

Prognosis

The prognosis is guarded to poor, but complete clinical recovery is possible.

INFILTRATIVE BONE MARROW DISEASE (MYELOPHTHISIS)

Definition/Overview

The replacement of normal hematopoietic tissue in the bone marrow is termed *myelophthisis*.

Etiology

The marrow may be replaced by collagen (myelofibrosis), inflammatory cells (e.g., infectious myelitis due to histoplasmosis, other fungal infections, or toxoplasmosis), or neoplastic cells (e.g., hematopoietic or metastatic neoplasms).

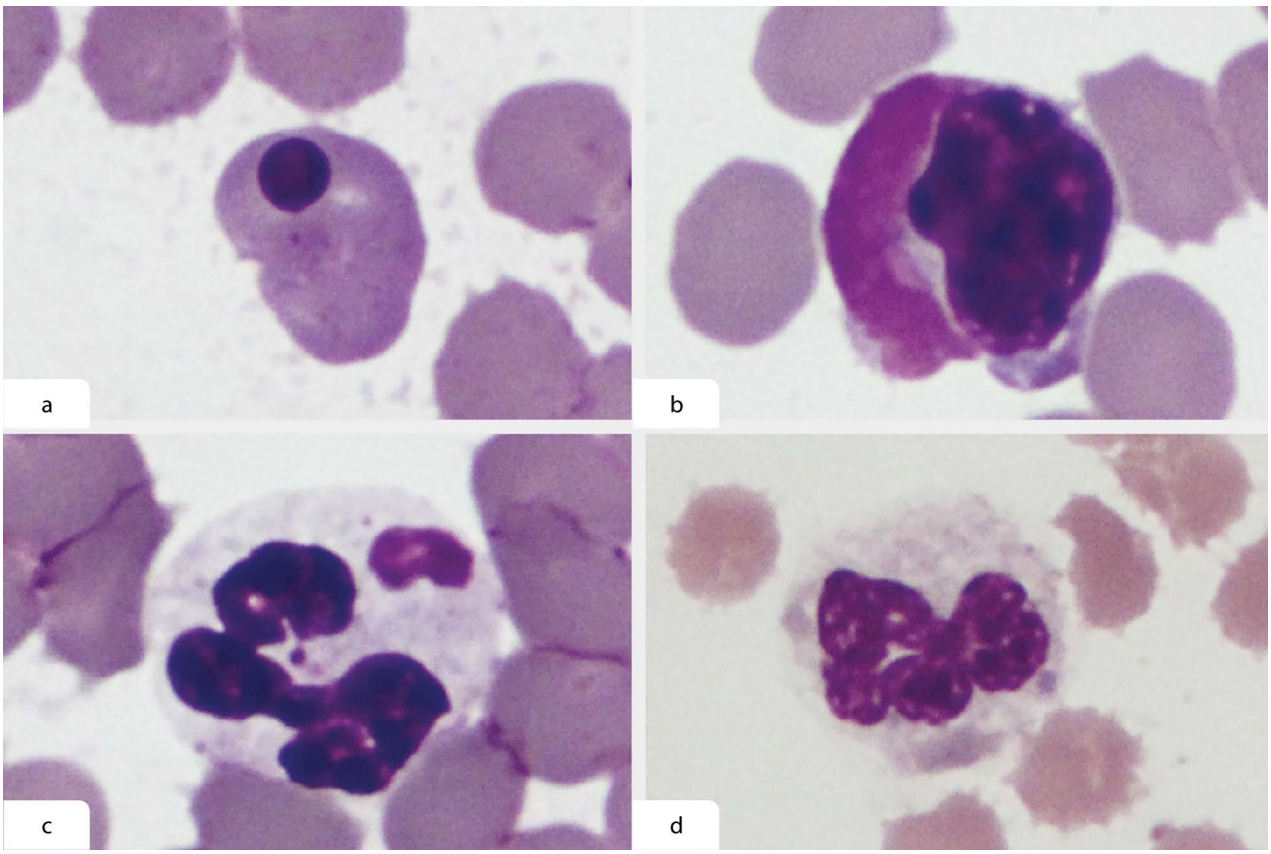


FIGURE 16.32 Canine distemper viral inclusions in an erythrocyte **(a)**, lymphocyte **(b)**, and neutrophils **(c and d)**. Vibrant magenta staining occurs with aqueous Romanowsky staining **(a–c)**, but methanolic Romanowsky stains impart a light pink–blue appearance **(d)**.

Pathophysiology

Mild infiltrates or focal lesions within the bone marrow produce minimal peripheral blood changes. Cytopenia occurs if involvement is diffuse and severe. Myelofibrosis usually occurs because of marrow damage produced by inflammation, necrosis, neoplasia, and toxic agents and may be seen in the terminal stages of chronic hemolytic anemia. Myelofibrosis is also associated with myelodysplastic syndrome and acute myelogenous leukemia in cats or with chronic myeloid neoplasia in dogs and cats.

Clinical Presentation

Animals are often presented with pale mucous membranes, fever, and bleeding, occasionally accompanied by hepatomegaly, splenomegaly, and lymphadenopathy.

Differential Diagnosis

Drug toxicosis, myelodysplastic syndrome, hematolymphatic neoplasia, and endogenous hyperestrogenism.

Diagnosis

Myelophthisis is likely if there is bicytopenia or pancytopenia with circulating neoplastic cells or evidence of systemic infection (e.g., fungal or protozoal organisms seen in blood smears or in tissue biopsies). Dacryocytes may be seen on blood smears (Figure 16.33). However, the definitive diagnosis of an infiltrative process requires bone marrow examination by both aspirate and core biopsies. Bone marrow aspiration attempts on fibrotic marrow usually produce "dry taps" (i.e., blood alone, without marrow particles). In such cases, bone marrow core biopsy is diagnostic (Figure 16.34).

Management

Treatment is directed at the underlying cause of cytopenia and may include immunosuppressive, antibiotic/antifungal, or antineoplastic therapy for nonassociative myelofibrosis, infectious myelitis, or neoplasia, respectively. Supportive care, including antibiotics, blood transfusions, anabolic steroids, and glucocorticoids, is often needed in severe cases. The condition may be reversible.

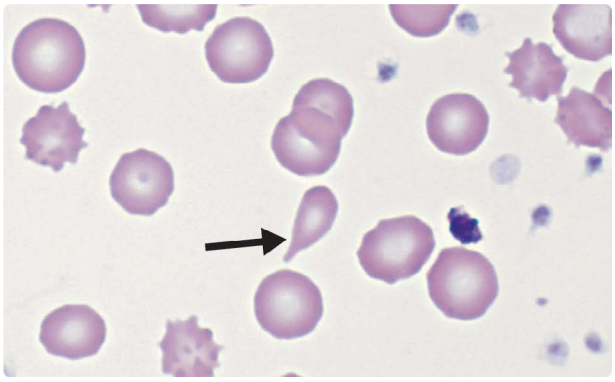


FIGURE 16.33 Dacryocyte (arrow) from the blood of a dog with myelofibrosis.

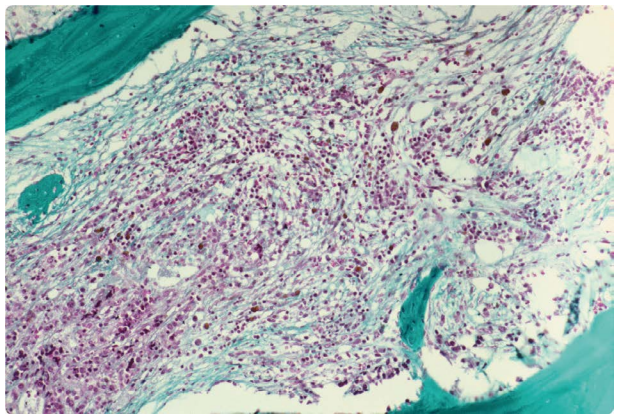


FIGURE 16.34 Bone marrow core section with trichrome stain for collagen (in green). Note the tight fibrillar arrangement of connective tissue, demonstrating myelofibrosis.

FELINE LEUKEMIA VIRUS-ASSOCIATED ANEMIA

Definition/Overview

Anemia is a major nonneoplastic complication of FeLV infection in cats. The anemia is variable in severity and regenerative status and is dependent on the underlying mechanism.

Etiology

FeLV infects hematopoietic stem cells and the supporting marrow stromal cells.

Pathophysiology

Most FeLV-associated anemias are nonregenerative. Mild-to-moderate nonregenerative anemia may occur secondary to AID. More severe nonregenerative anemia is expected with selective erythrocyte atrophy, PRCA, erythroid leukemia, or neoplastic myelophthisis. PRCA is associated with FeLV-C infection. When the virus infects erythroid precursors, it may cause either selective erythroid precursor damage (erythroid atrophy or PRCA) or neoplastic transformation of erythroid precursors. Erythroid neoplastic transformation leads to the proliferation of abnormal erythroid cells with defective metabolism, function, and maturation. These dysfunctional neoplastic cells fail to mature or prematurely die within the marrow, resulting in ineffective erythropoiesis in the marrow and anemia in the peripheral blood. Defective mitosis may cause macrocytic RBCs. Approximately 10% of FeLV-associated anemias are regenerative. Virus-induced immune suppression may allow secondary hemoplasmosis and infectious hemolytic anemia. FeLV may induce the expression of foreign antigens on erythrocyte surfaces, thereby inciting IMHA. Hemorrhage may occur secondary to

thrombocytopathia (i.e., platelet dysfunction) or suppressed platelet production causing marked thrombocytopenia (<50,000 platelets/μL).

Clinical Presentation

Clinical presentation is dependent on the severity and cause of anemia. Affected cats with moderate-to-marked nonregenerative anemia often show chronic wasting disease characterized by pale mucous membranes, lethargy, and anorexia.

Differential Diagnosis

Lymphoma, systemic mycoses, or other chronic inflammatory conditions, other viral infections, chronic kidney disease.

Diagnosis

Most FeLV-associated anemias are mild to severe, normocytic to macrocytic, normochromic, and nonregenerative or poorly regenerative. Nucleated erythrocytes in circulation with inadequate RBC regeneration (inappropriate metarubricytosis) or nucleated erythrocytes with asynchronous maturation (megaloblasts) may be noted. Concurrent neutropenia and thrombocytopenia occur with aplastic anemia, leukemia, or myelophthisis. Bone marrow findings vary from PRCA to erythroid hypoplasia to erythroid neoplasia (myelodysplastic syndrome or acute myeloid leukemia-M6). Concurrent findings with regenerative anemia may include hemotropic mycoplasma infection or marked thrombocytopenia. A definitive FeLV association is diagnosed with positive ELISA, PCR, or IFA tests.

Management

Treatment will vary depending on the presence of concurrent conditions such as neoplasia, hemoplasmosis, FIV infection, or FIP. Hematologic abnormalities due to defective production are mostly irreversible. However, marrow hypoplasia may be cyclical, so temporary life support may be considered during times of cytopenias. See Chapter 21.

Prognosis

Cats with PRCA often relapse with cessation of treatment, while those with aplastic anemia typically do not respond to treatment. Regardless of the cause, regenerative FeLV-associated anemias tend to respond favorably to treatment.

ERYTHROID DYSPLASIA

BONE MARROW DYSCRASIA OF POODLES

Definition/Overview

Bone marrow dyscrasia is a hereditary disorder of Toy and Miniature Poodles characterized by erythrocyte macrocytosis without anemia or reticulocytosis.

Etiology

The underlying etiology is unknown.

Pathophysiology

Measurements of folate or vitamin B12 are normal, and there is no response to therapeutic doses of vitamin B12. The abnormality appears to originate from bone marrow, as precursors are dysplastic.

Clinical Presentation

There are no associated clinical signs (incidental finding).

Differential Diagnosis

Myelodysplastic syndrome, drug-induced dysplasia, vitamin deficiency dysplasia, causes of regenerative anemia.

Diagnosis

Diagnosis is based on the breed and hematologic findings of normal PCV and reticulocyte results, macrocytosis (MCV >80 fL), inappropriate metarubricytosis with megaloblasts, Howell–Jolly bodies, and neutrophil hypersegmentation and gigantism (**Figure 16.35**).

Management

Treatment is not needed.

Prognosis

No negative clinical effects.

LEAD POISONING

See also Chapter 20.

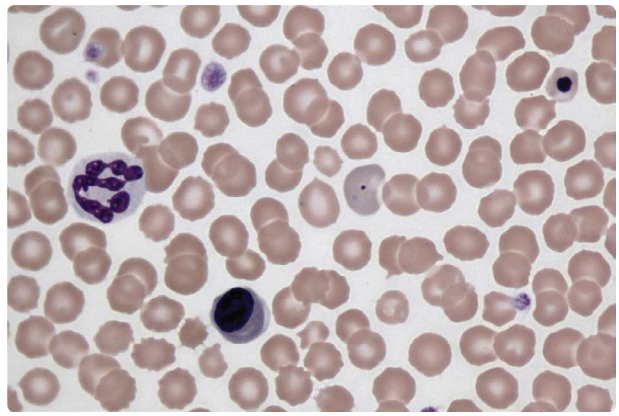


FIGURE 16.35 Blood from a Poodle with marrow dyscrasia demonstrating a hypersegmented neutrophil, inappropriate metarubricytosis, and nuclear fragments within erythrocytes. The MCV was 99.1 fL (reference range 66.4–77.4) without reticulocytosis.

Definition/Overview

Young animals are particularly susceptible to lead poisoning because it is absorbed quickly and may cross the blood–brain barrier in larger amounts than in older animals. Dietary calcium may increase lead absorption.

Etiology

Causes of lead poisoning include lead shot, especially if it is embedded in tissue in or near joints, and ingestion of lead-containing paint, linoleum, plumbing solder, and window caulking.

Pathophysiology

This condition causes mild anemia in some cases, possibly due to increased RBC fragility and abnormal erythropoiesis. Lead primarily affects heme synthesis, causing defective maturation.

Clinical Presentation

See Chapter 20. The anemia is usually not the reason for presentation.

Differential Diagnosis

Iron deficiency, FeLV infection, drug toxicosis, neurologic disorders, GI disorders, splenic neoplasia (e.g., hemangiosarcoma).

Diagnosis

Diagnosis is often based on a history of exposure to lead and increased lead concentrations in heparinized blood. The most consistent hematologic findings are nucleated RBCs with normal or slightly decreased PCV and no RBC regeneration (54% of cases have inappropriate metarubricytosis). When present, the anemia is often normocytic and normochromic but may be microcytic and hypochromic. Basophilic stippling is present in 25% of dogs with lead poisoning (Figure 16.36). Bone marrow aspirates or core biopsies are characterized by maturation arrest at the metarubricyte stage.

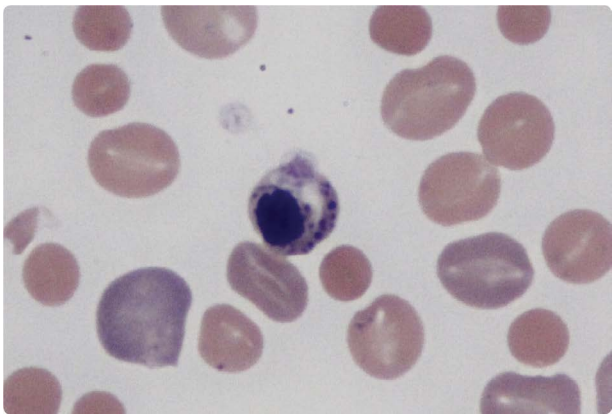


FIGURE 16.36 Basophilic stippling in a nucleated erythrocyte from a dog with lead poisoning.

Management

See Chapter 20.

Prognosis

See Chapter 20.

ERYTHROCYTOSIS

Erythrocytosis is an increased RBC concentration in peripheral blood that is detected by an increased PCV, Hct, RBC count, or Hgb concentration. Erythrocytosis may be relative (i.e., there is hemoconcentration or redistribution of RBCs in circulation) or absolute (increased RBC mass due to increased RBC production). Absolute erythrocytosis is further classified as primary or secondary. If erythroid proliferation is independent of EPO concentration, then absolute erythrocytosis is primary or erythroid neoplasia. Secondary erythrocytosis is either appropriate or inappropriate (Figure 16.37). If the RBC hyperplasia is secondary to systemic hypoxemia (arterial O_2 <92%, e.g., underlying cardiopulmonary disease), it is considered appropriate. Secondary inappropriate erythrocytosis develops with EPO-producing tumors or local renal hypoxemia secondary to renal disease with increased EPO production (neoplastic or pyelonephritis). Polycythemia is sometimes used interchangeably with erythrocytosis but is also used to mean absolute erythrocytosis. Polycythemia vera (PV) is a neoplastic proliferation of hematopoietic cells that produce mature erythrocytes.

RELATIVE ERYTHROCYTOSIS

Definition/Overview

The increased RBC concentration is due to redistribution of fluid or RBCs.

Etiology

Etiologies include dehydration, excitement, and endotoxic shock.

Pathophysiology

Fluid loss from the blood vessels causes a relative increase in the proportion of RBCs. Fluid may be lost from the body with dehydration or shifted into the interstitial tissues with endotoxic shock. The spleen contracts during an excitement/physiologic response to epinephrine, releasing erythrocytes from the splenic sinusoids into peripheral circulation.

Clinical Presentation

Dehydrated patients may be presented with tacky mucous membranes, prolonged CRTs, and skin tents. Animals with epinephrine-induced physiologic responses are often young, healthy animals that are easily excited.

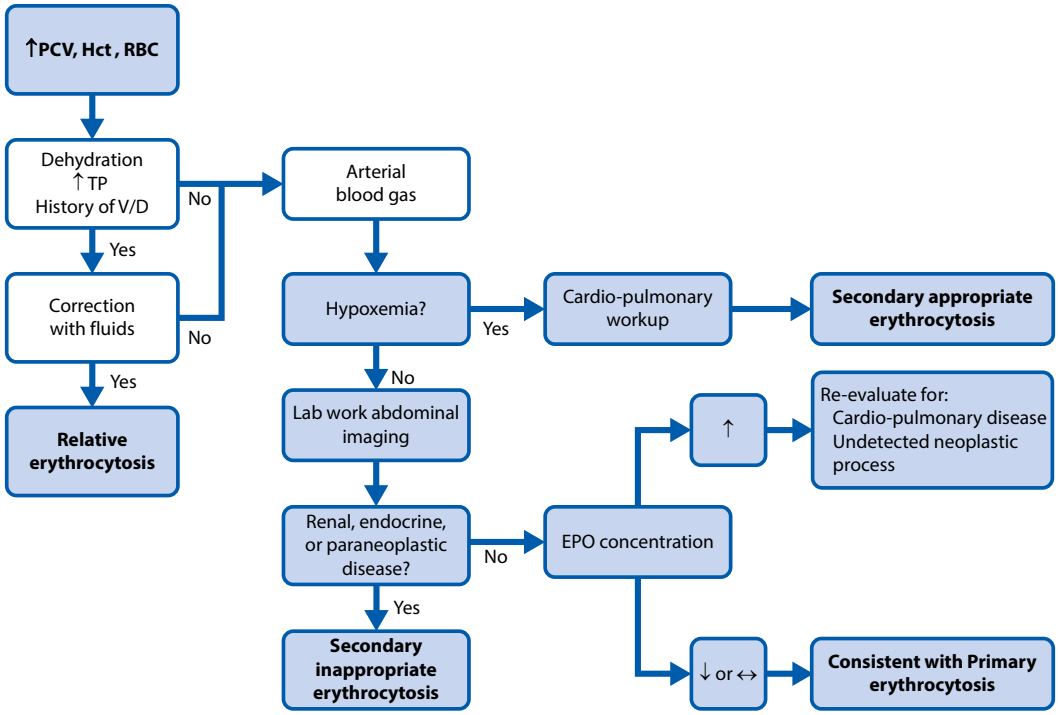


FIGURE 16.37 Workup considerations for the animal with erythrocytosis.

Differential Diagnosis

Causes of absolute erythrocytosis (heart disease, chronic pulmonary disease, hyperthyroidism, renal neoplasms, nonrenal neoplasms, PV, and acute erythroid leukemia).

Diagnosis

The diagnosis is based on the CBC, history, and physical examination. The hemogram indicates a red cell mass (PCV, Hct, Hgb, and/or RBC) that exceeds the normal reference interval for that species or breed. Greyhounds and Dachshunds normally have a high PCV of 0.6 L/L (60%), which should not be misinterpreted as erythrocytosis. Highly concentrated urine, azotemia, and concurrent increases in serum total protein, sodium, and chloride concentrations may be present with dehydration. Epinephrine release may also cause an excitement leukogram (mild neutrophilia and lymphocytosis without a left shift), thrombocytosis, and hyperglycemia.

Management

Dehydrated patients may need fluid therapy. Treatment is not necessary for excitement-induced erythrocytosis, as the response often normalizes within 30 minutes. If the erythrocytosis resolves with rehydration and does not recur, then the diagnosis is confirmed.

SECONDARY ABSOLUTE ERYTHROCYTOSIS

Definition/Overview

Secondary erythrocytosis involves overproduction of EPO or an EPO-like substance. The erythrocytosis is appropriate if it is in response to hypoxia but inappropriate if oxygen transport and tissue use are normal.

Etiology

Causes of secondary appropriate erythrocytosis include hypoxia (e.g., high altitude, chronic pulmonary disease, cardiac disease with right-to-left shunting, hyperthyroidism, or chronic methemoglobinemia). Secondary inappropriate erythrocytosis is caused by tumors that produce erythropoietin (e.g., renal lymphoma, renal carcinoma, and renal fibrosarcoma) and renal disease (e.g., pyelonephritis, local hypoxemia).

Pathophysiology

As a physiologically appropriate response to hypoxia, EPO production is stimulated by cardiopulmonary disorders. When the hypoxic stimulation is absent, an inappropriate production of EPO or EPO-like substance occurs related to tumor development or renal disease. Marked erythrocytosis can cause blood hyperviscosity and then poor tissue perfusion.

Clinical Presentation

Signs may be acute despite the chronic nature of the disorder. Initial findings are dependent on the initiating disease and the presence of hyperviscosity. Findings directly resulting from the erythrocytosis may include erythema, splenomegaly, and bright red mucous membranes. Clinical signs associated with hyperviscosity include functional abnormalities of the CNS and hemorrhage (epistaxis, hyphema, or GI bleeding).

Differential Diagnosis

PV and relative erythrocytosis.

Diagnosis

An arterial blood gas enables the clinician to determine if hypoxemia is present (Figure 16.37). If O_2 <92%, then workup for cardiopulmonary disease is indicated (thoracic radiographs, echocardiography, EKG, and BP). If there is no hypoxemia, laboratory workup (hematology, biochemistry including TT4, urinalysis, and culture) and abdominal diagnostic imaging is indicated to identify the underlying cause such as significant renal pathology, hyperthyroidism, or a paraneoplastic process. If no underlying disease is identified, EPO concentration can be measured (species-specific test). A low or normal EPO concentration is consistent with primary erythrocytosis. An elevated EPO suggest that an underlying disease has been missed, and the animal should be reassessed for cardiopulmonary disease or undetected neoplastic process. Serum EPO levels are currently measured by radioimmunoassay and ELISA methods.

Management

Treatment of secondary erythrocytosis often involves removal of the inciting cause (e.g., nephrectomy). Phlebotomy is indicated if there are signs of hyperviscosity.

METHEMOGLOBINEMIA

Definition/Overview

Methemoglobin may be produced in amounts that exceed normal protective antioxidant mechanisms. This form of Hgb is unable to bind and carry oxygen. Normal amounts of methemoglobin are <1% of total Hgb.

Etiology

Methemoglobinemia occurs most commonly from exposure to oxidative agents mentioned under Heinz body formation (p. 668). Rarely, a hereditary deficiency of methemoglobin reductase (cytochrome-b5 reductase) may cause methemoglobinemia. The latter has been documented in several dog breeds and a DSH cat.

Pathophysiology

The erythrocyte antioxidant pathways are overwhelmed, which results in heme oxidation from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state. Hemoglobin within the ferric state is termed methemoglobin and is unable to bind oxygen, producing a state of hypoxia.

Clinical Presentation

Clinically, the mucous membranes appear blue–gray or cyanotic (Figure 16.38) if methemoglobin levels exceed 0.2 L/L (20%). The patient is often dyspneic, weak, and ataxic when the methemoglobin content exceeds 0.5 L/L (50%).



FIGURE 16.38 This cat with methemoglobinemia as a result of acetaminophen toxicity has blue–gray gums. (*Courtesy of S. Ford.*)

Differential Diagnosis

Causes of multisystemic hypoxia without anemia (e.g., pulmonary disease, right-to-left cardiac shunts), causes of hemolytic anemia (e.g., IMHA, hemoplasmosis, babesiosis).

Diagnosis

The appearance of dark red or chocolate-colored blood, even after exposure to air, is diagnostic for the condition and is readily visible by a spot test on filter paper. When normal blood is exposed to air it becomes bright red, while the blood of affected animals stays dark red if the methemoglobin content exceeds 10% (Figure 16.39). Methemoglobin content is measured by spectrophotometry by a CO-oximeter or at specialized laboratories;



FIGURE 16.39 Two tubes of blood recently exposed to air. The tube on the left remains a dark color compared with normal blood in the right tube, indicating methemoglobinemia. (*Courtesy of J. Harvey.*)

the pulse oximeter cannot detect methemoglobinemia. Other erythrocyte changes may include mild secondary polycythemia in animals with methemoglobin reductase deficiency or regenerative anemia, Heinz bodies, and eccentrocytes in animals with oxidant-induced hemolytic anemia.

Management

Treatment is similar to that for Heinz body anemia. The source of oxidant should be removed with emetics if recent ingestion has occurred. For acetaminophen (paracetamol)-induced toxicity, acetylcysteine (Mucomyst®) is given initially IV at 140 mg/kg of a 5% solution diluted with saline and then 70 mg/kg (of a 5% solution) q.4 h. for 3–5 treatments. In addition, sodium ascorbate (vitamin C) may further reduce methemoglobin levels. A dose of 100–500 mg/day IV is recommended for dogs, and a dose of 100 mg/day IV is recommended for cats (see Chapter 20). Therapy is usually not required for animals with the reductase enzyme deficiency.

LEUKOCYTE DISORDERS (NONNEOPLASTIC)

LEUKOCYTOSIS

Leukocytosis is an increased concentration of the collective white blood cell (WBC) concentration above its reference interval. It does not distinguish which leukocyte type is increased.

Note that some hematology analyzers (e.g., impedance analyzers) cannot distinguish nucleated RBCs (NRBCs) from WBCs. Therefore, the automated WBC count is the sum of WBCs and NRBCs and should be considered the total nucleated cell count (TNCC) in these cases. If a metarubricytosis is present, the corrected WBC (CWBC) count can be calculated using the TNCC and a blood smear quantification of NRBCs (NRBCs/100 WBCs):

$$CWBC = TNCC \times 100/(100 + NRBCs/100\ WBCs)$$

NEUTROPHILIA

Neutrophilia is defined as a neutrophil concentration above the upper reference interval, which is generally >11,500/µL in the dog and >12,500/µL in the cat. Common causes of neutrophilia are excitement, stress, and inflammation, whereas uncommon to rare causes include paraneoplastic syndromes, myeloid leukemia, and canine leukocyte adhesion deficiency (CLAD).

Neutrophilia is further classified as "mature" or "left shifted" based on the absence or presence of immature neutrophils in blood, respectively. Mature neutrophils have condensed and dark chromatin with indentations or pinches in the nucleus that creates alternating segments of wide and narrow nuclear diameters. Mature neutrophils are, therefore, termed, "segmented neutrophils." Immature neutrophils lack segments and include band neutrophils (parallel nuclear walls), metamyelocytes (kidney bean-shaped nuclei), myelocytes (round or oval nuclei), promyelocytes (round or oval nuclei with pink cytoplasmic granules), and myeloblasts (round or oval nuclei with a nucleolus). In blood, segmented neutrophils predominate with no or rare band neutrophils. An increased concentration of immature neutrophils in blood is termed "left shift" and indicates increased demand for neutrophils during inflammation or inappropriate release of neutrophils in the absence of inflammation (e.g., leukemia). When immature neutrophils are released into blood during inflammation, the most mature neutrophil is released first, and earlier stages are released when more mature stages are depleted. Consequently, band neutrophils are first released during inflammation and are the most common immature neutrophil seen in blood. When attempting to distinguish the cause of the neutrophilia as inflammation or noninflammatory (excitement or stress), the presence of one or more of the following observations supports an inflammatory etiology: Neutrophilia >2–3 times the upper reference limit, presence of left shift, or neutrophil toxicity.

PHYSIOLOGIC AND CORTICOSTEROID-INDUCED NEUTROPHILIA AND MONOCYTOSIS

Definition/Overview

Physiologic (excitement or shift) neutrophilia and monocytosis are a transiently increased neutrophil and monocyte concentrations associated with epinephrine release during a fight or flight response. See **Table 16.12**.

CORTICOSTEROID-INDUCED NEUTROPHILIA AND MONOCYTOSIS

Definition/Overview

Neutrophilia and monocytosis (the latter especially in dogs) may be related to exogenous administration or endogenous release of glucocorticoids or ACTH. See **Table 16.12**.

Signs will reflect the underlying condition. See Chapter 11 for hyperadrenocorticism.

INFLAMMATORY NEUTROPHILIA

Definition/Overview

Inflammation causes increased mobilization of neutrophils from the bone marrow to the site of tissue inflammation (**Table 16.12**). The main indicators of inflammation are increased numbers of immature neutrophils in the blood, termed a left shift, and neutrophil toxicity.

TABLE 16.12 Common neutrophilia patterns and mechanisms of leukocyte concentration change*

Peripheral leukocyte	Physiologic leukogram (epinephrine)†	Stress leukogram (glucocorticoids)‡	Acute inflammatory leukogram	Chronic inflammatory leukogram
Segmented Neutrophils	↑ Marginal to circulating	↑ Marginal to circulating	↑–↑↑↑ Marginal to circulating Storage to circulating	↑–↑↑↑ Marrow hyperplasia
Band Neutrophils	N	N	±↑–↑↑ Maturation to circulating	±↑–↑↑ Marrow hyperplasia
Lymphocytes	±↑ Marginal to circulating Lymphatics to circulating	↓ "Homing" to lymph nodes Lympholysis	↓ "Homing" to lymph nodes	±↑ Lymphoid hyperplasia
Monocytes	N	±↑ Marginal to circulating	±↑ Marginal to circulating	±↑ Marrow hyperplasia
Eosinophils	N	±↓ Sequestered in marrow	±↓ Sequestered in marrow	±↑ Marrow hyperplasia

* Increased concentrations of nonlymphoid leukocytes in the blood circulating pool (free-flowing cells sampled during phlebotomy) may occur by (1) release of the bone marrow storage pool of mature cells into blood, (2) release of immature cells from the bone marrow maturation pool into blood, (3) or shifting from the blood marginal pool (leukocytes reversibly adhered to endothelium) to the blood circulating pool. Altered concentrations of lymphocytes in the blood circulating pool may occur with lymphocytes moving between the blood marginal pool, blood circulating pool, and secondary lymphoid tissues, such as lymph nodes. In dogs, there are equal numbers of blood marginal and circulating neutrophils, while cats have three times more neutrophils in the marginal pool compared to the circulating pool. Therefore, shifting of neutrophils from the marginal pool to the circulating pool may be greater in cats, in which a threefold increase in neutrophils may occur compared with a twofold increase in dogs.

† Transient increase due to epinephrine release during times of physiologic excitement or flight-fight response. Concurrent abnormalities include relative erythrocytosis, thrombocytosis, and hyperglycemia. Resolution is expected within 30 minutes.

‡ Secondary to stress, hyperadrenocorticism (Cushing's syndrome), or exogenous administration of glucocorticoids or ACTH. Resolution is expected within 24 hours after a single dose of prednisolone. At higher glucocorticoid concentrations, lymphocyte cell death (lympholysis) may occur.

A marked inflammatory neutrophilia that exceeds 50,000 neutrophils/μL is called a leukemoid response.

Etiology

The etiology can involve infectious or noninfectious sources. Infectious agents include bacteria, fungi, protozoa, or rickettsiae. Noninfectious conditions involve tissue necrosis such as necrotizing pancreatitis, neoplasia, immune-mediated disease, severe GI disease, thrombosis, and thermal burns. A leukemoid response may be associated with IMHA, pancreatitis, pyelonephritis, pyometra, peritonitis, pneumonia, hepatozoonosis, and malignant neoplasms with necrotic centers, especially carcinomas.

Pathophysiology

Inflammatory conditions produce cytokines, such as granulocyte colony-stimulating factor (G-CSF) and granulocyte/macrophage colony-stimulating factor (GM-CSF), which promote release of neutrophils from the bone marrow and stimulate granulopoiesis.

Clinical Presentation

Sites of inflammation may be apparent from physical examination or diagnostic procedures. Signs will reflect the underlying condition. Pyrexia is often present.

Differential Diagnosis

Physiologic neutrophilia, corticosteroid-induced neutrophilia, hematopoietic leukemia.

Diagnosis

Diagnosis of inflammatory neutrophilia is based on a careful history and CBC evaluation. The most specific hematologic indicators of inflammation are the presence of a left shift or neutrophil toxicity.

Management

Treatment will depend on the inciting cause.

OTHER CAUSES OF NEUTROPHILIA

Paraneoplastic neutrophilia is caused by production of G-CSF by neoplasms, such as rectal adenomatous polyp, renal tubular carcinoma, and fibrosarcoma. CLAD is a genetic disorder characterized by marked neutrophilia and recurrent, life-threatening infections due to the inability of neutrophils to exit blood vessels and enter tissues. Both paraneoplastic neutrophilia and CLAD tend to produce neutrophilia that exceed 50,000/μL. Canine granulocytopathy syndrome is a rare condition of Irish Setter dogs characterized by recurrent life-threatening bacterial infections, pyrexia, and leukemoid response with impaired neutrophil bactericidal activity.

EOSINOPHILIA

Eosinophils are identified by pink–orange cytoplasmic granules that are round and variably sized in dogs and small and rod-shaped in cats (Figure 16.40). In some Greyhounds, Golden Retrievers, and Shetland Sheepdogs,

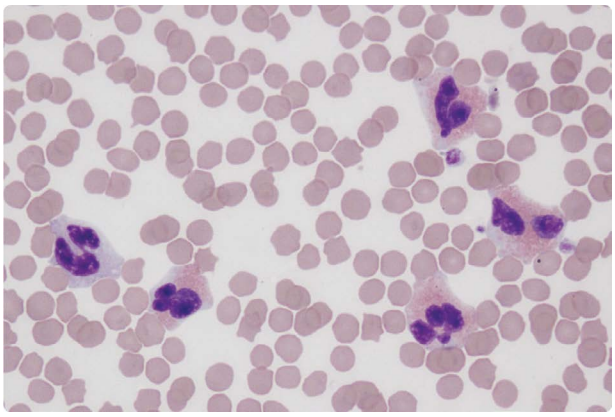


FIGURE 16.40 Blood from a cat with hypereosinophilic syndrome. Note the four eosinophils and one neutrophil (far left). These have the usual pink-staining cytoplasmic granules typical of eosinophils.

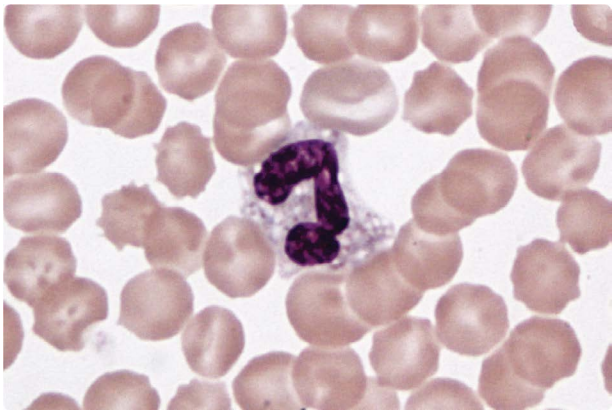


FIGURE 16.41 Canine eosinophil with poorly staining granules (gray eosinophil).

and, rarely, cats, eosinophils may have granules that do not stain with Romanowsky stains and are termed gray eosinophils (Figure 16.41). *Eosinophilia* is defined as an eosinophil concentration above the upper reference interval, which is generally >1,250/µL in the dog and >1,500/µL in the cat. Nonneoplastic eosinophilia is due to inflammation, fungal disease, parasitic disease, hypoadrenocorticism, or paraneoplastic response.

INFLAMMATORY EOSINOPHILIA

Definition/Overview

Eosinophilia may be seen with tissue parasitism or allergic (hypersensitivity) disorders.

Etiology

Peripheral eosinophilia may result from infiltration of the skin, respiratory tract, and alimentary tract by such parasites as *Ancylostoma* spp., *Trichuris vulpis*, *Toxocara canis*, *Dirofilaria immitis* (Figure 16.23), *Acanthocheilonema* (formerly *Dipetalonema*) *reconditum*, *Aelurostrongylus abstrusus*, *Eucoleus* (formerly *Capillaria*) spp., *Filaroides* spp., and *Paragonimus kellicotti*. Hypersensitivity reactions can occur from the effects of fleas, food, grasses, and nonspecific allergens. Many idiopathic eosinophilic conditions are thought to be hypersensitivity reactions, including feline eosinophilic granuloma complex and canine degranulation eosinophilic bronchopneumopathy.

Pathophysiology

T cell–dependent eosinophils are associated with parasitic infections and hypersensitivities. This type of eosinophilia is mediated by soluble factors, especially IL-5 and GM-CSF.

Clinical Presentation

Signs reflect the organ systems affected, such as skin rashes, diarrhea, coughing, and scratching.

Differential Diagnosis

Hypoadrenocorticism, paraneoplastic eosinophilia, hypereosinophilic syndrome, and leukemia.

Diagnosis

Diagnosis of parasitism or hypersensitivities includes history, physical examination, food trials, skin tests, laboratory testing (e.g., heartworm antigen test), and evaluations of blood smears for microfilaria (Figure 16.23), fecal floats and sediment, tracheobronchial washes, and cytologic or histologic biopsies.

Management

Treatment is aimed at the underlying cause.

HYPOADRENOCORTICISM (ADDISON'S DISEASE)

See also Chapter 12.

Definition/Overview

Glucocorticoids (e.g., cortisol) and mineralocorticoids (e.g., aldosterone) are hormones produced by the adrenal cortex. Deficient production of these hormones leads to hypoadrenocorticism. Eosinophilia is present in 20% of dogs with hypoadrenocorticism.

Etiology

Hypoadrenocorticism in dogs is typically a result of immune-mediated destruction of the adrenal cortex. Pituitary disease-causing ACTH deficiency is uncommon.

Pathophysiology

The pathophysiology of eosinophilia is not completely known but probably involves cortisol deficiency.

Clinical Presentation

See Chapter 12. The anemia is usually not the primary cause of presentation.

Differential Diagnosis

Inflammation, paraneoplastic eosinophilia, hypereosinophilic syndrome, and leukemia.

Diagnosis

Diagnosis is often based on history, physical examination findings, and blood tests for electrolytes and serum basal and post-ACTH cortisol levels. The most consistent hematologic abnormality is lack of a stress leukogram in a clinically ill animal. Less frequently, lymphocytosis and eosinophilia are seen.

Management

See Chapter 12.

PARANEOPLASTIC EOSINOPHILIA

Definition/Overview

Paraneoplastic syndromes are disorders caused by neoplasms but are not a direct result of the physical presence of the tumor in the organ or tissue.

Etiology

Tumor-associated eosinophilia has been reported in dogs with fibrosarcoma, anaplastic mammary carcinoma, T-cell lymphoma, or mast cell tumors, as well as in cats with mast cell tumors or lymphoma.

Pathophysiology

Tumor production and release of GM-CSF, IL-5, histamine, or chemotactic mediators enhance eosinophil production.

Clinical Presentation

Signs reflect the organ systems affected by the neoplasm and often involve one or more tissue masses in the skin, lymphatic system, or urogenital system.

Differential Diagnosis

Inflammation, hypoadrenocorticism, hypereosinophilic syndrome, and leukemia.

Diagnosis

Diagnosis of a paraneoplastic eosinophilia requires normalization or reduction of the eosinophil concentration in response to cancer remission.

Management

Treatment will reflect the underlying disease and may include surgery, radiation therapy, or chemotherapy.

HYPEREOSINOPHILIC SYNDROME

Definition/Overview

Hypereosinophilic syndrome is an uncommon form of peripheral eosinophilia in cats and has also been reported in dogs, mostly Rottweilers. The disease is accompanied by severe infiltration of eosinophils into many organs, often including the GI tract, liver, spleen, lymph nodes, and lung. It is difficult to differentiate from chronic eosinophilic leukemia, and at least in human medicine, it is now considered a form of chronic leukemia.

Etiology

The etiology is unknown.

Pathophysiology

There is often evidence of intestinal thickening and involvement of the bone marrow that resembles leukemia of well-differentiated eosinophils. Counts have been reported to exceed 50,000/μL (**Figure 16.40**). It is usually a multisystemic disease with involvement of other organs, especially the GI tract.

Clinical Presentation

Clinical signs reflect organ involvement and may include anorexia, weight loss, fever, vomiting, diarrhea, and lymphadenopathy. Death results from organ dysfunction caused by tissue infiltration.

Differential Diagnosis

Inflammation, paraneoplastic eosinophilia, and eosinophilic leukemia.

Diagnosis

Diagnosis is based on history, physical examination, presence of multisystemic involvement, and ruling out other causes of eosinophilia with fecal examination, heartworm testing, and diagnostic imaging with sampling as indicated. Bone marrow evaluation establishes the number of eosinophil precursor cells and the degree of marrow involvement. Needle and tissue biopsies show eosinophilic infiltrates.

Management

Prednisolone (1–3 mg/kg p.o. q.12 h.), with or without hydroxyurea (7.5 mg/kg p.o. q.12 h.), has been used to reduce eosinophil numbers and clinical signs. Other considerations include cyclosporine and one report of the use of a tyrosine kinase inhibitor.

Prognosis

Cats often respond poorly to chemotherapy for long-term control. Long-term response or remission has been reported in some dogs and some Rottweilers going into remission without specific immunosuppressive treatment.

BASOPHILIA

Basophilia is defined as an increased blood basophil concentration above the upper reference interval, generally >200/μL in the dog and cat (Figure 16.69). With the exception of hypoadrenocorticism and hypereosinophilic syndrome, nonneoplastic causes of basophilia are similar to those for eosinophilia—inflammation due to parasitic infections or hypersensitivities and paraneoplastic basophilia due to mast cell neoplasia or other malignancies. Marked basophilia with atypical leukocytes in the circulation or bone marrow should suggest basophilic leukemia, which is a rare presentation.

It is important to note that basophil granules in dogs and cats stain poorly. In these cases, the cells may be mistaken for toxic neutrophils in dogs or faded eosinophils in cats. In addition, basophilia must be distinguished from circulating mast cells in the dog.

LYMPHOCYTOSIS

Lymphocytosis is an increased concentration of lymphocytes in blood, usually >4,800/μL in the dog and >7,000/μL in the cat. Young animals within the first year of life typically have physiologically higher lymphocyte concentrations relative to adults, so appropriate reference intervals should be used.

Note that the general classifications of lymphocytosis are reactive (physiologic, chronic inflammation, hypoadrenocorticism) and neoplastic. Reactive lymphocytosis tends to be mild to moderate in severity (e.g., <15,000/μL in dogs and <20,000/μL in cats), consists of lymphocytes of varying morphology, and normalizes when the underlying disorder is appropriately treated. Neoplastic lymphocytosis has varying presentations but may be mild to marked in severity, consists of a single lymphocyte morphology, and persists without immunosuppressive or chemotherapy.

PHYSIOLOGIC LYMPHOCYTOSIS

See physiologic neutrophilia and lymphocytosis.

CHRONIC INFLAMMATORY LYMPHOCYTOSIS

Definition/Overview

Chronic antigenic or cytokine stimulation results in lymphoid hyperplasia.

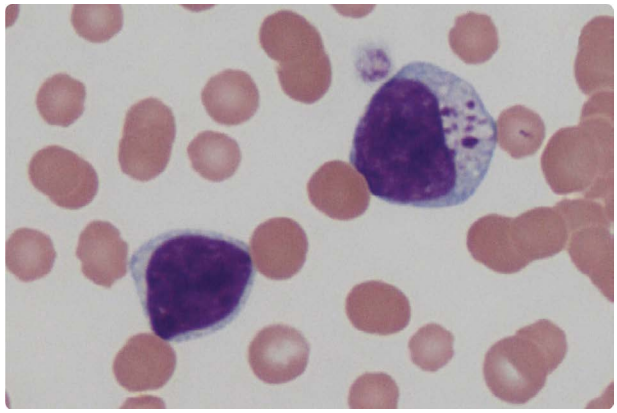


FIGURE 16.42 Compared with a small lymphocyte (left), a large granular lymphocyte (right) has a moderate amount of basophilic cytoplasm containing several coarse pink–purple granules.

Etiology

Chronic inflammation of an infectious or noninfectious etiology can cause lymphoid hyperplasia and subsequent lymphocytosis. In particular, lymphocytosis involving intermediate-sized granular lymphocytes (Figure 16.42) has been associated with *E. canis* infection in dogs. Modified live vaccines may also produce lymphocytosis about 1-week post immunization.

Pathophysiology

Antigen-presenting cells, such as macrophages and dendritic cells, process and present inciting antigens to T lymphocytes. B-cell development often requires costimulatory signals from T-helper cells, along with cytokines, for activation and differentiation into plasma cells that produce antibodies against the inciting antigen.

Clinical Presentation

Signs reflect the underlying inflammatory condition.

Differential Diagnosis

Excitement, hypoadrenocorticism, and lymphoid neoplasia.

Diagnosis

There is typically a mixed lymphoid population of small and large lymphocytes of varying morphology. Slightly enlarged lymphocytes with deeply basophilic cytoplasm (reactive lymphocytes) may be noted (Figure 16.43). Hyperglobulinemia due to a polyclonal gammopathy and plasma cell infiltration of tissues may also occur (Figure 16.44). The presence of intermediate-sized lymphocytes characterized by abundant pale blue cytoplasm with or without granules suggests T-cell stimulation (Figure 16.45). Maximum lymphocytosis in extreme immune reactions is usually <15,000/μL in dogs and <20,000/μL in cats.

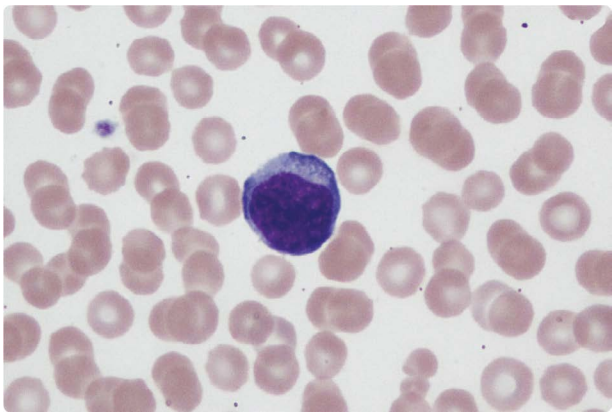


FIGURE 16.43 A reactive lymphocyte with a moderate amount of deeply basophilic cytoplasm and a perinuclear pale zone (Golgi apparatus).

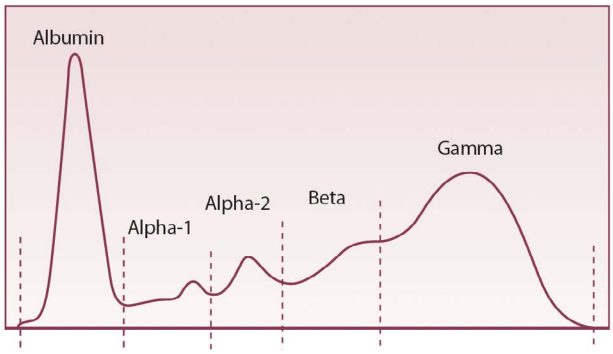


FIGURE 16.44 Serum protein electrophoretic tracing with a broad peak in the gamma region, indicating the presence of a polyclonal gammopathy in a case of canine ehrlichiosis.

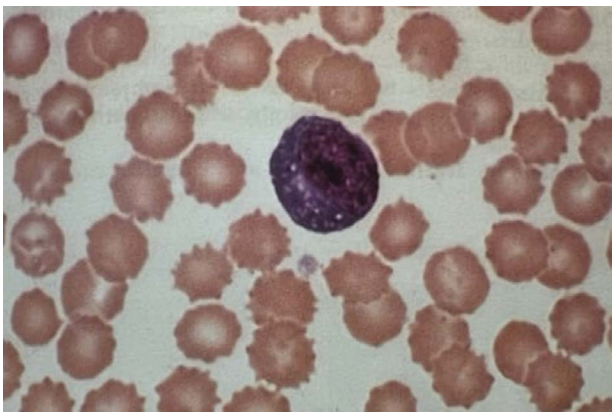


FIGURE 16.45 Intermediate-size lymphocytes.

Management

Treatment should be aimed at the underlying cause.

HYPOADRENOCORTICISM

See also Chapter 12.

Definition/Overview

Glucocorticoids (e.g., cortisol) and mineralocorticoids (e.g., aldosterone) are hormones produced by the adrenal cortex. Deficient production of these hormones leads to hypoadrenocorticism. Lymphocytosis is present in 10%–20% of dogs with hypoadrenocorticism.

Etiology

Hypoadrenocorticism in dogs is typically a result of immune-mediated destruction of the adrenal cortex. Pituitary disease causing ACTH deficiency is uncommon.

Pathophysiology

Corticosteroids cause lymphocytes to leave the circulation and enter lymphoid tissues. A lack of glucocorticoids inhibits this redistribution and allows lymphocyte numbers to increase in the circulation.

Clinical Presentation

See Chapter 11.

Differential Diagnosis

Physiologic lymphocytosis, chronic inflammation, and lymphoid leukemia.

Diagnosis

Lack of a stress leukogram in a visibly ill dog is the most consistent hematologic abnormality. See Chapter 11 for diagnosis.

Management

See Chapter 11.

MONOCYTOSIS

Monocytosis is defined as a blood monocyte concentration above the upper reference interval, generally >1,350/µL in the dog and >850/µL in the cat. It most frequently results from an increased demand for monocytes and tissue macrophages, which function in the defense against infectious agents, phagocytosis of damaged cells and debris, and secretion of many important biologically active molecules. Monocytes are not stored in the bone marrow during production but are immediately released. However, they may marginate in blood vessels for short periods of time or enter tissues from the circulating pool. Monocytes entering the tissues differentiate into macrophages, which can persist for days to months. Myeloid leukemia should be considered when monocyte counts exceed 15,000/µL or immature monocytoid forms are predominant.

CORTICOSTEROID-INDUCED MONOCYTOSIS

See corticosteroid-induced neutrophilia and monocytosis.

CHRONIC INFLAMMATORY MONOCYTOSIS

Definition/Overview

Monocytosis may occur with acute or chronic inflammation. However, the monocytosis associated with acute conditions is secondary to stress, whereas chronic inflammatory monocytosis results from monocytic hyperplasia.

Etiology

Inflammatory diseases that cause a high demand for tissue macrophages may produce monocytosis. These include immune-mediated disorders, tissue necrosis, foreign body reactions, and mycobacterial or fungal infections.

Pathophysiology

Inflammatory conditions produce cytokines, such as GM-CSF, macrophage colony-stimulating factor, and IL-3, which stimulates marrow production of monocytes.

Clinical Presentation

Signs will reflect the underlying inflammatory condition.

Differential Diagnosis

Corticosteroid-induced monocytosis, myeloid leukemia.

Diagnosis

Other hematologic abnormalities with chronic inflammation may include neutrophilia, neutrophil left shifting, toxic neutrophils, and lymphocytosis.

Management

Treatment is aimed at the inciting cause.

MASTOCYTEMIA

Mast cell precursors are produced in the bone marrow as nongranular mononuclear cells. They travel through peripheral blood to complete their maturation in solid tissues. As such, mast cell precursors cannot be distinguished from other mononuclear cells in blood. Mastocytemia is, therefore, defined as the presence of mast cells in peripheral blood, since the observance of any mast cells in blood is abnormal. Hematology analyzers cannot identify mast cells, so blood smear evaluation is imperative to identify mastocytemia. Mast cells are identified by the presence of purple cytoplasmic granules and a round nucleus (Figure 16.46) and should be distinguished from basophils, which have segmented nuclei. Methanolic Romanowsky stains are preferable to aqueous Romanowsky stains for identification of mast cells, since their granules are soluble in the latter stains and may not be visible. Mastocytemia typically indicates disseminated mast cell neoplasia (systemic mastocytosis) in cats, but most dogs with mastocytemia have disease other than mast cell neoplasia. Feline mast cell neoplasms often exhibit erythrophagocytosis.

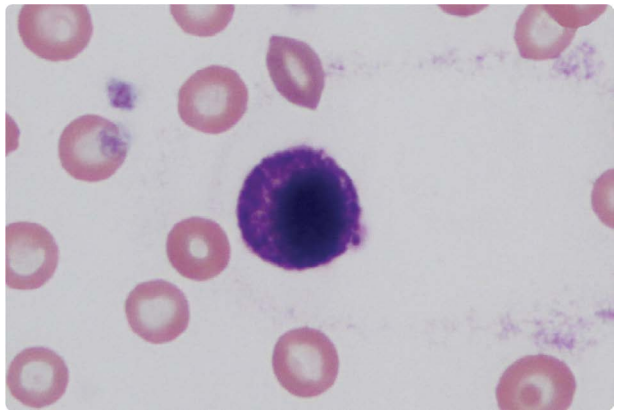


FIGURE 16.46 Mast cells are identified by dark purple cytoplasmic granules and a round nucleus.

Note that when present, mast cells tend to localize within the feathered edge of the blood smear.

REACTIVE MASTOCYTEMIA

Definition/Overview

Nonneoplastic conditions that present with mast cells in blood are termed mastocytemia.

Etiology

Mastocytemia in dogs is associated with inflammatory disease (parvovirus enteritis, hypersensitivities, and acute pancreatitis), regenerative anemia, neoplasms other than mast cell tumors, and trauma.

Pathophysiology

It is suggested that inflamed tissues, such as the GI tract or skin, may release these mast cells more readily than normal.

Clinical Presentation

Signs are dependent on the underlying disorder.

Differential Diagnosis

Mast cell neoplasia.

Diagnosis

History, physical examination, diagnostic imaging, and tissue biopsies are necessary to rule out mast cell neoplasia.

TABLE 16.13 Causes of lymphopenia

Lymphopenia
Corticosteroids – Stress – Cushing's syndrome – Glucocorticoid administration
Acute inflammation
Lymph loss – Gastrointestinal disease – Repeated drainage of chylous effusion
Lymphoid atrophy, hypoplasia, or aplasia – Immunosuppressive drugs – Generalized lymphadenopathy – Viruses (CDV, FeLV, FIV, parvoviruses) – Whole body irradiation – Severe combined immunodeficiency

Management

Treatment will reflect the underlying condition.

LEUKOPENIA

Leukopenia is a decreased concentration of all WBCs combined. Leukopenia may be due to decreases in neutrophils or lymphocytes. Because of their normally low concentrations in blood, decreases in monocytes, eosinophils, or basophils tend not to cause leukopenia. Monocytopenia and basopenia are not clinically significant in dogs and cats. Causes of eosinopenia and lymphopenia are listed in Tables 16.12 and 16.13.

NEUTROPENIA

Neutropenia is decreased blood neutrophils, often <3,000/μL in the dog and <2,500/μL in the cat. It may result from excessive tissue demands, redistribution within the vasculature, peripheral destruction, or decreased production (e.g., chemotherapy). Some breeds, such as Greyhound, have a lower neutrophil count, and breed-specific interval is required to interpret their CBC.

Note that patients with neutrophil concentrations <1,000/μL are at risk for secondary, life-threatening infection, termed neutropenic sepsis. Prophylactic administration of broad-spectrum antibiotics should be considered in these cases.

INFLAMMATORY NEUTROPENIA

Definition/Overview

Tissue utilization of neutrophils exceeds bone marrow production of neutrophils during times of severe inflammation.

Etiology

Causes of severe inflammation are typically infectious and include Gram-negative septicemia, severe enteritis, systemic mycoses, and systemic protozoal infections.

Pathophysiology

Neutrophil migration into inflamed tissues exceeds the release of neutrophils from the bone marrow.

Clinical Presentation

Signs are often indicative of infectious disease, including anorexia, pyrexia, and lethargy. Additional signs are dependent on the affected tissues or organs. If the neutropenia is severe, pyrexia might not be present.

Differential Diagnosis

Myelosuppression, endotoxemia, immune-mediated neutropenia, hemophagocytic syndrome, and cyclic hematopoiesis.

Diagnosis

Diagnosis is based on history, complete physical examination, and tests for infectious diseases. The presence of a left shift or neutrophil toxicity supports inflammation, but a mild left shift or slight toxicity may be seen with other causes of neutropenia. Sequential evaluation of the leukogram should exclude cyclic or transient neutropenia. If the neutropenia is persistent or bone marrow pathology is of concern, then cytology or histopathology of bone marrow should be considered.

Management

Treatment is directed at the inciting cause.

REDISTRIBUTION NEUTROPENIA

Definition/Overview

Increased margination of circulating neutrophils can result in neutropenia.

Etiology

Endotoxins from Gram-negative sepsis produce a transient neutropenia.

Pathophysiology

After a single exposure to endotoxin, neutrophils rapidly shift from the circulating pool to the marginal pool for 1–3 hours. The neutropenia is short lived since endotoxins also stimulate release of neutrophils from the bone marrow and neutropoiesis within the bone marrow.

Clinical Presentation

Signs of Gram-negative infection include pyrexia, anorexia, and lethargy. However, given the peracute time frame for the neutropenia, redistribution neutropenia is often no longer present on presentation of the animal.

Differential Diagnosis

Myelosuppression, severe inflammation, immune-mediated neutropenia, hemophagocytic syndrome, and cyclic hematopoiesis.

Diagnosis

Diagnosis is based on history, complete physical examination, tests for infectious diseases, and cytology or histopathology of bone marrow. Sequential evaluation of the leukogram may reveal a normal or increased neutrophil concentration with or without signs of inflammation (e.g., left shift, neutrophil toxicity).

Management

Treatment for sepsis involves appropriate antibiotics.

PERIPHERAL DESTRUCTION NEUTROPENIA

Definition/Overview

Neutropenia may be due to immune targeting of neutrophil antigens (immune-mediated neutropenia) or nonspecific destruction of hematopoietic cells by dysregulated phagocytes (hemophagocytic syndrome).

Etiology

Drugs responsible for suspected immune-mediated neutropenia include antithyroid drugs (e.g., thiouracil, methimazole) and cephalosporins. Hemophagocytic syndrome is caused by inappropriate activation of normal macrophages secondary to infectious (canine parvovirus, bacterial sepsis, ehrlichiosis, blastomycosis, and Lyme disease), neoplastic (lymphoid neoplasia and myelodysplastic syndrome), or immune-mediated (SLE) disease. Idiopathic hemophagocytic syndrome has also been described.

Pathophysiology

The disorder may involve antibody directed against surface antigens on the cell itself or antibody directed toward drug antigens attached to the neutrophil as an "innocent bystander." Autoantibodies may also produce defects in neutrophil function.

Clinical Presentation

Signs may reflect those of immune-mediated, infectious, or neoplastic diseases.

Differential Diagnosis

Other immune-mediated hematologic disorders, SLE, immune-mediated arthritis, neoplasia, drug-induced myelosuppression, severe systemic inflammation, endotoxemia, hypersplenism, cyclic hematopoiesis, and myelophthisis.

Diagnosis

Diagnosis of immune-mediated neutropenia requires detection of antineutrophil antibodies on the cells or in serum. However, such assays are not widely available and are not specific for immune-mediated neutropenia. Immune-mediated neutropenia is more commonly diagnosed by excluding other causes of neutropenia and demonstrating improvement with appropriate therapy. Hemophagocytic syndrome may cause bicytopenia or pancytopenia. Cytologic or histologic tissue biopsies reveal many phagocytic macrophages. An underlying disease may be identified with a complete diagnostic workup, including physical examination, thoracic and abdominal imaging, and fluid and tissue biopsies.

Management

Immune-mediated neutropenia may be resolved by stopping administration of the inciting drug and commencing immunosuppressive therapy. Treatment for hemophagocytic syndrome is directed at the inciting disease.

DECREASED PRODUCTION NEUTROPENIA

Definition/Overview

Decreased neutrophil production may occur with certain drugs, infectious agents, myelophthisis, and irradiation that affect the bone marrow. Trapped neutrophil syndrome (TNS) is an autosomal recessive disease reported in Border Collies that causes neutropenia.

Etiology

Drugs that cause neutropenia due to myelotoxicity include estrogen, chloramphenicol, trimethoprim–sulfadiazine, griseofulvin, and chemotherapeutic agents. Antineoplastic agents that can cause neutropenia include cyclophosphamide, chlorambucil, busulfan, melphalan, cisplatin, cytosine arabinoside, methotrexate, mitoxantrone, doxorubicin, and hydroxyurea. Cephalosporins and certain nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with myelotoxicity. Reduced granulopoiesis may be associated with such viruses as FeLV, FIP virus, feline panleukopenia virus, and canine parvovirus. *E. canis* infection, when severe, may also cause bone marrow atrophy. Leukemia, myelitis (e.g., systemic histoplasmosis), or idiopathic myelofibrosis may cause myelophthisis. TNS is caused by a mutation in the gene VPS 13B.

Pathophysiology

Normal hematopoietic precursors may be crowded out with myelophthisis. Irradiation, drugs, and infectious agents destroy rapidly dividing precursor cells. Aplastic anemia and myelofibrosis may be nonassociative.

Note that if there is generalized marrow injury, cells with short circulating life spans decrease prior to those with longer life spans. Neutrophils circulate for hours, platelets circulate for days to weeks, and erythrocytes circulate for months. Therefore, neutropenia often precedes other cytopenias, but moderate-to-marked anemia is appreciated for months after the initial insult.

Clinical Presentation

Signs may include those due to severe neutropenia (severe bacterial infections or sepsis) with or without signs of marked thrombocytopenia (petechiae and hemorrhage) and nonregenerative anemia (lethargy, pale mucous membranes). Other signs reflect the animal's underlying condition. Border Collies with TNS often present with pyrexia and joint effusion. They also have a ferret-like skull (narrow and elongated).

Differential Diagnosis

Cyclic hematopoiesis, severe systemic inflammation, endotoxemia, hemophagocytic syndrome, and immune-mediated neutropenia.

Diagnosis

Diagnosis of the underlying disorder may require a thorough history and physical examination, blood tests for viral disease and organ health (CBC, serum chemistry, and urinalysis), diagnostic imaging, tissue biopsy, bone marrow evaluation, and bacterial culture. Genetic testing is available for TNS. Evaluation of the bone marrow reveals myeloid hyperplasia.

Management

Treatment requires cessation of myelotoxic drugs and supportive care, particularly antibiotics. The use of recombinant canine G-CSF (5 µg/kg SC q.24 h.) has shown promise in reducing the severity of drug-induced myelosuppression in the dog and the cat. Specific treatment is dependent upon the underlying disorder. Dog with TNS often respond initially to antibiotic and prednisolone, but relapses are common.

CYCLIC HEMATOPOIESIS

Definition/Overview

Congenital cyclic hematopoiesis is an inherited autosomal recessive disorder of gray Collies characterized by periodic fluctuations in neutrophils and, to a lesser extent, in monocytes, platelets, and reticulocytes. Nonhereditary cyclic hematopoiesis may involve other breeds of dogs. Cyclic neutropenia in cats has been associated with FeLV infection.

Etiology

The molecular basis of the genetic defect in dogs is unknown but seems to be associated with a defect in the intracellular trafficking of neutrophil elastase. FeLV infection is associated with cyclic neutropenia in cats.

Pathophysiology

In gray Collies, cyclic differentiation of stem cells toward committed lineages results in 11- to 14-day cycles of erythrocyte, neutrophil, monocyte, and platelet production. Decreases in blood neutrophil concentrations are most prevalent given their shorter circulating life spans. Dogs with nonhereditary cyclic hematopoiesis have variable cycle lengths from 10 to 29 days. Cats infected with FeLV have neutrophil cycle lengths reported to range from 8 to 16 days.

Clinical Presentation

Clinical signs during neutropenic episodes include lethargy, pyrexia, anorexia, arthritis, keratitis, diarrhea, and respiratory infections. Affected Collies present with other distinctive features such as abnormal hair pigmentation, bilateral scleral ectasia, enteropathy, and gonadal hypoplasia.

Differential Diagnosis

Severe systemic inflammation, noncyclic myelosuppression from drugs, infections, or irradiation, immune-mediated neutropenia, hemophagocytic syndrome, and endotoxemia.

Diagnosis

Diagnosis is based on history, signalment, clinical signs, and cyclic decreases in cell counts. Carrier animals can be determined only by test mating. All affected dogs have a diluted coat color. Amyloidosis is commonly found in many tissues.

Management

Antibiotics and supportive care are necessary during neutropenic cycles. Experimental treatment for dogs with the "gray Collie syndrome" involves bone marrow transplantation and administration of lithium carbonate (21–26 mg/kg/day) or recombinant canine G-CSF (5 µg/kg/day). Cyclic neutropenia in FeLV-infected cats can respond to prednisolone.

Prognosis

Most affected dogs die within 6 months following chronic recurrent infection.

SEVERE COMBINED IMMUNODEFICIENCY

Definition/Overview

Congenital defects in lymphocyte development result in lymphoid hypoplasia or aplasia and subsequent marked lymphopenia and hypoglobulinemia. The disease is rare but has been documented in Basset Hounds, Cardigan Welsh Corgis, Jack Russell Terriers, and Frisian Water Dogs.

Etiology

The deficiency in Basset Hounds and Cardigan Welsh Corgis is X-linked due to separate mutations in an IL receptor. An autosomal recessive mode of inheritance occurs in Jack Russell Terriers due to mutated

DNA-dependent protein kinase. Frisian Water Dogs have a mutation of RAG1.

Pathophysiology

Defective lymphocyte development results in immune incompetence, which becomes fatal when maternal antibodies wane. There is depressed T-cell function, low IgG and IgA concentrations, and variable IgM concentrations. Affected animals usually die from infectious disease.

Clinical Presentation

Puppies may be small, thin, and inactive. Signs of recurrent infections occur as bacterial pyoderma and otitis externa within the first 6 weeks of life. Mucopurulent ocular and nasal discharges are common. Lymphadenopathy is not present. Death may occur within 50 hours of administering a modified live vaccine.

Differential Diagnosis

Systemic infections, PLE, and exogenous corticosteroids.

Diagnosis

Diagnosis is based on the history of high morbidity and mortality in puppies from the same breeding pair of dogs. Affected puppies have lymphopenia, hypoglobulinemia, and depressed T-lymphocyte function. Necropsy reveals profound lymphoid hypoplasia.

Management

Antibiotics may be administered, but death due to infectious disease is expected. Bone marrow transplantation is the only means to regain immune competence. Carrier animals should not be bred.

Prognosis

Mortality occurs when maternal antibodies wane at 8–14 weeks of age.

ABNORMAL NUCLEAR MORPHOLOGY

INFLAMMATORY LEFT SHIFT

Definition/Overview

A left shift is defined as an increase in immature neutrophils over the reference interval. Immature neutrophils include band neutrophils (bands), metamyelocytes, myelocytes, and promyelocytes. Left shifts are further classified as "regenerative" if there is neutrophilia and segmented neutrophils outnumber immature neutrophils or "degenerative" if immature neutrophils outnumber segmented neutrophils or if there is a decreased neutrophil concentration (neutropenia) with a left shift. Regenerative left shifts are a proper marrow response during inflammation, but degenerative left shifts often indicate more severe inflammatory states, such as sepsis.

Etiology

A left shift is usually caused by a systemic inflammatory lesion, such as in pyometra, pneumonia, large neoplasm, or immune-mediated disorders (e.g., IMHA). A degenerative left shift is typically a result of severe infectious disease.

Pathophysiology

Inflammatory cytokines (e.g., IL-1, IL-6, IL-8, GM-CSF, and G-CSF) enhance neutrophil release from the bone marrow into blood. Release is sequential in that bands enter the blood before metamyelocytes and earlier stages. With continued inflammation, cytokines stimulate neutrophil production, taking 5–7 days for a myeloblast to mature into a segmented form. A left shift may accompany acute or chronic inflammation.

Clinical Presentation

Signs reflect the affected organ system.

Differential Diagnosis

Pelger–Huët anomaly, myelodysplastic syndrome, granulocytic leukemia.

Diagnosis

Blood smear evaluation shows increased numbers of immature neutrophils, particularly band neutrophils (Figure 16.47). Sites of inflammation can be determined by history, physical examination, biochemical profile, urinalysis, diagnostic imaging, and sampling.

Management

Treatment is directed toward the underlying cause.

Prognosis

Animals with degenerative left shifts tend to have poorer outcomes relative to those with regenerative left

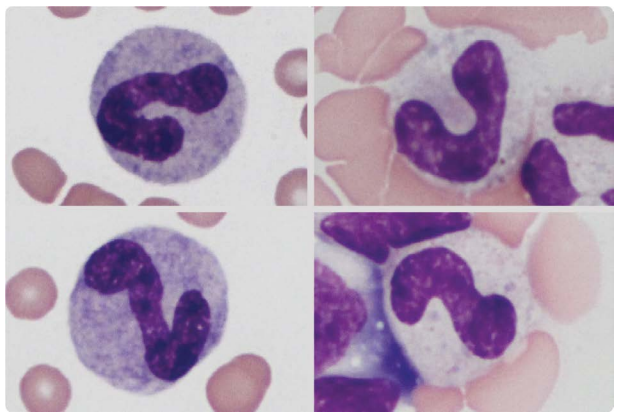


FIGURE 16.47 Band neutrophils from a cat (left) and dog (right) lack nuclear segments and have slightly open chromatin. The two feline neutrophils display cytoplasmic basophilia (toxicity).

shifts. Worsening of the left shift is a negative prognostic indicator, whereas dampening or resolution of a left shift indicates clinical improvement.

PELGER–HUËT ANOMALY

Definition/Overview

This nonneoplastic developmental abnormality is an inherited disorder in dogs and cats involving all granulocytes.

Etiology

Pelger–Huët anomaly is inherited in an autosomal dominant manner due to a mutated lamin B receptor. Affected dog breeds include, but are not exclusive to, Australian Heelers, Australian Shepherd Dogs, Basenjis, Border Collies, Cocker Spaniels, Coonhounds, German Shepherd Dogs, and Samoyeds. It has been reported in one family of Domestic Shorthair cats.

Pathophysiology

This condition is suggested to be a stem cell defect, since megakaryocytes may also appear hyposegmented.

Clinical Presentation

Chondrodysplasia has been recognized in a stillborn homozygous kitten. Heterozygote kittens may be stillborn or viable. Heterozygote dogs do not present with signs of infection.

Differential Diagnosis

Inflammatory left shift, myelodysplastic syndrome, and granulocytic leukemia.

Diagnosis

Diagnosis is based on the appearance of blood leukocytes that have mature chromatin (condensed, coarse, and patchy) and nuclear shapes that reflect immaturity (band, indented, or round) (Figure 16.48). The cytoplasm undergoes normal maturation. Pelger–Huët anomaly is frequently found during routine preoperative screening.

Note that the significance in diagnosing Pelger–Huët anomaly is that it is not misinterpreted as a degenerative left shift due to severe inflammation.

Management/Prognosis

No treatment is necessary. No leukocyte dysfunction.

Prognosis

Dogs: No leukocyte dysfunction. Cats: The homozygous condition is lethal and may be associated with increased susceptibility to infection.

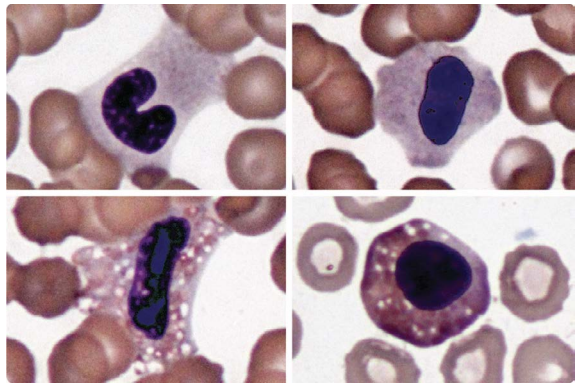


FIGURE 16.48 Nuclei of neutrophils (top) and eosinophils (bottom) fail to segment with Pelger–Huët anomaly. However, the chromatin pattern is dense, indicating nuclear maturity.

HYPERSEGMENTATION

Definition/Overview

Hypersegmentation is defined as a neutrophil with more than five nuclear segments, and it indicates aging or dysplasia.

Etiology

Hypersegmentation is seen with delayed sample analysis, glucocorticoid administration, hyperadrenocorticism, hyperthermia (e.g., heatstroke, malignant hyperthermia), CLAD, dysplastic processes (e.g., Poodle macrocytosis, vitamin B12 deficiency), and myeloid leukemias.

Pathophysiology

Hypersegmentation occurs as part of the normal aging process and reflects a prolonged transit time in blood. Dysplastic and neoplastic processes are due to abnormal neutrophil maturation.

Clinical Presentation

Signs reflect the underlying condition.

Differential Diagnosis

Hyperadrenocorticism, exogenous glucocorticoids, heatstroke, malignant hyperthermia, CLAD, Poodle macrocytosis, vitamin B12 (cobalamin) deficiency, myeloid leukemia.

Diagnosis

Affected neutrophils present with five or more distinct nuclear lobes on blood smears (Figure 16.49). Blood smears should be made at the time of sample acquisition to prevent in-vitro neutrophil aging and hypersegmentation.

Management

Treatment is directed toward the underlying cause.



FIGURE 16.49 Hypersegmented neutrophils in a dog with canine leukocyte adhesion deficiency.

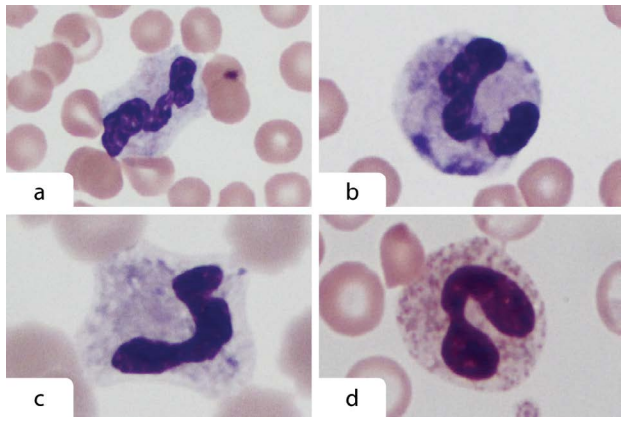


FIGURE 16.50 Signs of neutrophil toxic change include diffuse cytoplasmic basophilia **(a–c)**, cytoplasmic aggregates of basophilia termed Döhle bodies **(b, c)**, foamy cytoplasm **(b, c)**, and prominent pink primary granules or toxic granulation **(d)**.

ABNORMAL CYTOPLASMIC MORPHOLOGY

NEUTROPHIL TOXICITY

Definition/Overview

In addition to a left shift, neutrophils may exhibit toxic change during times of inflammation.

Etiology

Antibiotic responsiveness suggests a bacterial cause, but toxic change may also be found in cases of sterile inflammation or drug toxicity.

Pathophysiology

Toxic change is a result of a shortened maturation time or direct toxic injury to developing neutrophils. Döhle bodies represent lamellar aggregates of rough endoplasmic reticulum. Persistent ribosomes cause diffuse cytoplasmic basophilia. Foamy cytoplasmic vacuolation occurs with dispersed organelles. Enhanced primary granule staining contributes to the fine red granules known as *toxic granulation*.

Clinical Presentation

Signs reflect the site of inflammation or underlying condition.

Differential Diagnosis

EDTA storage artifact, lysosomal storage disease, granulation syndrome in Birman cats, Chédiak–Higashi syndrome in cats.

Diagnosis

Neutrophil toxicity is diagnosed via blood smear evaluation (Figure 16.50a–d). Tests for specific infectious agents and immune-mediated disorders may be indicated.

Management

Treatment is directed toward the underlying illness.

Prognosis

Reduction of toxic changes implies a favorable prognostic indicator.

LYSOSOMAL STORAGE DISEASES

Definition/Overview

Lysosomal storage diseases are a group of inheritable disorders caused by enzyme deficiencies that result in intralysosomal accumulations of undigested molecules. All these diseases are rare in dogs and cats.

Etiology

Lysosomal storage diseases produce granules or vacuoles in leukocytes include fucosidosis, GM1 gangliosidosis, GM2 gangliosidosis, alpha-mannosidosis, mucopolysaccharidosis (MPS) I, MPS IIIB, MPS VI, and MPS VII.

Pathophysiology

As lysosomes become engorged with degradation material, they compress surrounding organelles and impair cellular respiration and function. Waste products build up and damage the cell.

Clinical Presentation

Signs will vary with the type of enzyme deficiency but may include failure to thrive, growth retardation, seizures, ataxia, corneal clouding, hepatosplenomegaly, cardiac murmurs, renal dysfunction, and skeletal abnormalities.

Differential Diagnosis

EDTA storage artifact, toxic granulation, granulation syndrome in Birman cats, Chédiak–Higashi syndrome in cats.

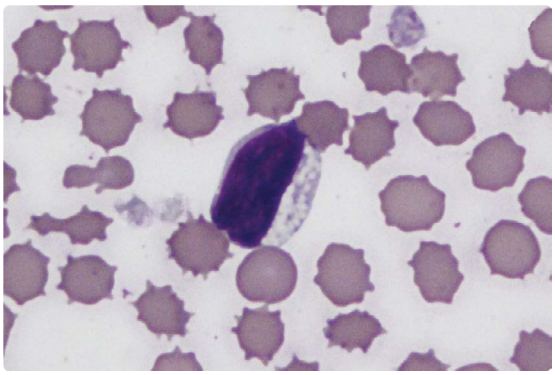


FIGURE 16.51 Vacuolated lymphocyte from a cat with lysosomal storage disease, consistent with mannosidosis.

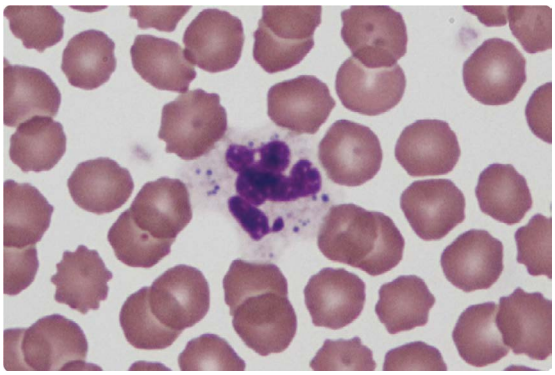


FIGURE 16.52 Granulated neutrophils in a dog with mucopolysaccharidosis I.

Diagnosis

Cytoplasmic granules or vacuoles are present in leukocytes depending on the type of enzyme deficiency (Figures 16.51 and 16.52). A urine spot test is used to screen for glycosaminoglycans, while a cell enzyme activity test is diagnostic. DNA-based tests are available for some diseases with known mutations.

Management

Experimentally, bone marrow transplantation has been used to treat some of these disorders. Affected animals should not be bred.

Prognosis

Without bone marrow transplantation, these diseases are progressive and fatal.

ABNORMAL NEUTROPHIL GRANULATION IN BIRMAN CATS

Definition/Overview

Abnormal neutrophil granulation is a genetic anomaly recognized in some Birman cats without associated clinical disease.

Etiology

Autosomal recessive disorder.

Pathophysiology

Neutrophil ultrastructure and function are normal.

Clinical Presentation

No clinical signs.

Differential Diagnosis

Toxic granulation, lysosomal storage disease.

Diagnosis

Diagnosis is based on the presence of fine, pink granules within the cytoplasm of neutrophils (Figure 16.53).

Management and Prognosis

No treatment is required.

FELINE CHÉDIAK–HIGASHI SYNDROME

Definition/Overview

Feline Chédiak–Higashi syndrome is a rare, inherited disorder of blue-smoke Persian cats with yellow eye color.

Etiology

The disorder is inherited as an autosomal recessive trait and caused by a mutant lysosomal docking protein, LYST.

Pathophysiology

Granule defects are present in leukocytes, melanocytes, and platelets, leading to abnormal and enlarged lysosomal granules in leukocytes, decreased neutrophil chemotaxis, bleeding diathesis, and oculocutaneous color dilution.

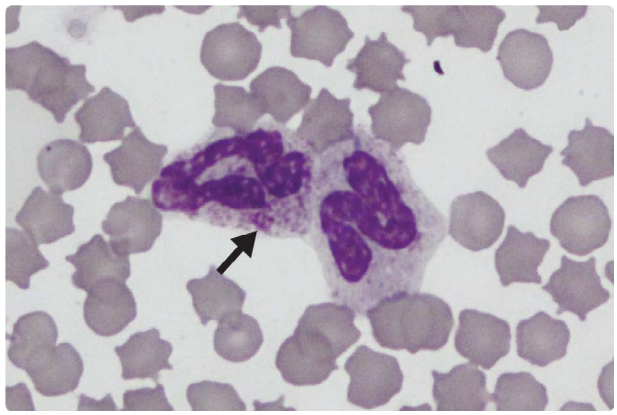


FIGURE 16.53 Fine pink granules (arrow) in a neutrophil from a Birman cat.

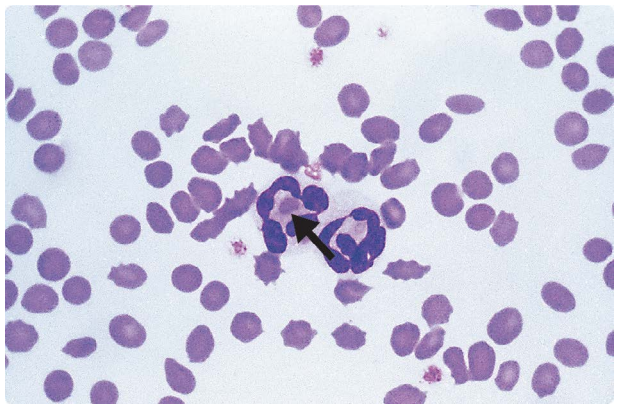


FIGURE 16.54 Feline Chédiak–Higashi syndrome presenting as large lavender cytoplasmic structures (arrow) within granulocytes. (*Courtesy of J. Harvey*.)

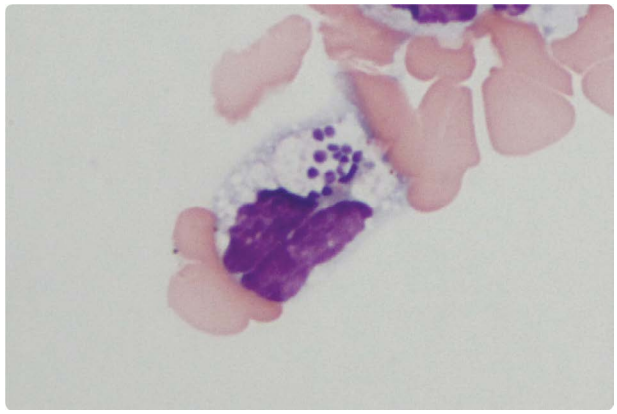


FIGURE 16.55 Blood smear from a dog with sepsis showing bacteria within a toxic neutrophil. Culture of the blood, liver, and lungs grew *Salmonella choleraesuis* subspecies *arizonae*.

Clinical Presentation

Affected cats may be photophobic with cataract formation. There is increased bleeding time due to platelet granule defects.

Differential Diagnosis

Cytoplasmic toxicity, lysosomal storage disease.

Diagnosis

Diagnosis is based on signalment, physical examination, and characteristic large, pink to magenta neutrophil granules (Figure 16.54) that are positive with peroxidase and Sudan black B stains. Neutropenia may also be present.

Management

Supportive therapy (e.g., blood transfusions, antibiotics) as needed. Neutrophil chemotaxis has been reported to improve following administration of canine G-CSF in cats. Neutrophil and platelet function can be restored with bone marrow transplantation.

Prognosis

Life expectancy can exceed 10 years.

INFECTIOUS AGENTS

See also Chapter 21.

A variety of infectious agents may be found within leukocytes during examination of the blood or bone marrow. These include bacterial (Figure 16.55), rickettsial, protozoal, and fungal organisms (Figure 16.56a–f), or canine distemper virus (CDV) inclusions (Figure 16.32). See further section for description of common findings on blood smear review. The reader is referred to Chapter 21 for further details.

EHRLICHIOSIS

Acute disease in dogs and cats most consistently causes thrombocytopenia and mild nonregenerative anemia. With chronic canine infection, hyperglobulinemia, pancytopenia, or granular lymphocytosis (Figure 16.42) is possible. The gammopathy is typically polyclonal but is rarely monoclonal (Figure 16.44). Blood smear evaluation may show intracytoplasmic bacterial colonies (morulae) in mononuclear cells (*E. canis* and *E. chaffeensis*) or granulocytes (*E. ewingii* or *A. phagocytophilum*) during acute infection (Figure 16.56c).

HEPATOZOONOSIS

Hepatozoon canis is classically diagnosed by blood smear evaluation, as gamonts are plentiful within blood neutrophils (Figure 16.56d). Blood PCR tests are also available. *Hepatozoon americanum* should be suspected based on clinical signs, marked neutrophilia (leukemoid response). In contrast to *H. canis*, only rare gamonts are present in the blood (<0.1% of WBCs).

LEISHMANIASIS

Characteristic organisms are present in macrophages of the bone marrow, lymph nodes, spleen, liver, kidney, and skin (Figure 16.56e). Amastigotes are recognized by the presence of a small purple nucleus and a perpendicular rod-shaped kinetoplast in Romanowsky-stained smears.

HISTOPLASMOSIS

Routine laboratory tests are not specific for histoplasmosis but may reflect the extent of systemic involvement. Some cats may develop pancytopenia due to marrow infection. Hypercalcemia associated with granulomatous disease is infrequent. Yeast forms are found within monocytes/

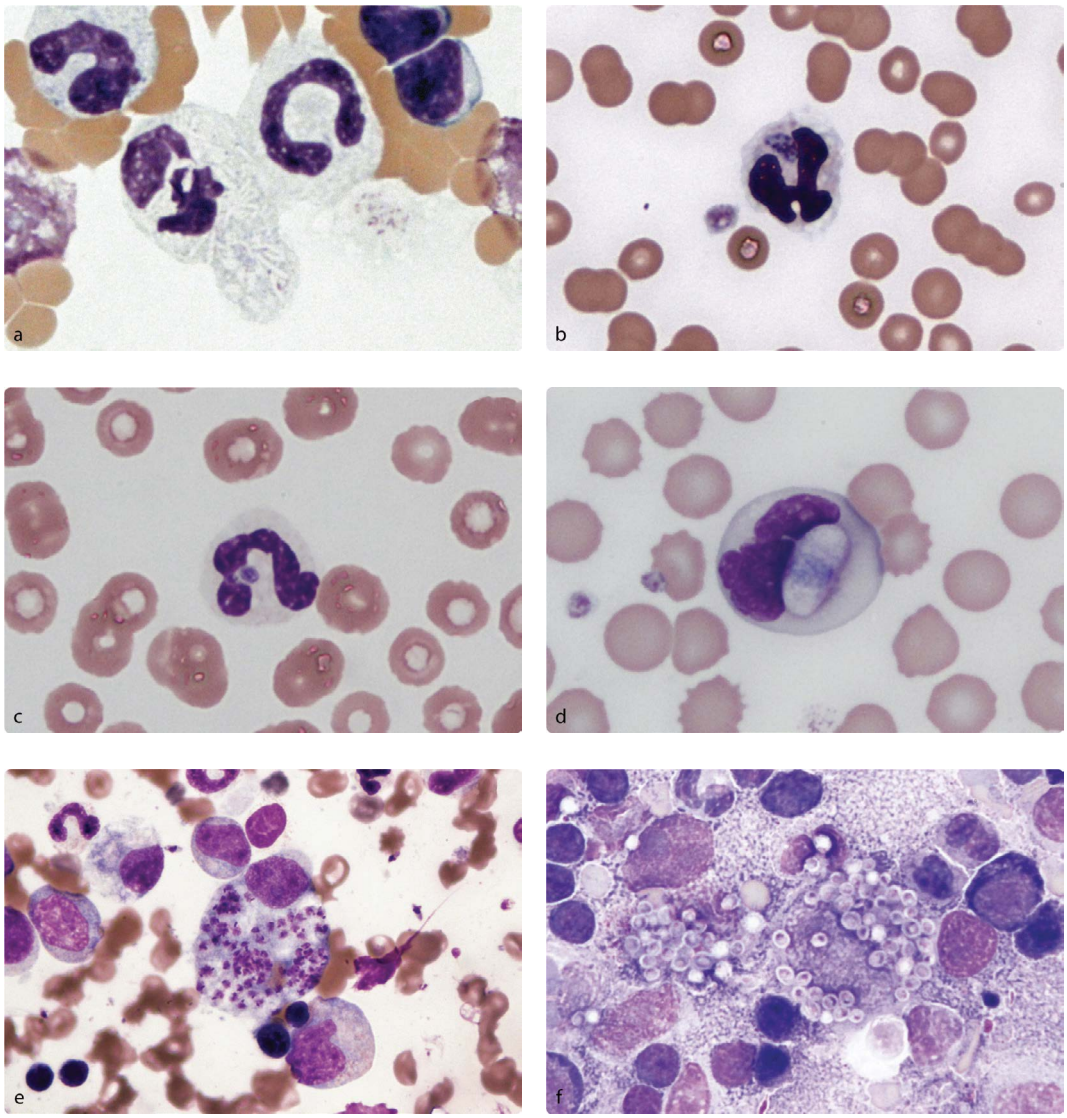


FIGURE 16.56 Leukocyte parasites in cats and dogs. **(a)** Circulating feline neutrophils with multiple intracytoplasmic nonstaining linear shapes identified as *Mycobacterium* spp. **(b)** Blood neutrophil containing a tachyzoite in a cat with toxoplasmosis. **(c)** *Ehrlichia ewingii* morula in a canine neutrophil. **(d)** A large, ovoid, nonstaining *H. canis* gamont within a neutrophil. **(e)** *Leishmania* amastigotes within a bone marrow macrophage from a dog. **(f)** Bone marrow smear from a cat with systemic histoplasmosis. There are numerous small, round to ovoid yeasts within two macrophages.

macrophages of the blood, bone marrow, lung, lymph node, liver, rectal scrapings, spleen, effusions, tracheal or bronchoalveolar washes, and, rarely, within cerebrospinal fluid (Figure 16.56e). The organism may also be found within neutrophils and, rarely, in eosinophils. They are oval structures measuring 2–4 microns and having a thin clear space or halo around them.

PLATELET DISORDERS (NONNEOPLASTIC)

Platelets are anucleate cells produced in the bone marrow from the cytoplasmic shearing of megakaryocytes. Platelets are a critical component of hemostasis and will, therefore, primarily be presented in the next chapter (Chapter 17). However, causes of nonneoplastic thrombocytosis and dysplasia are offered here.

REACTIVE THROMBOCYTOSIS

Definition/Overview

A nonneoplastic thrombocytosis is termed *reactive thrombocytosis*.

Etiology

Etiologies include exercise and epinephrine, inflammation, iron deficiency, recovery from thrombocytopenia, blood loss, nonhemic neoplasia, vincristine, vinblastine, splenectomy, and hyperadrenocorticism.

Pathophysiology

Exercise and epinephrine cause splenic smooth muscle contraction and increased blood flow, which leads to redistribution of platelets from the spleen and lungs into circulating blood. Other etiologies cause enhanced platelet production. For example, inflammatory cytokines, especially IL-6, stimulate thrombopoietin production and, subsequently, thrombopoiesis.

Clinical Presentation

Signs are dependent on the underlying disorder.

Differential Diagnosis

Essential thrombocythemia, primary myelofibrosis, PV.

Diagnosis

Diagnosis is based on an increased platelet concentration in the presence of an underlying cause for reactive thrombocytosis. Epinephrine release also causes erythrocytosis, neutrophilia, lymphocytosis, and hyperglycemia. Moderate-to-marked neutrophilia, a left shift, or the observation of toxic neutrophils supports inflammation. Blood loss is identified by anemia and decreases in albumin and globulin concentrations. Microcytic hypochromic nonregenerative or poorly regenerative anemia suggests iron deficiency. History and physical examination findings are also helpful. Persistent, marked thrombocytosis without an underlying etiology should raise concern for leukemia.

Management

Treatment is directed at the underlying cause.

MACROTHROMBOCYTOPENIA

Definition/Overview

Macrothrombocytopenia (thrombocytopenia with giant platelets) is an inherited disorder of Cavalier King Charles Spaniels, as well as Norfolk and Cairn Terriers, and in other breeds without hemorrhage or clinical signs. The giant platelets have diameters greater than those of RBCs.

Etiology

The disorder is caused by a mutant beta1-tubulin gene.

Pathophysiology

The mutant beta1-tubulin forms unstable dimers, which results in altered platelet formation and the release of large platelets. Small numbers of giant platelets result in a normal or near-normal total platelet mass in the blood.

Clinical Presentation

Macrothrombocytopenia is typically an incidental finding when the patient presents for routine evaluation or for other disease.

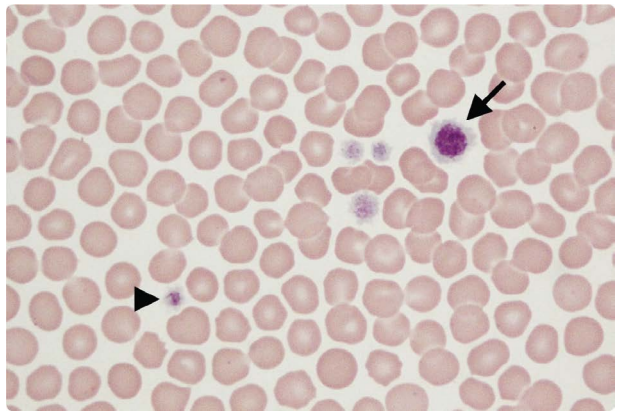


FIGURE 16.57 The platelets of Cavalier King Charles Spaniel dogs with macrothrombocytopenia range from normal (arrowhead) to giant (arrow) in size.

Differential Diagnosis

Immune-mediated thrombocytopenia, DIC, megakaryocytic leukemia.

Diagnosis

Diagnosis is based on the presence of thrombocytopenia and giant platelets in affected dogs (Figure 16.57). Median measurements in one study of platelets in Cavalier King Charles Spaniels compared with other breeds were 2.5–3.75 µm and 1.25–2.5 µm, respectively. The reduced platelet count is partially related to giant platelets being missed by automated hematology analyzers with small platelet size thresholds. Platelet counts measured by platelet mass (e.g., QBC hematology analyzer) better reflect the true platelet concentration. Studies indicate that male dogs have significantly lower platelet counts than females of the breed. A genetic test is available to confirm the diagnosis.

Management

Treatment is not warranted.

Prognosis

The disorder is not known to affect hemostasis.

DYSPLASTIC DISORDERS

Dysplastic disorders are characterized by developmental changes within the erythrocytes, granulocytes, and platelets. The etiology may be related to inheritable, infectious, drug-induced, and nutritional conditions. While dysplastic disorders often affect multiple hematopoietic lineages, abnormal growth of one cell line typically results in the patient's clinical manifestations. For this reason, select dysplastic disorders are included with the cell lineage that is chiefly deregulated. Disorders that primarily present as erythroid dysplasia include iron-deficiency anemia, FeLV infection, Poodle marrow dyscrasia, folate or cobalamin (vitamin B12)

deficiency, and lead poisoning. Manifestations of leukocyte dysplasias are Pelger–Huët anomaly, cyclic hematopoiesis of gray Collies, and leukocyte granule abnormalities. The most common platelet dysplastic disorders are macrothrombocytopenia of Cavalier King Charles Spaniels and vincristine-associated macrothrombocytes. Previously considered a preleukemic dysplasia, myelodysplastic syndrome is now considered a form of myeloid neoplasia and will be addressed in the corresponding section.

DRUG-INDUCED DYSPLASIA

Definition/Overview

Antibiotics and antineoplastic agents can produce reversible morphologic changes in blood cells.

Etiology

Drugs implicated are azathioprine, cyclophosphamide, cytosine arabinoside, vincristine, and chloramphenicol.

Pathophysiology

The drugs disrupt the normal production of erythroid cells within hours to days following administration. The mechanism is not related to folate deficiency.

Clinical Presentation

Signs will reflect the underlying conditions.

Differential Diagnosis

Myelodysplastic syndrome, acute myeloid leukemia, and nutrition-related dysplasia.

Diagnosis

Diagnosis is based on blood and bone marrow samples taken during routine post-treatment hematologic evaluations. Morphologic changes involve dyserythropoiesis characterized by macrocytosis, megaloblastoid changes, nuclear fragmentation, sideroblastosis, and siderocytosis. Folate concentrations are within normal limits.

Management

Normal morphology of hematopoietic cells occurs several days after cessation of drug therapy.

HEMATOPOIETIC MALIGNANCIES

Hematopoietic malignancies include neoplasms of lymphoid cells (lymphocytes and plasma cells), myeloid cells (erythrocytes, nonlymphoid leukocytes, and megakaryocytes), and uncommitted stem cells. Lymphoid neoplasms are more common than those of myeloid origin.

LYMPHOID NEOPLASIA

Lymphoid malignancies may originate from in any tissue. The most common sites include the lymph nodes, liver, spleen, bone marrow, alimentary tract, thymus, and skin. The term leukemia is used when neoplastic cells appear in blood or bone marrow and lymphoma when lymphoid neoplasia arises from other sites. However, this distinction can be challenging as lymphoma frequently involves the blood and bone marrow, and involvement of lymph nodes or other tissues is common in lymphoid leukemias. Lymphoid leukemia is further classified based on the maturity of the neoplastic cells. In acute lymphoid leukemia, immature (blast) cells predominate, whereas small mature lymphocytes predominate in chronic lymphocytic leukemia. A neoplasm of plasma cells arising from the bone marrow is called myeloma, whereas those in nonmarrow sites are referred to as plasmacytomas. The term myeloma-related disorder is sometimes used to refer to any plasma cell malignancy, especially in cats, as the clinical presentation in this species can vary from what is typically seen in dogs and people, and extramedullary origin is common. Lymphoid neoplasms, in descending frequency of occurrence, are lymphoma, plasmacytoma, myeloma, chronic lymphocytic leukemia, and acute lymphoblastic leukemia.

LYMPHOMA

Definition/Overview

Lymphoma (the preferred term over lymphosarcoma) is the most common hematopoietic tumor of dogs and cats. Multicentric disease is the most common presentation in dogs and usually involves the peripheral lymph nodes, spleen, and liver. Other sites of canine lymphoma include the alimentary tract, thymus, skin, and other extranodal locations in decreasing frequency. The most common anatomic location for lymphoma in cats is the alimentary tract. Thymic lymphoma is most common in young, FeLV-positive cats, while alimentary lymphoma is more common in older cats. Cats may also develop multicentric, renal, intranasal, laryngeal/tracheal, CNS, ocular, and cutaneous lymphoma.

Classification of Lymphoma

Lymphoma in dogs can be classified based on anatomic location, histologic subtype, and immunophenotype. Anatomic location has been discussed previously, though some specific sites warrant separate discussion. Primary hepatic and hepatosplenic lymphoma in dogs generally have a poor prognosis. Primary splenic lymphoma can have a better prognosis, but this may depend on the histologic subtype. Although rectal lymphoma in dogs is most often large cell/high grade, prognosis can be good with chemotherapy and appears much better than for other locations of high-grade/large-cell alimentary lymphoma.

TABLE 16.14 Most common canine lymphomas in decreasing frequency using the REAL/WHO system

REAL/WHO system
– Diffuse large B-cell lymphoma
– Peripheral T-cell lymphoma not otherwise specified
– T-zone lymphoma
– T-cell lymphoblastic lymphoma
– Marginal zone lymphoma

There are several histologic classification systems that have been applied to lymphoma in domestic animals. Using the Revised European American Lymphoma/World Health Organization (REAL/WHO) system, each subtype is classified as a distinct disease entity (Table 16.14). The National Cancer Institute Working Formulation (WF) and the Kiel systems categorize lymphomas by grade (low, intermediate, or high) and other features rather than specific diseases. Low-grade lymphomas are generally composed of small cells, have a low mitotic rate, and indolent progression. High-grade lymphomas have a high mitotic rate, usually are composed of intermediate to large cells, and progress rapidly.

In clinical practice, full REAL/WHO subtyping may not be performed in every case, and strong evidence to recommend different treatment for specific subtypes in many cases does not exist. However, determining whether lymphoma in a dog is likely to be aggressive or indolent based on factors such as cytology and/or histopathology, immunophenotype, and anatomic location is imperative in determining the most appropriate treatment.

In cats, different anatomic locations of lymphoma are often associated with certain histologies and immunophenotype, and to some degree biological behavior can be predicted based on the location. For example, nasal lymphoma tends to be quite treatment responsive and has a fair-to-good prognosis with treatment, whereas renal lymphoma is often aggressive with a poor prognosis. The effect of histologic features and immunophenotype on prognosis differs with different anatomic locations. For example, the prognosis of nasal lymphoma is not influenced by histologic grade, but in alimentary lymphoma, the most common low-grade, small-cell, T-cell form has a much better prognosis than the intermediate- to large-cell, high-grade forms.

Etiology

Prior to widespread FeLV testing and vaccination programs, about 60%–80% of feline cases were associated with FeLV infection. However, positive FeLV antigenemia is only identified in 10%–20% of contemporary cases. A possible breed predisposition to lymphoma has been identified in Siamese, especially young, FeLV negative cats with thymic/mediastinal lymphoma. Strong evidence for a retroviral etiology in dogs does not exist. Environmental exposures are considered possible etiologies. Overrepresented breeds include Boxer, Bulldog, Bull Mastiff, Dobermann, Golden Retriever, Labrador Retriever, Basset Hound, St. Bernard, Scottish Terrier, Airedale, Irish Setter, Rottweiler, and Briard. Breeds at risk are also geographical dependent (see Recommended Further Readings).

Pathophysiology

Lymphoma originates in peripheral lymphoid tissues, which causes local tissue injury and dysfunction. Over time, neoplastic cells will infiltrate widely into a variety of sites, which often include multiple lymph nodes, spleen, liver, and bone marrow.

Clinical Presentation

Clinical signs depend on the anatomic location of disease. In dogs with multicentric lymphoma, the most common presentation is nonpainful swellings of superficial lymph nodes. Splenomegaly or hepatomegaly may be present, along with internal lymphadenomegaly. Weight loss, vomiting, and inappetence often suggest an advanced stage with worse prognosis. Animals with alimentary lymphoma typically present with nonspecific gastrointestinal signs which may be acute or chronic and vary in severity depending on the nature of the disease (low grade/small cell versus high grade/large cell). Mediastinal or thymic masses can produce dyspnea due to the mass itself or associated pleural effusion. Cutaneous lesions can arise as a mild eczematous pruritic plaque and progress to a nodular lesion. Paraneoplastic hypercalcemia can cause clinical signs such as polydipsia and polyuria.

Differential Diagnosis

Differential diagnoses for dogs and cats with lymphoma vary depending on the anatomic form and clinical presentation. For generalized lymphadenopathy: Disseminated infections, immune-mediated disorders, and other hematopoietic tumors (e.g., advanced leukemia). For alimentary disease, lymphoplasmacytic enteritis, other neoplasms, granulomatous bowel disease, and hypereosinophilic syndrome should be considered. For cutaneous disease, pyoderma, other infectious or immune-mediated disease, parasitic infestation, and other neoplasms should be considered. For nasal lymphoma: Other nasal tumors, fungal rhinitis, lymphoplasmacytic rhinitis, and foreign body.

Diagnosis

The diagnostic approach to an animal with suspected lymphoma will vary depending on the clinical presentation.

Large- or intermediate-cell lymphoma is frequently diagnosed from fine-needle aspirates of affected tissues or fluids; these usually disclose a homogeneous population of lymphoblasts (Figures 16.58 and 16.59). Lymphoma of large granular lymphocytes has characteristic pink

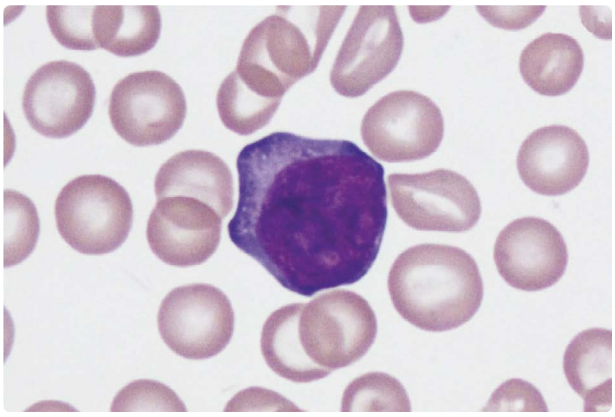


FIGURE 16.58 A lymphoblast in a dog with stage V lymphoma. Note the cell's large size, immature chromatin, and nucleoli.

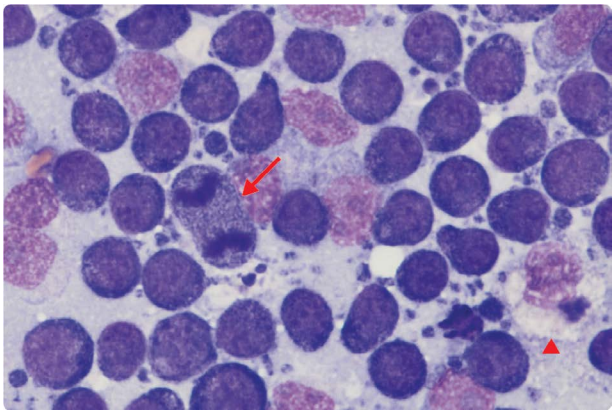


FIGURE 16.59 Cytologic preparation of large-cell lymphoma in a dog. The neoplastic lymphocytes are large with open chromatin and prominent nucleoli. Mitotic figures (arrow) and macrophages (arrowhead).

granules (Figure 16.60) and is most associated with splenic origin. If cytology is equivocal in distinguishing lymphoid hyperplasia from early lymphoma, a surgical biopsy may provide a definitive diagnosis based on changes in normal follicular architecture. In nodal small-cell lymphoma, cytology is typically not diagnostic. A homogenous population of monomorphic small lymphocytes can increase the index of suspicion, but for these and other cases where cytology is not definitive, then histopathology and immunohistochemistry, flow cytometry, and PCR for antigenic rearrangement (PARR) can be rewarding.

For an animal with a definitive diagnosis of lymphoma, determining immunophenotype via immunohistochemistry, immunocytochemistry, or flow cytometry may be prognostic in some clinical situations, including the most common canine presentation of multicentric lymphoma.

Hematology often reveals anemia of chronic disease, but a full CBC with blood smear evaluation is recommended to assess for concurrent blood loss or hemolysis, FeLV-associated macrocytosis, myelophthisis-associated cytopenias, and circulating atypical lymphocytes

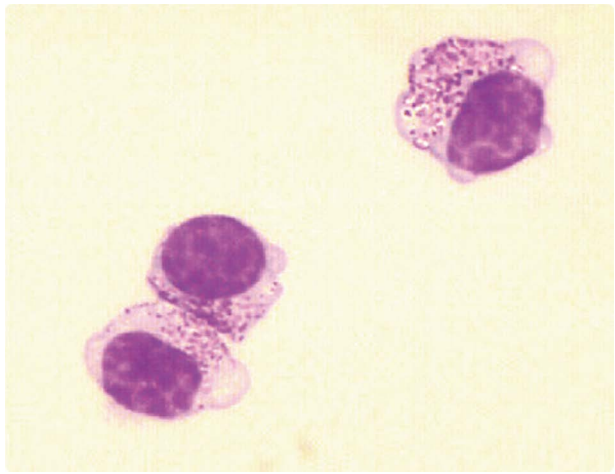


FIGURE 16.60 Cells from a cat with large granular lymphoma containing abundant magenta coarse cytoplasmic granules. Methanolic Romanowsky stain.

suggestive of stage V disease (Figure 16.60). Bone marrow aspiration can be performed for staging, prognosis, and in cases in which lymphoma is suspected but otherwise not proven.

Serum biochemical abnormalities include hypercalcemia in 15% of dogs with lymphoma (especially T-cell lymphoma) due to parathyroid hormone-related peptide production by neoplastic cells, azotemia with renal infiltration or secondary to hypercalcemia, elevated liver enzyme activity due to hepatic involvement, or hyperglobulinemia and monoclonal gammopathy with some B-cell lymphomas and plasma cell neoplasms. Cats should be screened for retrovirus (FeLV and FIV) infection for diagnostic, prognostic, and husbandry purposes.

Imaging, including radiographs, ultrasound, and CT, may be important for diagnosis, clinical staging, and monitoring response to treatment. However, in dogs with multicentric lymphoma, stage has not been a repeatable prognostic factor, and so full staging is not considered mandatory.

Management

In general, lymphoma requires systemic therapy. CHOP-based protocols involve combination chemotherapies of cyclophosphamide (C), doxorubicin (hydroxydaunorubicin [H]), vincristine (Oncovin [O]), and prednisone (P). The University of Wisconsin-Madison CHOP protocols are commonly recommended (see Recommended Further Readings). Prior to administering any potentially myelotoxic drug, a CBC should be performed to assess neutrophil and platelet concentrations. Cases of solitary lymphoma may be treated with surgery or radiation therapy. Nasal lymphoma in cats is often localized and responds well to radiation therapy.

Protocols utilizing a single cytotoxic agent such as doxorubicin or lomustine, usually in combination with prednisolone, can be effective in cases where the combination CHOP protocol is not desirable; however,

response rates and remission durations are typically less than for CHOP-based protocols. Doxorubicin and vincristine, as well as some other chemotherapy drugs, are P-glycoprotein substrates. Breeds at risk for mutations in ABCB1 (MDR1), which causes decreased P-glycoprotein function and increased toxicity of substrate drugs, should undergo ABCB1/MDR1 gene mutation analysis prior to chemotherapy. The most affected breed worldwide is the Collie, but multiple other breeds are reported, including the Australian Shepherd, Shetland Sheepdog, and Long-haired Whippet. Up to 5% of mixed-breed dogs overall and 10% of herding breed crosses may have the mutation.

After remission is achieved, relapse eventually occurs in most cases. If the duration of remission is judged to be good in patients that have completed their initial protocol, repeat treatment with the same protocol is often undertaken. Response rates are generally good. Duration of second remission in these cases is generally approximately half that of the first. In cases where lymphoma is refractory, or there is progressive disease during chemotherapy, rescue therapy may be pursued. Many protocols have been reported, and the complexity and toxicity of the chemotherapies often requires consultation with a veterinary oncologist.

Small-cell or indolent lymphoma is usually treated with a combination of oral chlorambucil and prednisolone, but in some cases, such as indolent nodal lymphoma in dogs, treatment is not initiated unless there are clinical signs associated with the disease or rapid disease progression.

Prognosis

Prognosis varies significantly depending on lymphoma classification. In general, for nonindolent lymphomas, progression and death within weeks is expected.

For dogs with nonindolent, multicentric lymphoma treated with combination or single-agent doxorubicin protocols, response rates vary from approximately 60% to over 90%, with combination protocols likely to have improved response rates. Median remission duration with these protocols ranges from approximately 4 to 11 months. Factors that influence prognosis in these dogs include WHO substage and lymphoma immunophenotype. Dogs showing no clinical signs of disease (i.e., WHO substage a) and B-cell lymphoma phenotype have better prognoses. Heavy bone marrow involvement may be associated with a poorer prognosis, but the effect of WHO stage on prognosis in these dogs requires further investigation. Prior steroid treatment is associated with shortened response durations.

In cats with nonindolent lymphoma treated with chemotherapy, usually CHOP- or COP-based, the overall response rates range from approximately 30% to 70%. Overall prognosis varies depending on the anatomic location, but in general, cats having a complete response to chemotherapy have a better prognosis, and approximately 25% of cats live longer than 2 years. Cats with a partial response generally have progressive disease within a few months.

In both dogs and cats with an indolent form of lymphoma, typically low grade/small cell, prognosis is better than for nonindolent forms, and survival times of several years are common.

CHRONIC LYMPHOCYTIC LEUKEMIA

Definition/Overview

Chronic lymphocytic leukemia (CLL) has a slow and protracted course of months to years. It occurs mostly in middle-aged or older dogs (mean 10 years). This form of leukemia occurs infrequently in cats but also appears to affect older individuals. The one case series reported in cats describes a 2:1 male-to-female distribution.

Etiology

An etiology has not been proven. Possible breed associations have been reported including German Shepherd Dogs, Golden Retrievers, and small-breed dogs in general. A syndrome of polyclonal expansion of small B cells has been described in English Bulldogs, which may have been previously misdiagnosed as CLL.

Pathophysiology

Phenotypically mature lymphocytes proliferate, and there is an increase in the stem cell compartment. In dogs, about 70% are of T-cell origin (CD8+, CD4+), with the remainder B cells or null cells. CLL arises from mature cells, but one form with granular morphology has been shown to develop initially from the spleen. Generally, liver, spleen, and lymph nodes become involved late in the disease. Cases of B-cell origin may present with hyperviscosity owing to increased gamma globulins, though this appears to be rare.

Clinical Presentation

Dogs with CLL are often asymptomatic, and lymphocytosis is detected incidentally on routine hematology. Lethargy and inappetence may be reported in advanced disease. More severe clinical signs are rare. On physical examination, lymphadenomegaly and splenomegaly may be detected. These are generally mild but may be marked in advanced disease. Cats similarly may have no clinical signs or mild, nonspecific signs, such as weight loss, inappetence, lethargy, vomiting or diarrhea.

Differential Diagnosis

Canine ehrlichiosis, other infectious diseases, postvaccinal responses in young dogs, polyclonal lymphocytosis in English Bulldogs.

Diagnosis

There is marked lymphocytosis of mature, small lymphocytes with condensed chromatin (**Figure 16.61**). Cell counts range from just above the normal reference interval to 300,000 cells/μL or more. A subset of CLL

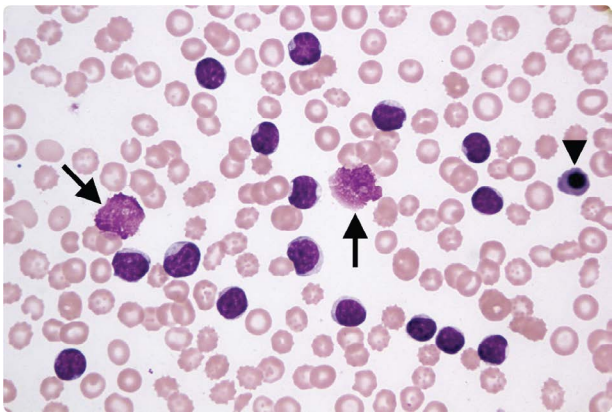


FIGURE 16.61 Chronic lymphocytic leukemia in a dog with a lymphocytosis of 183,000 cells/μL. The lymphocytes are small (i.e., ≤1.5 times the diameter of an RBC) with mature, dense chromatin. There are also two lysed cells (arrows) and one metarubricyte (arrowhead).

has granular lymphocyte morphology with an increased amount of pale blue cytoplasm and fine-to-coarse cytoplasmic pink granules. In dogs, lymphocyte counts exceeding 25,000/μL in blood or greater than 15% in bone marrow strongly suggest a malignant process. Mild normocytic, normochromic nonregenerative anemia is common. Neutropenia and thrombocytopenia occur late in disease with myelophthisis. Histopathology may better document the infiltration into nodal tissues by neoplastic lymphocytes, with loss of tissue architecture, though this is not generally required for diagnosis. Causes of chronic systemic disease (e.g., ehrlichiosis, leishmaniasis) should be ruled out.

Immunophenotyping is considered important both to assist with definitive diagnosis and for prognosis. However, flow cytometric features alone may not be sufficient to confirm leukemia, as the recently described syndrome in English Bulldogs demonstrates. These dogs have an expansion of small B cells on flow cytometry but on PCR for antigen receptor rearrangement have polyclonal or restricted polyclonal gene rearrangements, suggesting nonmalignant disease. These dogs often have hyperglobulinemia, which is an uncommon finding in dogs with CLL generally.

Management

When CLL is an incidental diagnosis, monitoring with regular physical examination and CBCs is generally recommended rather than immediate treatment initiation. There is no consensus on when treatment should commence. In general, if there are clinical signs or significant hematologic abnormalities beyond mild anemia, treatment is warranted. Excessive lymphocytosis may be considered a cue to start treatment, but there is no consensus on what constitutes this. The most common treatment is a combination of chlorambucil with prednisolone. Chlorambucil doses in dogs often start at 0.2 mg/kg or 6 mg/m^2 daily for 1–2 weeks then reduced to 0.1 mg/kg or 3 mg/m^2 daily and tapered further depending on response.

Prognosis

Most dogs and cats treated with chlorambucil and prednisolone have reduction or normalization of their lymphocytosis. Survival times in dogs and cats range from approximately 1–3 years. Progression to high-grade lymphoid malignancy, known as Richter's syndrome, is uncommonly described, and prognosis after this occurs is poor. Prognostic factors for CLL in dogs are not well established, but T-cell CLL may be associated with an improved prognosis compared with B cell or atypical CLL.

ACUTE LYMPHOBLASTIC LEUKEMIA

Definition/Overview

Acute lymphoblastic leukemia is a rapidly progressive disorder that occurs mostly in middle-aged dogs (mean 6 years). In cats, with the overall reduced incidence and prevalence of FeLV infection, ALL has become less common.

Etiology

Viral agents (FeLV) or environmental exposure are possible causes.

Pathophysiology

Bone marrow or peripheral blood contains morphologically immature precursor cells or lymphoblasts. Acute lymphoblastic leukemia is thought to arise from the bone marrow and later involves the liver, spleen, and other tissues.

Clinical Presentation

Clinical signs in dogs include lethargy, anorexia, vomiting, weight loss, and diarrhea for several weeks. On physical examination, splenomegaly is common, and hepatomegaly and lymphadenomegaly may also be present. Signs associated with cytopenias, such as bleeding due to thrombocytopenia or fever and infection due to neutropenia, may be present.

Differential Diagnosis

Stage V lymphoma, acute myeloid leukemia without maturation, acute undifferentiated leukemia.

Diagnosis

Hematologic abnormalities include increased numbers of immature lymphoid cells in the blood or bone marrow (Figure 16.62), nonregenerative anemia, neutropenia, thrombocytopenia, and an occasional monoclonal gammopathy. Flow cytometry may be useful to confirm an acute leukemia phenotype (CD34+), as well as lymphoid origin, since acute myeloid leukemia appears morphologically similar. Approximately 10% of cases are confined to the bone marrow without detectable blood involvement (aleukemic leukemia). Bone

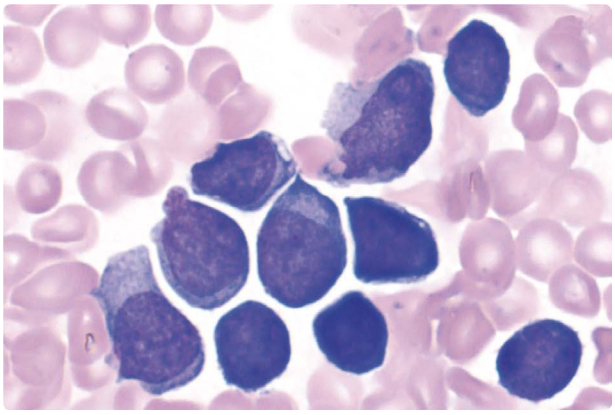


FIGURE 16.62 Acute lymphoblastic leukemia from a dog bone marrow. Note the large (i.e., ≥2.5–3 times the diameter of an RBC) immature cells with high nuclear-to-cytoplasmic ratio, finely stippled chromatin, and round-to-ovoid nuclei that contain multiple prominent nucleoli.

marrow evaluation is warranted in these cases and in cases with low numbers of circulating blasts (subleukemic leukemia). PCR tests for B- or T-cell antigen receptor rearrangement are available for difficult to diagnose cases.

Management

Treatment most often involves the same combination chemotherapy used for lymphoma. The prognosis is poor, with median survival (untreated or treated) being less than 3 months.

MULTIPLE MYELOMA

Definition/Overview

Multiple myeloma (MM, plasma cell myeloma) is a malignant disease of plasma cells. In dogs, bone marrow is primarily affected. In cats, widespread abdominal organ involvement without significant bone marrow involvement has been described. It affects older dogs (mean 9–10 years) and cats (median 12–14 years).

Etiology

The etiology is unknown.

Pathophysiology

Malignant plasma cells produce a clonal or, rarely, biclonal population of immunoglobulins (M proteins or paraproteins), light chains (Bence–Jones proteins), or heavy chains (heavy chain disease). These proteins may inhibit platelet function, causing bleeding diathesis, or result in hyperviscosity syndrome, renal failure, amyloidosis, or cryoglobulinemia. Infiltration into bone marrow by neoplastic plasma cells produces hematologic cytopenias. The destruction of bone by osteoclast-activating factors released by tumor cells causes lytic lesions and hypercalcemia. Bone pain and pathologic fractures are common sequelae. Plasma cell dysfunction can lead to immunodeficiency and increased susceptibility to infection.

Clinical Presentation

Clinical signs may be vague and variable, with lethargy and anorexia the most commonly reported signs in both dogs and cats. Lameness is reported in approximately 35% of dogs but is less common in cats. Other signs, such as paresis, blindness, bleeding from mucous membranes, vomiting and diarrhea, neurologic signs, or polydipsia and polyuria, can occur.

Differential Diagnosis

- *Causes of monoclonal gammopathy:* Ehrlichiosis, lymphoma, Leishmaniasis.
- *Causes of hepatosplenomegaly in cats:* Mast cell tumor, myelogenous leukemia, lymphoma, inflammatory, infectious.
- *Causes of bone lesions:* Primary or metastatic bone tumors, osteomyelitis.

Diagnosis

In dogs, identification of a monoclonal gammopathy detected in serum or urine (Bence–Jones proteinuria), radiographic or advanced imaging detection of osteolytic lesions, and bone marrow plasmacytosis with a cutoff of >20% are sufficient for a diagnosis of multiple myeloma (Figure 16.63). Urine protein reagent strips will not detect light chain proteinuria. In cats, monoclonal gammopathy and bone marrow plasmacytosis (>10% and/or atypical morphology) or visceral organ infiltration are suggested as diagnostic criteria.

Hematologic abnormalities in dogs and cats with multiple myeloma include nonregenerative anemia in 50%–80%, thrombocytopenia in approximately 40%–50%, neutropenia in approximately 25%–40%, and plasma cell leukemia in 5%–25% of cases. Hypoalbuminemia is common, azotemia is reported in

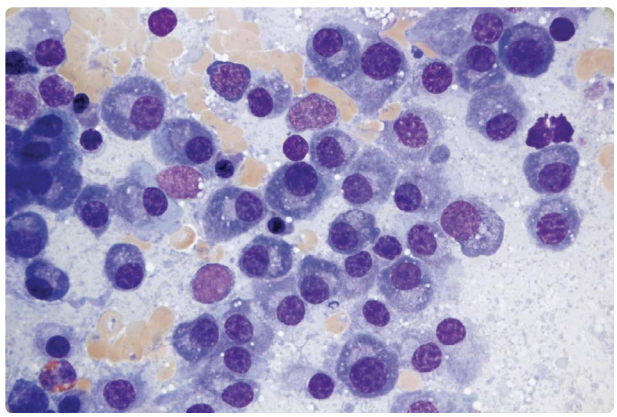


FIGURE 16.63 Aspirate preparation from a lytic bone lesion in a dog with multiple myeloma showing many plasma cells with abundant basophilic cytoplasm, prominent perinuclear pale zones, and peripherally placed nuclei with clumped chromatin.

approximately one-third, and hypercalcemia in approximately one-quarter of cases.

Management

Combination therapy with melphalan and prednisolone is considered standard of care in the dog. Melphalan may be given as a continuous dose starting at 0.1 mg/kg p.o. q.24 h. for 10 days, then 0.5 mg/kg q.24 h., or as a pulse dose of 7 mg/m^2 once daily for 5 consecutive days every 3 weeks. Prednisolone is initiated at 0.5 mg/kg once daily for 10 days then reduced to 0.5 mg/kg every other day. Discontinuation of prednisolone should be considered depending on the response.

In cats, melphalan appears to be myelosuppressive at doses generally tolerated by dogs. Cyclophosphamide and prednisolone have been suggested as an alternative either as 250 mg/m^2 every 2–3 weeks or 25 mg per cat twice weekly.

With either melphalan or cyclophosphamide, therapy is generally continued for as long as there is clinical benefit and no unacceptable toxicity. Patients should be monitored for myelosuppression with regular CBCs, the frequency of which will vary depending on the drug and protocol chosen, but at least monthly in the initial phase of treatment. Depending on which complications of MM are present, additional therapy may include plasmapheresis for hyperviscosity, fluid therapy for renal failure, orthopedic stabilization of pathologic fractures, and antibiotics for immunodeficiency.

Prognosis

While complete elimination of disease is rarely achieved, chemotherapy is effective at reducing tumor burden, improving clinical signs, and reducing serum globulins concentration. Assessment of response is based on clinical signs, serum globulins, and ideally repeat M component assessment. Dogs with normalization of hyperglobulinemia can have persistent paraproteinemia. Repeat bone marrow assessment may be required, especially in animals with cytopenias during chemotherapy treatment, where toxicity must be differentiated from progressive disease. In dogs treated with melphalan and prednisone, greater than 80% respond, and median survival times are approximately 1.5–2.5 years. Extensive bone lesions, light chain proteinuria, hypercalcemia, and azotemia have been identified as possible negative prognostic factors. Treatment and response data is scarcer in cats, but approximately 50%–80% will respond to chemotherapy, and although earlier reports suggested a poor prognosis with median survival time of approximately 4 months, better outcomes with median survival times of 8–13 months have been reported.

EXTRAMEDULLARY PLASMACYTOMA

Definition/Overview

Extramedullary plasmacytoma is a neoplastic proliferation of plasma cells that arises from tissues other than the bone marrow. The cells may be benign or malignant.

Etiology

The etiology is unknown.

Pathophysiology

Neoplastic plasma cells proliferate in the tissues. Malignant neoplasms may cause local and systemic tissue injury. Monoclonal gammopathies are less common than with MM.

Clinical Presentation

Clinical signs depend on the anatomic location, with skin being the most common location. Cutaneous plasmacytomas in dogs and cats are typically solitary, small, raised, alopecic, dermal nodules affecting the digits and pinnae more often than other sites. A syndrome of cutaneous plasmacytosis is described in dogs, where multiple lesions are present at the time of diagnosis. Oral plasmacytomas are also typically solitary but may become ulcerated and interfere with eating and drinking. Alimentary plasmacytomas can cause nonspecific gastrointestinal signs such as tenesmus and hematochezia in colorectal plasmacytomas and vomiting with gastric plasmacytomas. Solitary osseous plasmacytomas present with lameness or other signs depending on location, such as paresis in the case of vertebral lesions.

Differential Diagnosis

Cutaneous plasmacytoma: Other cutaneous neoplasms, especially mast cell tumor and histiocytoma, lymphoplasmacytic hyperplasia or inflammation, abscesses.

Alimentary plasmacytoma: Other alimentary neoplasia, inflammatory polyp, granuloma.

Solitary osseous plasmacytoma: Other primary bone tumor, multiple myeloma, secondary bone tumor, fungal or bacterial osteomyelitis.

Diagnosis

Diagnosis requires cytologic or histopathologic biopsy. For noncutaneous plasmacytomas, additional diagnostics (survey radiographs, bone marrow aspirate, serum electrophoresis) are important to ensure the lesion is solitary. Identification of a monoclonal gammopathy is occasionally described in cases with apparently solitary lesions, and so for confirmation of systemic disease, other criteria as used to diagnose multiple myeloma should be applied. Progression from solitary plasmacytoma to systemic plasma cell neoplasia has been reported and appears to be more common with those affecting sites other than the skin and oral cavity.

Management

Solitary plasma cell tumors are usually successfully treated with surgical excision and/or external beam radiotherapy. Cutaneous plasmacytosis in dogs is an aggressive disease, which does not typically lend itself to local therapy due to the diffuse nature at the time of diagnosis. Treatment as for multiple myeloma is recommended.

Prognosis

Canine cutaneous and oral plasmacytomas tend to be benign. Progression from solitary plasmacytoma to systemic plasma cell neoplasia has been reported and appears to be more common with those affecting sites other than the skin and oral cavity.

MYELOID (NONLYMPHOID) NEOPLASMS

Myeloid leukemias are clonal proliferations of erythroid, granulocytic, monocytic, and megakaryocytic cells. The 2008 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues, revised in 2016, includes myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), and acute myeloid leukemia (AML). These categories have been applied in animals. There are also categories of myeloid/lymphoid neoplasms, which is composed of diseases with specific gene rearrangements, and myelodysplastic/myeloproliferative neoplasms such as atypical chronic myeloid leukemia, which are not defined in veterinary species. A consensus classification system for canine and feline myeloid neoplasms has not been established.

MYELODYSPLASTIC SYNDROME

Definition/Overview

MDS is characterized by persistent peripheral cytopenia(s), normocellular to hypercellular marrow, dysplasia in one or more cell lines, and <20% blast cells in the marrow. In people, MDS is categorized based on the major cytopenia and morphological changes in cells. These subtypes have been described in animals, but the effect on subtype on biological behavior and prognosis is not defined.

Etiology

A possible role for FeLV infection in cats with MDS has been proposed, but no other etiologies have been described.

Pathophysiology

MDS often precedes acute leukemia by several weeks to months. Increased apoptosis is considered the mechanism for cytopenias in the face of marrow proliferation.

Clinical Presentation

Clinical signs are related to cytopenias and can include fever due to secondary infection from neutropenia, lethargy due to anemia, and hemorrhage due to thrombocytopenia.

Differential Diagnosis

Immune-mediated nonregenerative anemia, drug-induced dysplasia, and nutrition-related dysplasia.

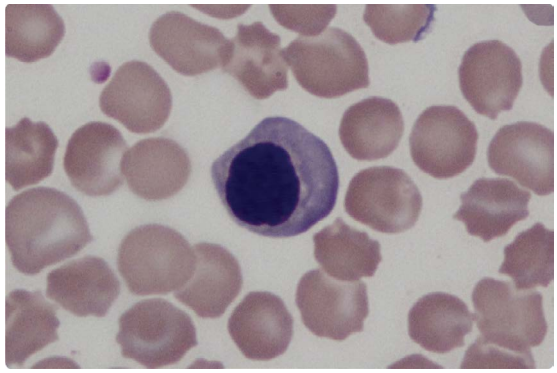


FIGURE 16.64 Inappropriate metarubricytosis and a dysplastic erythroid cell (megaloblast) in blood from a dog with myelodysplastic syndrome.

Diagnosis

Concurrent CBC and bone marrow cytology with or without histopathology are required for diagnosis. Other causes of dysplasia (e.g., drugs, breed-associated) should be excluded. Diagnosis requires detection of one or more cytopenias, normocellular to hypercellular marrow, <20% marrow myeloblasts, and myelodysplasia. Dysplastic changes in the blood or bone marrow include macrocytosis, megaloblastosis (Figure 16.64), nuclear fragmentation, abnormal cytoplasmic granulation, neutrophil hypersegmentation (Figure 16.65) or hyposegmentation, micromegakaryocytes or macrothrombocyte formation, and cell gigantism.

Management

As the condition may persist for long periods of time without major clinical disease, treatment is usually supportive and includes antibiotics and blood transfusions as needed. Dyserythropoiesis in the dog may respond to recombinant human EPO, but clinicians should bear in mind the risk of anti-EPO antibodies developing.

Prognosis

The prognosis is not well defined. Progression to AML can occur.

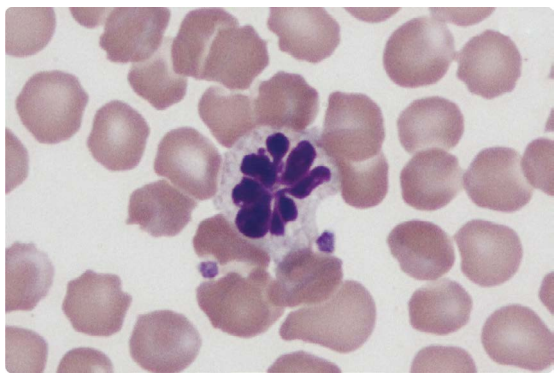


FIGURE 16.65 Dysplastic hypersegmented neutrophil from a dog with myelodysplastic syndrome.

MYELOPROLIFERATIVE NEOPLASMS

Definition/Overview

MPNs, previously known as chronic leukemias, consist of persistent, unexplained increases in one or more myeloid lineages with a predominance of morphologically mature neoplastic cells. MPNs in small animals include chronic granulocytic leukemia, essential thrombocythemia, polycythemia vera, and chronic myelomonocytic leukemia, and all are uncommon conditions. Primary myelofibrosis is an MPN described in humans which has been very rarely diagnosed in dogs and cats and is poorly defined.

Etiology

Feline MPN may be associated with FeLV infection.

Pathophysiology

Genetic mutations lead to cell proliferation and prolonged cell survival. BCR-ABL translocations have been documented in dogs with chronic monocytic and myelomonocytic leukemias. The leukemia slowly effaces the marrow, leading to a chronic disease course and cytopenias of other cell lines later in disease. Hyperviscosity syndrome is a potential complication of PV.

Clinical Presentation

Animals with leukocyte proliferations often have no clinical signs until late-stage disease. Therefore, diagnosis may be made with routine health screens. Late-stage disease consists of organ and marrow effacement, resulting in abdominal organomegaly, pallor if anemia is present, sepsis due to neutropenia or nonfunctional neutrophils, and hemorrhage from thrombocytopenia. Clinical signs in patients with PV relate to increased RBC mass and blood hyperviscosity. Mucous membranes may be dark red (Figure 16.66) because of PCVs of 0.65–0.82 L/L (65%–82%). Splenomegaly is usually not present. Polyuria, polydipsia, hemorrhage, and neurologic disorders occur in 50% of canine cases. Clinical signs of essential thrombocythemia include splenomegaly and platelet function abnormalities such as spontaneous bleeding and thromboembolism.

Differential Diagnosis

For PV: Causes of relative, appropriate absolute and inappropriate absolute erythrocytosis. For proliferations of neutrophils and monocytes: Causes of leukemoid response. For proliferations of eosinophils and basophils: Hypersensitivity reactions, parasitic infections, and hypereosinophilic syndrome. For essential thrombocythemia: Causes of reactive thrombocytosis.

Diagnosis

Since routine genetic testing is not available in veterinary medicine, these leukemias are diagnoses of exclusion. General features for all MPNs are persistent (>3 months) unexplained increases in one or more cell lines and relatively few blast cells in the bone marrow (<20% of all nucleated cells).

The subclassification is dependent on which cell lines are increased. Proliferations of neutrophils and/or monocytes include chronic myelogenous leukemia, chronic myelomonocytic leukemia, and chronic monocytic leukemia (Figure 16.67). Leukocyte counts are often markedly elevated (40,000–200,000/µL), and monocyte counts often exceed 4,000/µL (Figure 16.68). Neutrophilic leukemia must be differentiated from causes of a leukemoid inflammation, such as pyometra and pyelonephritis. Chronic eosinophilic leukemia is characterized by a high eosinophil count (often >50,000/µL) with a shift towards immaturity. It may be difficult to differentiate this malignancy from reactive hypereosinophilic conditions (e.g., allergies, parasitism, eosinophilic inflammatory diseases, paraneoplastic conditions). Chronic basophilic leukemia is mostly reported in dogs. It has been associated with thrombocytosis and anemia. Cytochemical staining with omega-exonuclease is helpful in identifying basophil precursors when cytoplasmic granulation is not apparent. Mature and immature basophils are increased in blood or bone marrow, and tissue infiltration may occur.



FIGURE 16.66 Brick red gums in a dog with polycythemia vera. (*Courtesy of J. Harvey.*)

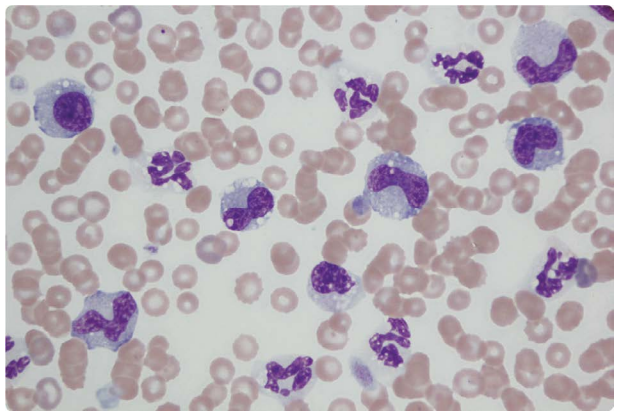


FIGURE 16.67 Chronic myelomonocytic leukemia in a dog with 116,491 neutrophils/µL and 26,277 monocytes/µL.

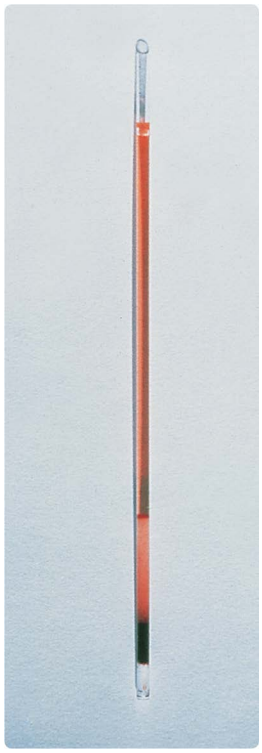


FIGURE 16.68 Large buffy coat present in a cat with acute myeloblastic leukemia displaying marked leukocytosis. (*Courtesy of J. Harvey.*)

Basophilic leukemia must be differentiated from mast cell leukemia.

PV, a proliferation of erythrocytes (primary erythrocytosis), occurs infrequently in dogs and cats. Diagnosis requires ruling out other causes of erythrocytosis. Arterial blood gas evaluations are normal with no evidence of hypoxemia. Erythropoietin levels are absent or reduced when measured at specialist laboratories. Leukocyte and platelet counts are normal to mildly elevated, and in a few cases, basophilia has been noted (Figure 16.69). Bone marrow examination indicates erythroid proliferation with normal morphology and maturation.

Essential thrombocythemia (primary thrombocythemia) is a rare neoplastic proliferation of megakaryocytes with subsequent thrombocytosis. Platelet counts are persistently above 600,000/μL (usually >1,000,000/μL), and platelet morphologic abnormalities may be present (Figure 16.57). Neutrophilia or basophilia may also be observed.

Management

For polycythemia vera, phlebotomy to remove 15–20 mL per kilogram of body weight with fluid replacement is indicated for immediate relief of clinical signs in many patients. Hydroxyurea is commonly used and is given in dogs at an initial dose of 30 mg/kg daily for 10 days, then reduced to 15 mg/kg daily and ultimately tapered to the lowest effective dose, with the goal of treatment being maintain the PCV as close to normal as possible. Repeated phlebotomies in combination with drug therapy may be required. Cats may be more prone to myelotoxicity from hydroxyurea and may require lower doses and more frequent monitoring.

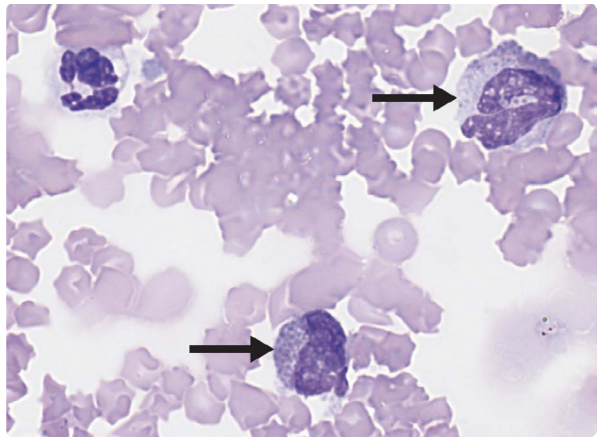


FIGURE 16.69 Feline blood with high hematocrit (0.64 L/L [64%]) and basophils (arrows) in a case of polycythemia vera.

For chronic myelogenous leukemia, hydroxyurea is also described and tapered to the lowest effective dose. Use of tyrosine kinase inhibitors such as imatinib and toceranib has been more recently described in dogs with CML due to the potential for them to have a BCR-ABL translocation similar to that responsible for a majority of CML in people.

There is little information on treatment for essential thrombocythemia (ET) in animals, but combination chemotherapy has been described in a dog, and in people, hydroxyurea is used in cases where clinical signs are present.

Supportive care (e.g., antibiotics, blood transfusions, and fluids) should be given when indicated.

Prognosis

Survival of months to years is expected, but eventual drug refractoriness or blast transformation is possible.

ACUTE MYELOID LEUKEMIA

Definition/Overview

AML is a proliferation of immature nonlymphoid hematopoietic cells that often results in myelophthisis and poor prognosis. In people, subtypes of AML are defined based on the identification of specific genetic abnormality or cell line. Genetic abnormalities including BCR-ABL translocation have been detected in dogs with AML, but their relevance is unknown. In dogs and cats, a uniform classification system has not been developed. However, utilizing morphology and immunophenotype, categories of AML without differentiation, AML with neutrophilic differentiation, AML with monocytic differentiation, AML with myelomonocytic differentiation, AML with megakaryoblastic differentiation, and AML with erythroid differentiation are described.

Etiology

FeLV is associated with feline AML.

Pathophysiology

Immature myeloid cells proliferate rapidly and efface the bone marrow, resulting in life-threatening cytopenia. Neoplastic cells often infiltrate tissues, causing widespread organ injury and dysfunction.

Clinical Presentation

Clinical signs are nonspecific with lethargy, weight loss, and hyporexia commonly reported. Clinical signs related to cytopenias may include fever due to secondary infection from neutropenia and bleeding due to thrombocytopenia. On physical examination, lymphadenopathy and hepatosplenomegaly are common.

Differential Diagnosis

Acute lymphoid leukemia, recovery following viral, toxin, or drug-induced leukopenia resulting in increased blasts in bone marrow.

For aleukemic cases: Other causes of cytopenia including immune-mediated (associative or nonassociative), drug toxicity, and myelodysplastic syndrome.

Diagnosis

Diagnosis is often made on a CBC and blood smear review. Peripheral blood findings often include immature myeloid cells and blast cells, as well as decreases in one or more cell lines due to myelophthisis. Thrombocytopenia-induced hemorrhage may also contribute to anemia. Bone marrow evaluation may be performed in cases with low or no circulating blasts or when AML subtype classification is desired. Flow cytometry or other special diagnostic techniques (e.g., cytochemistry on the blood or bone marrow) are often required to differentiate AML from ALL, as morphology alone is not definitive in most cases.

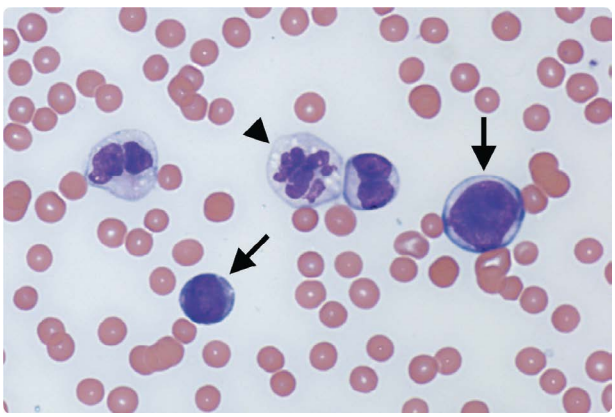


FIGURE 16.70 Blood from a dog with acute myelomonocytic leukemia with arrows indicating immature myeloid cells (myeloblasts) and an atypical segmented cell (arrowhead).

Within the marrow, there is hypercellular marrow, ≥20% blast cells, and variable proportions of myeloid cells. AML can be of myeloid, monocytic (Figure 16.70), erythroid, or megakaryocytic origin. When rebounding from neutropenia, such as following feline panleukopenia infection, the blood may appear neoplastic owing to the presence of large numbers of myeloblasts in the bone marrow. Persistent hematologic abnormalities must occur to confirm leukemia. Regenerative attempts following leukopenia are generally evident after 7–10 days for nonleukemic conditions.

Management

In general, AML is poorly responsive to chemotherapy, and consultation with an oncologist is recommended.

Prognosis

The prognosis is poor, as short-term responses are common but are not durable, in the order of weeks.

HISTIOCYTIC SARCOMA

Definition/Overview

Histiocytic sarcoma (HS) is a malignancy of histiocytes, which can be of dendritic cell or macrophage origin, and can manifest in a variety of ways. Localized HS is typically of dendritic cell origin and arises initially in one organ, though metastasis is common. Disseminated HS (previously known as malignant histiocytosis) is widespread at the time of diagnosis, commonly involving abdominal viscera (especially spleen and liver) and lungs, without an obvious primary site. Hemophagocytic HS arises from macrophages and affects the spleen, with widespread dissemination being common at diagnosis. Management and prognosis differ for the different manifestations.

Etiology

In dogs, several breed associations for HS have been identified, including Bernese Mountain Dogs, Flat-coated Retrievers, and Miniature Schnauzers, and an inherited predisposition with possible genetic drivers has been investigated in Bernese Mountain Dogs. An association between prior joint disease and periarticular HS has been found in Bernese Mountain Dogs and other breeds, though in other breeds this is largely related to cruciate ligament disease. There are some breed differences in clinical manifestation, with disseminated HS being more common in Bernese Mountain Dogs and localized HS being more common in Flat-coated Retrievers. No specific risk factors have been identified in cats, which are more likely to present with disseminated than localized HS.

Pathophysiology

Possible genetic drivers of HS have been identified in dogs, including gain-of-function mutations in PTPN11

and copy number alterations in tumor suppressor genes. Proliferation of malignant histiocytes in various tissues leads to clinical signs dependent on the organs involved. In hemophagocytic HS, malignant histiocytes of macrophage origin exhibit phagocytosis of red blood cells and other hematopoietic cells, and the animals often develop hypoalbuminemia.

Clinical Presentation

Clinical signs vary with sites of tumor involvement. Disseminated or visceral HS typically presents with vague clinical signs, including lethargy and inappetence. More common sites for localized HS include periarticular (presenting with lameness), pulmonary (presenting with coughing or other respiratory signs), or subcutaneous, often presenting with a mass without other clinical signs. Lymphadenomegaly (peripheral or internal) is common with disseminated or metastatic HS. Animals with hemophagocytic HS often present with clinical signs related to anemia or thrombocytopenia.

Differential Diagnosis

The most common neoplastic differential for HS is lymphoma, especially in disseminated or visceral HS. Anaplastic sarcoma is another common differential. Differentials for localized HS include:

- *Periarticular:* Primary or metastatic bone tumor, synovial sarcoma, myxoma, fungal osteomyelitis, primary orthopedic disease, hematoma
- *Pulmonary:* Other primary lung tumors, fungal granuloma, eosinophilic bronchopneumopathy
- *Hemophagocytic HS:* Immune-mediated hemolytic anemia, hemangiosarcoma, hemophagocytic syndrome, immune-mediated thrombocytopenia, immune-mediated neutropenia; primary protein-losing enteropathy is sometimes suspected in early cases presented with diarrhea and hypoalbuminemia

Diagnosis

Definitive diagnosis of HS on cytology or histopathology can be challenging due to the pleomorphic nature of the tumor cells. Immunocytochemistry or immunohistochemistry may be required, and antibodies to CD18, CD204, and Iba1 have been helpful. Fresh or frozen tissue evaluation of CD1 and CD11 subunits can further confirm the diagnosis or subclassify the cell of origin.

Full staging with thoracic and abdominal imaging is recommended for any case of HS, as metastasis of apparently localized disease is common. Bone marrow evaluation is recommended in animals with cytopenias not attributed to splenic hemophagocytic HS.

Management

For localized HS without evidence of metastasis at diagnosis, surgery or radiation therapy to the primary tumor and adjuvant chemotherapy is recommended where possible. For disseminated or metastatic disease, chemotherapy can be of benefit. CCNU (lomustine) appears to be the most effective drug against canine HS, with doxorubicin, epirubicin, and dacarbazine also having evidence of efficacy. In dogs with measurable disease, reported response rates to chemotherapy (single agent or combination) range from approximately 30%–60%. Treatment of feline HS is not well studied, though there are case reports of responses to therapies including CCNU.

Prognosis

Survival times for dogs with localized HS and no metastasis treated with adequate local control plus adjuvant chemotherapy can be very good, especially in dogs with periarticular HS in which a median survival time of approximately 2 years has been reported. However, development of metastatic disease is still common, and long-term outcome is guarded. Despite responses to chemotherapy, long-term prognosis for disseminated or metastatic HS is poor, with median survival times of approximately 6–9 months in those that respond to chemotherapy. Hemophagocytic HS appears to have an aggressive clinical course even with therapy, with most patients dying in days to weeks.

CASE EXAMPLES

Case 16.1: Systemic Histoplasmosis – Katie M. Boes, Julien R.S. Dandrieux, and Claire M. Cannon

Signalment/History

A 2-year-old indoor/outdoor spayed female Domestic Shorthair cat is presented for a 3-week history of weight loss and lethargy.

Clinical Examination

The cat is quiet, alert, responsive, and mentally dull with normal vital signs. There are general signs of ill thrift, including dull hair coat, poor BCS (2/9), and mild muscle atrophy of the hindlimbs. Mucous membranes are pale, and the cat is estimated to be 8% dehydrated. A grade 2/6 systolic heart murmur is auscultated.

Provisional Hematologic Abnormalities

Pale mucous membranes suggest anemia. Since icterus is not observed, hemolytic anemia is less likely. There is no evidence of external hemorrhage (e.g., trauma, external parasitism), internal hemorrhage (e.g., distended abdomen), or GI hemorrhage (e.g., perineal blood). Therefore, likely causes for the anemia are decreased RBC production and occult GI hemorrhage. The murmur is likely secondary to the anemia.

Differential Diagnosis

Causes of chronic disease, ill thrift, and anemia in a young cat include viral (FeLV, FIV, feline panleukopenia virus) infection; intestinal parasites; systemic fungal infection; lymphoma; mycoplasmosis; chronic or congenital kidney disease.

(Continued)

Laboratory Tests

A FeLV/FIV SNAP test was negative. A serum chemistry panel was consistent with stress (glucose = 184 mg/dL; RI 71–165), inflammation (albumin = 2.8 g/dL [RI 3.0–4.0]; globulins = 5.4 g/dL [RI 3.0–5.2]), and minimal cholestasis (GGT = 2 U/L [RI 0–1]; total bilirubin = 1.3 mg/dL [RI 0.0–0.4]). A CBC (**Table 16.15**) and blood smear review (**Figure 16.71**) were also performed.

TABLE 16.15 Hemogram results

Test	Result	Reference interval (from author's lab)
RBC	3.70 × 10^6/μL	7.28–11.36
Hemoglobin	5.3 g/dL	12.1–6.7
Hematocrit	17.1%	33.7–47.5
MCV	46.2 fL	38.4–49.2
MCHC	31.0 g/dL	34.1–37.0
Reticulocytes	15,400/μL	13,050–71,570
NRBCs	6/100 WBCs	0–1
WBCs	5,302/μL	4,250–11,360
Segmented neutrophils	3,287/μL	2,272–9,639
Band neutrophils	212/μL	0–0
Lymphocytes	1,750/μL	804–9,240
Monocytes	53/μL	0–952
Platelets	97,000/μL	148,700–531,600



FIGURE 16.71 Three small, ovoid yeasts (arrows) in the cytoplasm of a monocyte.

Blood smear review: Few schistocytes and acanthocytes; NRBCs are metarubricytes; many neutrophils with Döhle bodies and foamy cytoplasm; rare small ovoid yeast forms within monocytes.

Interpretation

The moderate-to-marked normocytic hypochromic anemia is primarily due to decreased production since it is nonregenerative. There is other evidence of hematopoietic hypoplasia (thrombocytopenia), and bone marrow injury is suspected (inappropriate metarubricytosis). Anemia of chronic disease may be contributing to the anemia but is not expected to cause this severity of anemia by itself. The schistocytes, acanthocytes, and thrombocytopenia raise concern for concurrent microangiopathic hemolysis and platelet consumption secondary to DIC. There is no evidence of blood loss anemia, such as increased BUN relative to creatinine or panhypoproteinemia. The left shift and toxic neutrophils (Döhle bodies and foamy cytoplasm) denote inflammation. The cause for the hematologic changes is present on the blood smear as intracytoplasmic yeast consistent with *Histoplasma capsulatum*.

Clinical Diagnosis

The diagnosis is systemic histoplasmosis with probable bone marrow infection and DIC.

Case Outcome

The cat was given a guarded prognosis for recovery, and the owners elected to euthanize the cat. A necropsy was not performed, but the owners authorized aspiration of the bone marrow after euthanasia. Cytologic evaluation of the bone marrow confirmed granulomatous fungal myelitis resulting in erythroid hypoplasia, myeloid hyperplasia, and megakaryocytic hypoplasia.

Treatment options include azole antifungal drugs such as itraconazole or fluconazole. Ketoconazole should be avoided as less effective and more likely to cause toxicity. In people, itraconazole is more effective than fluconazole, and although this might be the case as well in cats, there are reports of successful treatment with fluconazole monotherapy. If there is CNS involvement, treatment with amphotericin B should be used as first line with transition to itraconazole once the disease is better controlled. Treatment is typically long (6 months or more), and discontinuation can be considered when the lesions have resolved and potentially resolution of *H. capsulatum* antigen excretion.

Case 16.2: Gastrointestinal Stromal Tumor – Julien R.S. Dandrieux, Katie M. Boes, and Claire M. Cannon

Signalment/History

A 10-year 6-month-old spayed female Labradoodle is presented for a 2-week history of lethargy (worsening) and hyporexia. Previous history includes degenerative joint disease treated with pentosan polysulfate injections and a recent 4-week course of carprofen. The owner has noted increased defecation frequency since started carprofen and one episode of diarrhea. The owner has rat bait at home but in a closed cupboard, making exposure unlikely.

Clinical Examination

The dog is quiet, alert, and responsive. She is overweight (body condition score 6/9), and her mucous

(Continued)

membrane are pale with a normal capillary refilling time. The dog is tachycardic and tachypneic with tall and narrow pulses. Thoracic and cardiac auscultations are unremarkable. Abdominal palpation is unremarkable. Small amount of feces is present on rectal examination without evidence of fresh blood or melena. No obvious organomegaly or ascites is noted on AFAST and no pleural effusion on TFAST.

Provisional Hematologic Abnormalities

Pale mucous membranes and cardiovascular status suggest anemia. The absence of icterus makes hemolytic anemia less likely. There is no evidence of external blood loss reported by the owner and no evidence of internal hemorrhage; however, the dog has been treated with an NSAID and can potentially have secondary GI bleeding. GI bleeding in small amount cannot be excluded. Physical examination findings suggest marked anemia, and for this reason, anemia of inflammatory disease or endocrine disease are considered unlikely. The progressing lethargy, tachycardia, and tachypnea suggest that the dog would benefit from a blood transfusion.

Differential Diagnosis

Likely causes for the suspected marked anemia include either decreased RBC production or occult hemorrhage (GI or urinary) secondary to treatment (NSAID) or other pathology. Hemolytic anemia is less likely in the absence of icterus. Chronic renal disease is deemed unlikely in the absence of other suggestive clinical signs.

Laboratory Tests

A serum chemistry panel revealed mild panhypoproteinemia (42g/L [RI 52–82]) with mild hypoalbuminemia (21g/L [RI 22–39]) and hypoglobulinemia (21g/L [RI 25–45]). The rest of the serum chemistry results, including urea and bilirubin, were within normal limits.

A CBC (**Table 16.16**) and blood smear review (**Figure 16.72**) were also performed.

The blood smear review: The erythrocytes show moderate anisocytosis reflecting both macrocytosis and microcytosis, and many of the microcytes show prominent central pallor suggesting iron deficiency should be considered. Rare smaller cells show no central pallor, which mimic spherocyte morphology. Mild rouleau is present, but there is no agglutination.

Other testing included PT, aPTT (within RI), Coombs test (negative), and typing (DEA1- positive) in view of blood transfusion.

Interpretation

Although the anemia is strongly regenerative, there is some evidence of iron deficiency on blood smear with presence of microcytes with central pallor. The MCV would be expected to be higher with the degree of regeneration and reflects the combine presence of microcytes and reticulocytes. Although end-stage iron deficiency is characterized by nonregenerative to poorly regenerative microcytic, hypochromic anemia, earlier stages will still be strongly regenerative and should not be misinterpreted for a hemolytic process. The absence of agglutination and negative Coombs test together with normal bilirubin further suggest that hemolysis is unlikely.

TABLE 16.16 Hemogram results

Test	Result	Reference interval (from author's lab)
RBC	1.6 × 10^6/μL	5.5–8.5
Hemoglobin	2.9 g/dL	12.0–18.0
Hematocrit	12.0 %	37.0–55.0
MCV	65 fL	60–75
MCHC	252 g/L	320–380
Reticulocytes	350 x10^9/L	10–110
NRBCs	1/100 WBCs	0–1
WBCs	13,500/μL	6,000–17,000
Segmented neutrophils	11,500/μL	3,000–11,500
Band neutrophils	200/μL	0–300
Lymphocytes	1,100/μL	1,000–4,800
Monocytes	700/μL	200–1,400
Platelets	759,000/μL	200,000–500,00

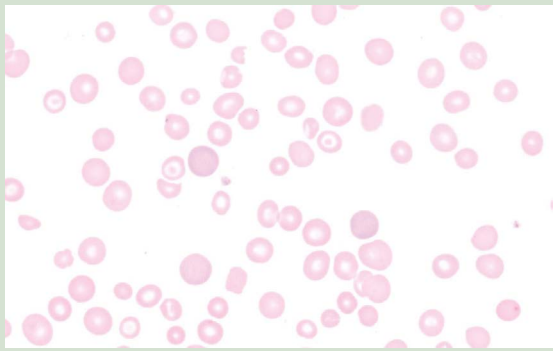


FIGURE 16.72 Blood smear. This blood smear shows a combination of polychromasia, anisocytosis, and occasional spherocytes.

Clinical Diagnosis

Iron-deficiency anemia.

Case Outcome

The dog was stabilized with packed red cell transfusion prior to further workup. Abdominal ultrasound revealed the presence of 4 cm diameter mass in the jejunum consistent with a mesenchymal cell proliferation on cytology. No evidence of metastasis was noted in the abdomen or on thoracic radiographs. The dog underwent surgery to remove the mass, and a final diagnosis of gastrointestinal stromal tumor (GIST) was obtained with immunohistochemistry.

(Continued)

The dog recovered well, and the GIST was fully excised. In dogs, that survive the perioperative period and have no visible metastasis, outcomes with GISTs can be very good, and adjuvant chemotherapy is not generally recommended. Tyrosine kinase inhibitors of c-Kit can be used in cases of unresectable or metastatic disease. The dog was euthanized 30 months later for an unrelated disease without recurrence of the GIST.

Case 16.3: Nonassociative Immune-Mediated Hemolytic Anemia – Julien R.S. Dandrieux and Katie M. Boes

Signalment/History

A 6-year-old spayed female German Shepherd Dog is presented for a 1-day history of decreased appetite and progressive lethargy. She also had a self-limiting episode of vomiting 4 days prior to presentation.

Clinical and Laboratory Examination

The dog is quiet, alert, responsive, and in a good body condition score (5/9, 28.5 kg). Her sclerae are mildly icteric. Her mucous membranes are pale with a normal capillary refilling time. Her heart rate is 132 beats/min with normodynamic pulses, and her respiratory rate 34 breaths/min with normal respiratory pattern. Thoracic and cardiac auscultation are within normal limits. There is some discomfort on cranial abdominal palpation but no masses noted.

Selected laboratory results are listed in **Table 16.17** and the blood smear is shown in **Figure 16.73**.

The anemia is marked, and there is marked agglutination on the smear that is confirmed with a saline agglutination test. Apart from the hyperbilirubinemia, the rest of the biochemistry panel is within reference interval, including the albumin and globulins concentrations. The urine was clear with negative dipstick and sediment.

Interpretation of Hematologic Abnormalities and Differential Diagnosis

Although the anemia is marked, and there is evidence of immune-mediated erythrocyte targeting (agglutination), the red cell regeneration is inadequate. This may occur with reticulocyte agglutination causing a falsely decreased reticulocyte count, peracute onset of the immune-mediated anemia (i.e., preregenerative anemia), or concurrent immune targeting of mature erythrocytes in peripheral blood and erythrocyte precursors in the bone marrow (i.e., nonregenerative anemia). The platelet count remains adequate, and the neutrophil count is usually expected to be higher with an immune-mediated hemolytic anemia. The albumin is normal, which does not support blood loss. Nonimmune-mediated hemolysis is deemed unlikely in view of the agglutination.

In view of these results, the dog is suspected to have immune-mediated hemolytic anemia, and further workup is required to determine if it is nonassociative or associative (i.e., primary or secondary). There is no history of recent drug administration, and the dog lives in a nonendemic area for arthropod-borne disease with no travel history. Further pertinent history in regard to blood transfusion requirement includes that the dog has not had a previous blood transfusion and never had a litter.

TABLE 16.17 Selected hemogram and chemistry panel results

Test	Result	Reference interval (from author's lab)
Red blood cell*	1.4 × 10^6/μL	5.5–8.5
Hemoglobin	57 g/L	120–180
Hematocrit*	0.10 L/L	0.35–0.53
PCV	0.16 L/L	0.37–0.55
MCV*	68 fL	60–75
MCHC	356 g/L	320–380
Reticulocytes*	93,000/μL	10,000–110,000
WBCs	13,500/μL	6,000–17,000
Segmented neutrophils	11,900/μL	3,000–11,500
Band neutrophils	0/μL	0–0
Lymphocytes	800/μL	1,000–4,800
Monocytes	700/μL	200–1,400
Platelets	302,000/μL	200,000–500,000
Bilirubin	25 μmol/L	0–20
Albumin	37 g/L	31–44
Globulins	37 g/L	14–37

* These results may be affected by agglutination and not be accurate in this instance.

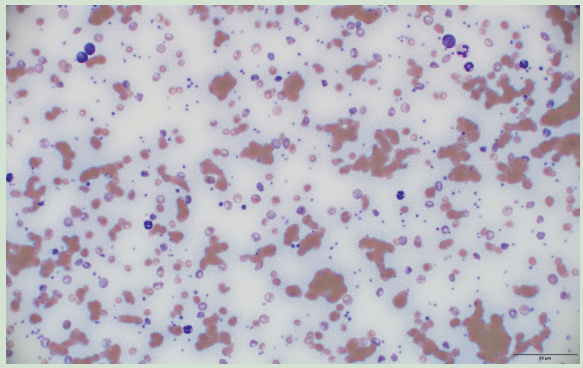


FIGURE 16.73 The body of the blood smear shows clustering of erythrocytes (agglutination) and linear arrays of erythrocytes (rouleaux). 50× objective field, Wright-Giemsa.

(Continued)

Other Diagnostic Procedures

The dog canine blood group was DEA 1-positive. In view of the agglutination, a Coombs test is not indicated.

Thoracic radiographs (including cranial abdomen) and abdominal ultrasound did not reveal any abnormalities.

The dog was stabilized with packed red blood cells and started on treatment with prednisolone for the suspected immune-mediated disease and clopidogrel to reduce the thromboembolic risk. However, the dog's PCV dropped rapidly over the following 5 days, and there was a lack of regenerative response. For this reason, a bone marrow aspiration was performed that showed ineffective hematopoiesis (i.e., lack of late-stage red cell precursors) and presence of frequent macrophages phagocytizing erythrocytes, reticulocytes, and metarubricytes. There were no dysplastic changes noted and no evidence of a neoplastic process in the bone marrow.

Clinical Diagnosis

In view of these results, the dog was diagnosed with a nonassociative or idiopathic immune-mediated hemolytic anemia targeting the peripheral red cells (agglutination) as well as the red cell precursors in the bone marrow (erythrophagia).

Case Outcome

The dog's prednisolone dosage was adjusted for her weight of 28.5 kg or 0.94 m^2 body surface area. She was treated with 40 mg/m^2, i.e., a total of 40 mg p.o. daily, rather than 60 mg (2 mg/kg daily) to reduce the risk of adverse effects as the treatment was expected to last several months.

In addition, she was treated with cyclosporine 5 mg/kg p.o. twice a day, as dogs with bone marrow involvement tend to respond more slowly, and no response was seen with 5 days of prednisolone monotherapy.

Although an anticoagulant such as rivaroxaban should be preferred, only clopidogrel was used in this instance to reduce the risk of thromboembolism.

The dog required an additional blood transfusion to stabilize her, but her anemia became regenerative 2 weeks after initiating treatment. Six months later, she remained clinically well with resolution of the IMHA, and her prednisolone had been tapered off. Her cyclosporine is currently being tapered off with the aim to discontinue all treatment within another 2 months.

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CHAPTER 17

Disorders of Hemostasis

Alex Lynch

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NORMAL HEMOSTASIS

Hemostasis represents a balance between prothrombotic (clotting) and antithrombotic (bleeding) tendencies. An antithrombotic tendency is necessary for blood to circulate as a fluid. This is achieved by an intact endothelium separating prothrombotic substances in the blood (i.e., platelets, clotting factors) from those in the perivascular tissues (e.g., subendothelial collagen, tissue factor, von Willebrand factor [VWF]). Several endogenous antithrombotics are also synthesized and released by endothelial cells. These include endogenous platelet inhibitors (e.g., nitric oxide) and inhibitors of clotting factors (anticoagulants) (e.g., antithrombin). In the event of blood vessel injury, there is a rapid switch to a prothrombotic tendency. Initially, a reflex autonomic vasoconstriction increases the probability of intraluminal and perivascular prothrombotic substances interacting with each other. These interactions ultimately lead to the formation of a blood clot (thrombus) preventing blood loss from the damaged vessel. The steps leading to thrombus formation are traditionally separated into primary and secondary hemostasis, although the cell-based model of hemostasis may represent a better representation of in vivo events.

PRIMARY HEMOSTASIS

Primary hemostasis is determined by platelet number and function. Platelets are simple anucleate disc-shaped cells that circulate in the blood for about a week in dogs and cats. Thrombopoiesis refers to the formation of platelets in the bone marrow from progenitor stem cells through to the megakaryocyte, the immediate precursor to mature platelets. Thrombopoietin, a hormone mainly synthesized by the liver, is the major regulator of the process. Despite their structural simplicity, platelets are capable of diverse biological functions related to an abundance of cell surface receptors and intracellular granules containing a myriad of biologically active substances. Platelet surface receptors fall into two major types: Adhesion receptors (facilitating tethering of platelets to the site of vessel injury) or agonist receptors (involved in platelet activation).

The first step in primary hemostasis involves platelet adhesion to the site of vessel injury (**Figure 17.1**). Adhesion is quite weak initially, associated with adhesion receptors engaging with subendothelial prothrombotic substances (e.g., VWF and glycoprotein Ib-IX-V [GPIb-IX-V] receptor, collagen and glycoprotein VI [GPVI] receptor). The specific interactions differ between arteries and veins based upon the vessel shear stress. Platelet adhesion triggers intracellular signaling pathways involved in platelet activation. Platelet activation also occurs when specific activators bind to agonist receptors. Numerous platelet activators exist but vary in terms of their potency and clinical importance. Thrombin (factor IIa) is considered the most important activator of platelets. Other substances of note include adenosine diphosphate (ADP), thromboxane, serotonin, collagen, and epinephrine. Three key events occur during platelet activation: (1) Membrane flipping (i.e., changes in platelet cell membrane structure to promote a prothrombotic cell surface), (2) shape change (i.e., disc-shaped platelets become star shaped), and (3) platelet degranulation (i.e., release of substances from the intracellular granules). Activated platelets are then capable of forming platelet-to-platelet interactions (aggregation), largely mediated through fibrinogen binding to GP IIb/IIIa receptors.

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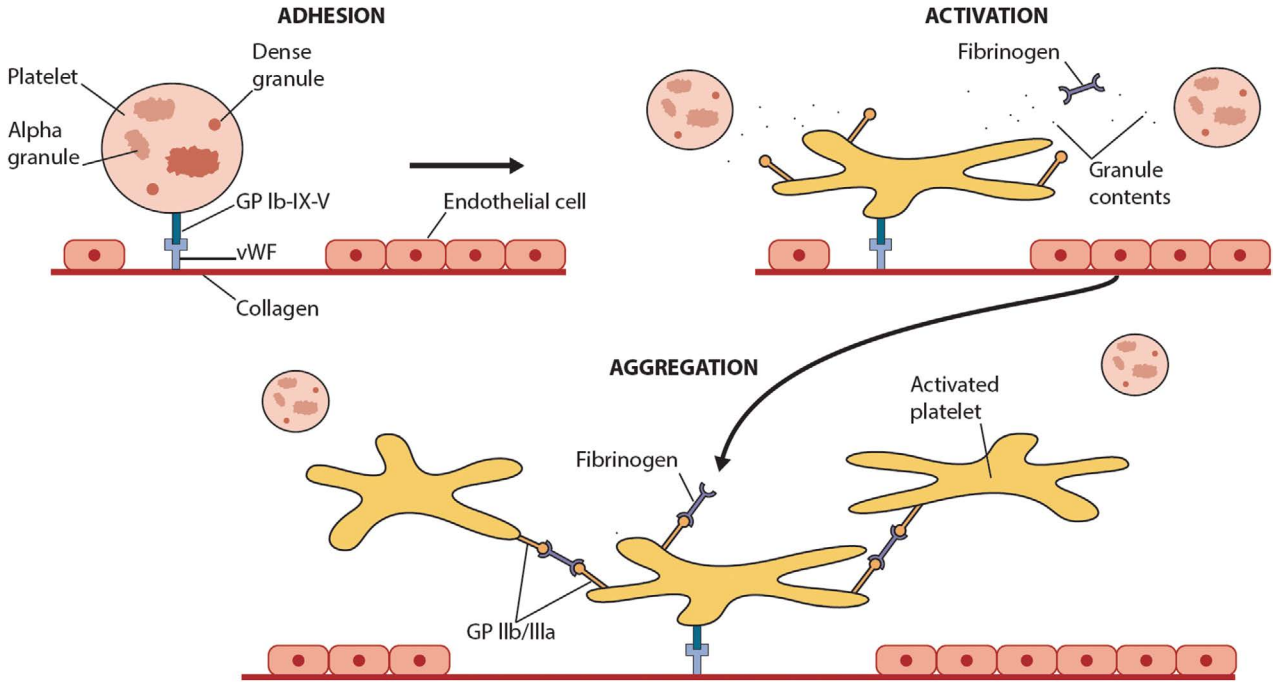


FIGURE 17.1 Platelet adhesion, activation, and aggregation. During adhesion, platelets bind to perivascular prothrombotic substances (e.g., subendothelial collagen). Platelet activation is characterized by plasma membrane flipping, shape change, and degranulation. Platelet aggregation (platelet-to-platelet interactions) mediated via fibrinogen binding to GP IIb/IIIa leads to the formation of the initial platelet plug. (*Courtesy of Bobbi Conner.*)

Aggregated platelets are the basis of the unstable platelet plug that forms as the initial defense against blood loss.

SECONDARY HEMOSTASIS

Secondary hemostasis is determined by the number and function of clotting factors, culminating in the formation of fibrin. Clotting factors are enzymes (serine proteases) that are released in their inactive form (zymogens). Similar to other enzymes, clotting factors work best within specific biological limits (e.g., temperature, pH). Clotting factors also must assemble on a phospholipid layer (e.g., cell membrane) to function appropriately, and some need cofactors (e.g., calcium, vitamin K). The clotting cascade describes the sequential activation of clotting factors, such that the preceding activated clotting factor activates the subsequent clotting factor (Figure 17.2). The nomenclature of clotting factors is somewhat confusing, since Roman numerals (e.g., factor X), names (e.g., fibrinogen), or a combination of both (e.g., thrombin and factor II) may be used to describe them. Activated clotting factors are indicated by the addition of a lowercase "a" (e.g., activated clotting factor X is FXa).

The clotting cascade is conventionally separated into extrinsic and intrinsic pathways that converge on the common pathway. The clotting factors are not numbered sequentially because individual factors were discovered prior to describing these pathways. For the clinician, distinguishing the extrinsic from the intrinsic pathway is useful when interpreting diagnostic tests.

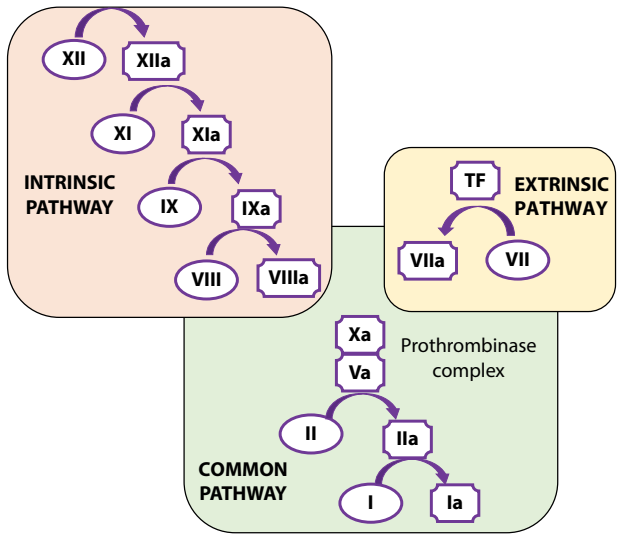


FIGURE 17.2 Depiction of the clotting cascade of serine proteases, separated into intrinsic and extrinsic pathways, converging on the common pathway culminating in fibrin formation. Activated clotting factors are denoted by "a." I, fibrinogen; Ia, fibrin; II, prothrombin; IIa, thrombin.

The extrinsic pathway, which is initiated by blood vessel injury, comprises tissue factor and FVII. Some FVII circulates in the activated form (FVIIa), making tissue factor–FVIIa interactions powerful and efficient initiators of thrombosis. In contrast, cross talk between inflammation and hemostasis is the major initiator of the intrinsic pathway (FXII, FXI, FVIII, FIX). The extrinsic and

intrinsic pathways converge on the common pathway culminating in fibrin formation. Initially, the prothrombinase complex (an enzyme complex composed of FVa–FXa) catalyzes the conversion of prothrombin (FII) to thrombin (FIIa), which in turn catalyzes the conversion of fibrinogen (FI) to fibrin (FIa). Polymerized fibrin cements the platelet plug formed at the end of primary hemostasis. Of all clotting factors, thrombin (FIIa) has greatest significance on hemostasis, since it has roles in primary and secondary hemostasis, as well as slowing clot degradation via thrombin activatable fibrinolysis inhibitor (TAFI).

CELL-BASED MODEL OF HEMOSTASIS

The cell-based model of hemostasis (Figure 17.3) provides an alternative description of the events leading to thrombus formation. The model incorporates three overlapping phases: Initiation, amplification, and propagation. Tissue factor-bearing cells (e.g., perivascular fibroblasts, macrophages, microparticles) are the major initiators of hemostasis, bearing resemblance to the events described in the extrinsic pathway. The initiation phase leads to the generation of a small amount of thrombin, which supports platelet activation during the amplification phase. The amplification phase is analogous to primary hemostasis. Finally, the propagation phase, which most closely resembles the intrinsic and common pathways, leads to the assembly of enzyme complexes (e.g., prothrombinase complex) on the surface of platelets. The propagation phase supports massive thrombin generation and effective thrombus formation.

FIBRINOLYSIS

Fibrin blood clots removal (fibrinolysis) occurs after blood vessel repair has occurred, restoring blood vessel patency. Clot breakdown is mediated by plasmin (Figure 17.4). The precursor to plasmin is plasminogen, which binds to lysine residues on the fibrin clot. Once clot bound, it is converted to plasmin under the influence of tissue plasminogen activator (tPA). Plasmin degrades the clot into fibrin degradation products (FDPs). A subset of FDPs, termed D-dimers, represent cross-linked subfractions of fibrin that were previously contained with blood clots. The fibrinolytic system is kept in check by inhibitors of tPA (i.e., plasminogen activator inhibitor-1), as well as endogenous inhibitors of plasmin (i.e., α2-antiplasmin).

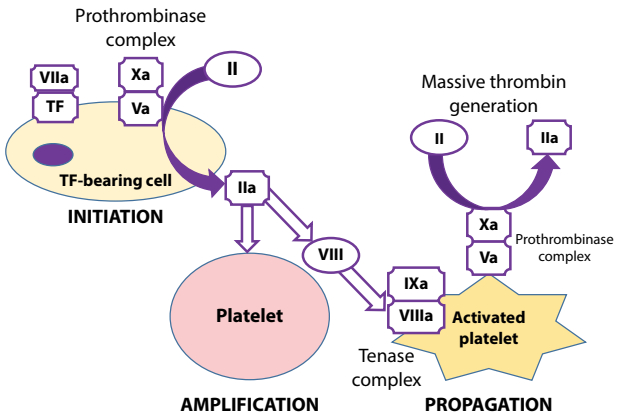


FIGURE 17.3 Depiction of the cell-based model of coagulation, consisting of initiation (on tissue factor-bearing cell surface), amplification (on nonactivated platelet surface), and propagation (on activated platelet surface) phases. Activated clotting factors are denoted by "a." TF, tissue factor.

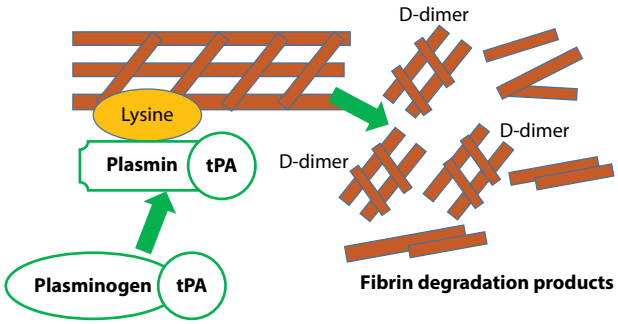


FIGURE 17.4 Plasminogen combines with tissue plasminogen activator (tPA) and is converted to plasmin. Plasmin binds to lysine residues on the surface of the fibrin clot, inducing fibrinolysis and formation of fibrin degradation products. Cross-linked fibrin degradation products are called D-dimers.

HEMOSTATIC DISORDERS

Dogs and cats with several primary diseases may develop abnormal hemostatic function. These animals may present with signs of dysfunction (i.e., bleeding or thrombosis) or be considered at increased risk of developing dysfunction in the future. Some patients can also suffer from complex hemostatic disorders, such as disseminated intravascular coagulation (DIC) that have features of both bleeding and thrombosis.

BLEEDING DISORDERS

Bleeding disorders (hypocoagulability) develop as a consequence of disordered primary hemostasis, secondary hemostasis, or fibrinolysis (Table 17.1). Primary hemostatic disorders occur with decreased platelet number (thrombocytopenia) or function (thrombocytopathia). Thrombocytopenia is most likely and must be ruled out first before considering platelet dysfunction. The hallmarks of primary hemostatic dysfunction (spontaneous small and superficial hemorrhages [petechia and ecchymoses]) contrast with the larger volume hemorrhages (e.g., body cavitary hemorrhage) more commonly seen with secondary hemostatic and hyperfibrinolytic disorders.

Table 17.1 represents the comparison of disorders of primary hemostasis, secondary hemostasis, and hyperfibrinolysis.

TABLE 17.1 Summary of the clinical features of bleeding disorders associated with primary hemostatic, secondary hemostatic, and hyperfibrinolytic disorders

	System components	Clinical signs	Diagnostic tests
Primary hemostasis	– Platelet number – Platelet function (intrinsic) – Platelet function (extrinsic)	– Spontaneous bleeding—petechiation, ecchymoses, mucosal bleeding, epistaxis, melena – Surgical/procedural/traumatic bleeding—variable but potentially severe, oozing	– Platelet count – Platelet indices – BMBT – Closure time – Aggregometry – Flow cytometry – Viscoelastic testing – Platelet mapping – VWF:Ag
Secondary hemostasis	– Clotting factor number – Clotting factor function	– Spontaneous bleeding—large volume, cavitary hemorrhage, hemarthrosis, SC bleeding, intramuscular bleeding – Surgical/procedural/traumatic bleeding	– PT – aPTT – ACT – Viscoelastic testing – Individual factor analysis – Thrombin generation
Hyperfibrinolysis	– Plasmin – Plasminogen activators – Plasminogen inhibitors	– Spontaneous bleeding—large volume, cavitary hemorrhage, hemarthrosis, SC bleeding, intramuscular bleeding – Surgical/procedural/traumatic bleeding	– FDPs – D-dimers – Viscoelastic testing

ACT, activated clotting time; aPTT, activated partial thromboplastin time; BMBT, buccal mucosal bleeding time; FDPs, fibrin degradation products; VWF:Ag, von Willebrand factor antigen.

THROMBOCYTOPENIA

Low platelet counts can be recognized by using an automated hematology analyzer and/or by reviewing blood smears. Automated platelet counts should be verified by blood smear, especially in cats, since platelet aggregation may cause falsely low numbers (pseudothrombocytopenia). Thrombocytopenia may also be seen as a normal variant in some breeds of dogs, most notably the Cavalier King Charles Spaniel. In this instance, there are a low number of larger platelets (macrothrombocytes) but without increased risk of bleeding (**Figure 17.5a, b**). It is helpful for the clinician to think about potential causes for true thrombocytopenia in terms of increased peripheral destruction, increased consumption, decreased production, or sequestration.

DESTRUCTION

Definition/Overview

Immune-mediated platelet destruction (immune-mediated thrombocytopenia [ITP]) is commonly seen in dogs but rarely seen in cats.

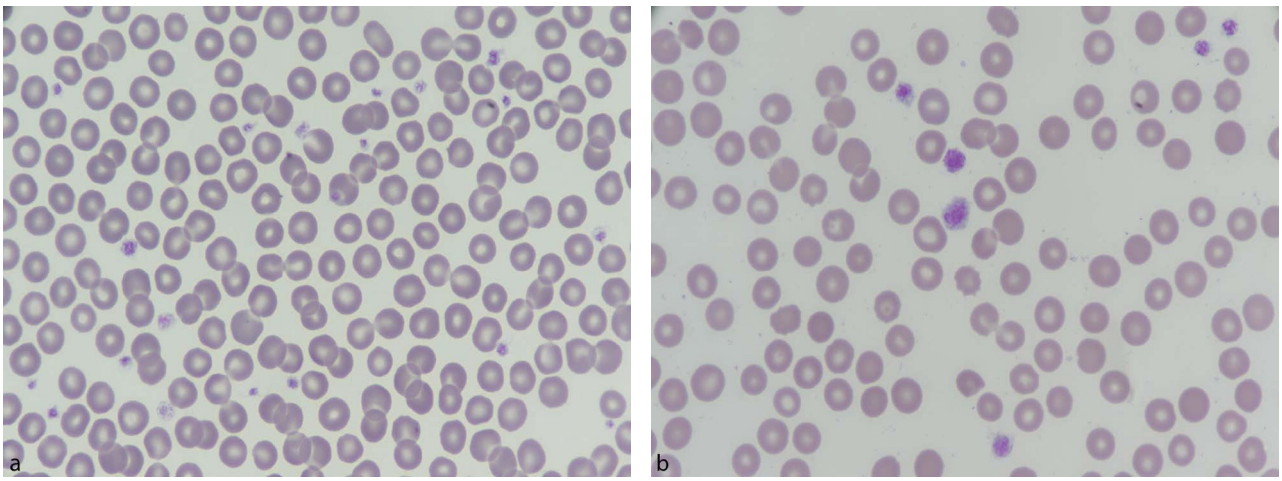


FIGURE 17.5 Comparison of **(a)** normal platelet number and platelet size in a dog with **(b)** macrothrombocytopenia in a Cavalier King Charles Spaniel. Note in the normal dog, platelets are consistently about a third to one-half the size of a red blood cell, while macrothrombocytes are about three-quarters the size of a red blood cell. (*Courtesy of Devorah Marks Stoew, DVM, DACVP.*)

Etiology

Both primary (idiopathic) and secondary forms of ITP occur. Possible triggers for secondary ITP include infections, drug or vaccine administration, neoplasia, and other immune-mediated disorders.

Pathophysiology

Antibodies directed toward glycoproteins on the platelet surface trigger a type 2 hypersensitivity reaction and subsequent platelet destruction. Spontaneous bleeding (petechiation and ecchymoses) occurs when platelets are unable to maintain normal endothelial intercellular junctions.

Clinical Presentation

Animals with ITP usually have evidence of spontaneous bleeding. Small surface bleeding (e.g., skin, conjunctiva) and mucosal bleeding (e.g., epistaxis, hematemesis, melena, gingival hemorrhage) are most common (Figure 17.6a–d), while frank hematuria can also occur. More severe bleeding may occur if trauma, surgery, or provocative procedures (e.g., biopsies) are performed. Some animals have subtle bleeding, but the systemic consequences of anemia may be more obvious (e.g., lethargy, dysrexia). Additional clinical symptoms referable to an underlying primary disease may be appreciated in patients with secondary ITP.

Differential Diagnosis

ITP typically results in severe thrombocytopenia, with alternative rule outs being bone marrow disease (e.g., neoplasia, myelofibrosis), Ehrlichiosis, destruction of platelet precursors (e.g., amegakaryocytic thrombocytopenia), and DIC.

Diagnosis

ITP leads to severe thrombocytopenia (<20,000 platelets/μL), although platelet counts <5,000/μL are most typical. Detection of antiplatelet antibodies, proving immune-mediated destruction, is uncommonly available, and more invasive tests (e.g., bone marrow sampling) to rule out other causes of severe thrombocytopenia are seldom done. Consequently, ITP is usually a diagnosis of exclusion. A diagnostic workup to assess for concurrent disease is recommended, although its extent will be



FIGURE 17.6 Classic signs of primary hemostatic dysfunction in dogs with immune-mediated thrombocytopenia. **(a)** Buccal mucosal petechiation, **(b)** ecchymoses on the trunk, **(c)** gross hematemesis in vomitus, **(d)** dark tarry stool melena in the perianal region.

determined by patient stability and owner finances. At a minimum, complete blood count, serum biochemistry, urinalysis, thoracic and abdominal imaging, and infectious disease testing endemic to your area are reasonable. A careful history to include recent drug exposure, recent vaccination, and any travel is also important.

Management

Therapeutic strategies for ITP are focused on three major aims: (1) Preventing further platelet destruction, (2) increasing platelet number, and (3) addressing the systemic consequences of thrombocytopenia. Preventing further platelet destruction involves immunosuppression and measures to combat any underlying inciting disease (e.g., doxycycline for vector-borne disease). Initial immunosuppression should involve oral prednisone in dogs (prednisolone in cats), but injectable dexamethasone sodium phosphate may be given initially in the hospital. Platelet recovery takes up to 7 days in most dogs with ITP treated with prednisone alone. It is noteworthy that spontaneous bleeding appears uncommon once platelet counts >40,000/μL are achieved. Prednisone plus another immunosuppressive drug may be considered, but there is no compelling evidence that two immunosuppressive drugs achieve faster remission than prednisone alone. Prednisone is typically tapered slowly (e.g., 3–6 months), since rapid discontinuation may lead to clinical relapse. A multitude of side effects may occur when long-term prednisone is used, however (e.g., polyuria, polydipsia, polyphagia, iatrogenic hypercortisolemia). A second immunosuppressive agent may enable faster tapering of prednisone with a lower chance of relapse. Several second-line immunosuppressive drugs could be considered (e.g., azathioprine, cyclosporine, mycophenolate, and leflunomide), and the decision is likely based on clinician preference. During the initial treatment of ITP in dogs, human intravenous immunoglobulin (IVIG) plus prednisone has been associated with faster recovery of platelet count compared to prednisone alone. The antineoplastic drug vincristine may also be considered to accelerate platelet recovery. Vincristine is thought to increase fragmentation of megakaryocytes and may also slow platelet destruction. Platelet recovery time is about 48 hours faster when dogs are managed with IVIG/prednisone or vincristine/prednisone compared to prednisone alone. Some dogs with systemic signs of anemia (e.g., weakness, tachycardia, tachypnea) may benefit from red blood cell transfusions. Hemostatic competence may also improve when red cells are administered, associated with improved platelet margination in blood vessels. Platelet containing blood products are not typically recommended in dogs with ITP, since transfused platelets are also destroyed rapidly. Platelet administration may be needed in the event of life-threatening bleeding (e.g., brain or lung hemorrhages). Gastroprotectants (e.g., antacids, sucralfate) are not likely to help gastrointestinal bleeding in dogs with ITP, since the bleeding is driven by their thrombocytopenia rather than gastric ulceration.

Prognosis

Up to 85% of dogs with ITP respond to treatment, but less information is available in cats since the disease is so rare. Worse outcome has been reported in dogs with ITP that have evidence of melena or high blood urea nitrogen (BUN) at presentation. Relapses may occur, especially if immunosuppressive therapies are discontinued quickly, and overall outcome may be worse if severe comorbidities are present.

CONSUMPTION

Consumptive thrombocytopenia is commonly seen in dogs and cats. Platelet extravasation leads to a low circulating platelet count. This may occur secondary to bleeding (e.g., hemangiosarcoma, trauma, DIC), sepsis (i.e., extravasation of neutrophil–platelet aggregates), thrombosis, endocarditis, pit viper envenomation, and vasculitis (Figure 17.7). Consumptive thrombocytopenia typically results in a platelet count in the region of 50,000–100,000/μL and should be considered less likely if a patient has a platelet count <20,000/μL. Consumptive thrombocytopenia is usually incidentally identified during the workup of different symptoms, since spontaneous bleeding is unlikely to occur. Hemostatic competence is generally preserved in these patients, such that dogs with splenic masses usually do not bleed during surgery even in the face of thrombocytopenia (Figure 17.8). It is wise to exert some caution, however, in thrombocytopenic animals, and specific risk should be considered on a case-by-case basis. In general, treatment of consumptive thrombocytopenia is usually directed at the primary disease process rather than the thrombocytopenia itself.

LACK OF PRODUCTION

Failure to generate new platelets most commonly occurs with bone marrow disease but could be a component of hepatic disease due to thrombopoietin deficiency.



FIGURE 17.7 Dog with sepsis secondary to infected bite wounds with a platelet count of 80,000/μL.

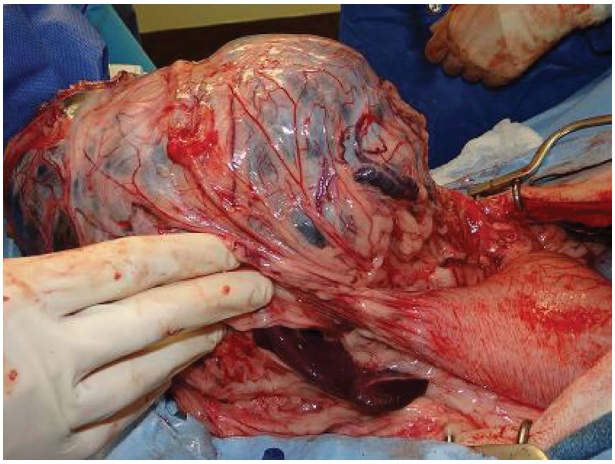


FIGURE 17.8 Splenic mass in a dog that was incidentally found in a dog with a platelet count of 107,000/μL identified on routine wellness blood work.

Severe thrombocytopenia is likely to occur with bone marrow disease and so can easily be confused with ITP. Bone marrow sampling would be necessary to confirm a diagnosis. Bone marrow sampling is uncommonly performed in severely thrombocytopenic dogs unless there is concern for deficiencies in other cell lines. A complete blood count is recommended in all animals with thrombocytopenia, therefore, since identifying bicytopenia or pancytopenia makes bone marrow disease more likely than ITP. Bone marrow sampling may also be recommended in some dogs with severe thrombocytopenia, once they have failed to respond to standard therapy. The nature of the underlying bone marrow disease can be variable (e.g., neoplastic, infectious, toxic, fibrosis).

SEQUESTRATION

Sequestration is the least common form of thrombocytopenia seen in dogs and cats. It occurs when platelets are effectively trapped and cannot circulate appropriately. This most likely occurs in splenic disease, particularly splenic torsion, but could also occur with severe hypothermia.

THROMBOCYTOPATHIA

Definition/Overview

Thrombocytopathia should be considered in patients with signs of primary hemostatic dysfunction that have normal platelet counts. Increased bleeding tendency may be appreciated after excessive bleeding following invasive procedures (e.g., cystocentesis, surgery).

Etiology

Thrombocytopathia may reflect an inherited or acquired problem, as well as an intrinsic or extrinsic dysfunction. Inherited intrinsic platelet disorders are uncommon but have identified in several dog and cat breeds. In contrast, von Willebrand disease (VWD) is a relatively common inherited extrinsic platelet disorder in dogs. Acquired platelet dysfunction may occur after administration of certain drugs and in some disease states. For example, clopidogrel and aspirin are commonly used to intentionally inhibit platelet dysfunction for treatment or prevention of thrombosis. Dose-dependent dysfunction may occur in animals receiving high doses of synthetic colloids. Several disease states may also lead to acquired thrombocytopathia, including, but not limited to, uremia, pit viper envenomation, babesiosis, heat stroke, and trauma-induced coagulopathy.

Pathophysiology

Clotting factors need to assemble on activated platelets in order to support thrombin generation. Intrinsic dysfunction represents an inherent issue with the platelet itself (e.g., failure to activate or aggregate). Inherited intrinsic platelet dysfunctions may represent diverse issues, including platelet receptor deficiency (e.g., Glanzmann thrombasthenia in Great Pyrenees dogs) and abnormal membrane flipping (e.g., Scott syndrome in German Shepherd Dogs). In contrast, extrinsic platelet dysfunction represents a failure of adhesion of otherwise normal platelets and is seen with VWD. Three variants of VWD are recognized (types 1, 2, and 3) based on the type and number of missing VWF multimers. Type 1 is the most common type seen, especially in Dobermanns. Affected patients have reduced numbers of both large and small multimers. Type 2 VWD has been described in German Shorthaired and Wirehaired Pointers and is characterized by fewer large multimers. Type 3 VWD is rarely seen but has been described in dog breeds, including Scottish Terriers and Shetland Sheepdogs. Type 3 affected dogs lack all multimers, and severe bleeding can occur. Most dogs with VWD do not experience spontaneous bleeding, but severe hemorrhage may occur after surgery or trauma.

Clinical Presentation

Depending on the disorder in question, spontaneous bleeding may or may not be noted, and the first hint of dysfunction may be related to abnormal bleeding after trauma, surgery, or other invasive procedures (Figure 17.9). In the latter scenario, severe and large-volume bleeding may be noted, which contrasts the superficial small bleeds typical of thrombocytopenia. It is also possible that the practitioner is faced with an animal known to have an issue or to be at risk of thrombocytopathia (e.g., Dobermann presented for elective surgery without known VWD status).

Differential Diagnosis

Thrombocytopenia; VWD also may resemble disordered secondary hemostatic disorders and hyperfibrinolysis.



FIGURE 17.9 Dog with heatstroke that developed marked epistaxis following placement of a nasogastric tube. The dog had a platelet count of 90,000/µL and normal PT and aPTT, suggesting the presence of thrombocytopathia as a cause for bleeding.

Diagnosis

As mentioned previously, verification of an accurate platelet count is important before performing any tests of platelet function. If an accurate count cannot be obtained due to excessive clumping, the possibility of significant intrinsic platelet dysfunction appears less likely, since aggregation has effectively been observed, but VWD cannot be excluded. It is also common for clinicians to perform tests of secondary hemostasis (PT, aPTT, ACT) and/or viscoelastic tests at this juncture to characterize hemostatic status as much as possible. For most clinicians, the first and most available insight into platelet function is the buccal mucosal bleeding time (BMBT) (Figure 17.10). This test is crude and subject to interoperator variation but provides good insight into primary hemostatic competence and is easily performed. Depending on patient tolerance, at least light sedation is usually necessary. The animal is restrained in lateral recumbency, and the upper lip is pulled upwards in order to expose the buccal mucosa. A proprietary lancet is used to make a uniform incision into the mucosa, avoiding obvious superficial blood vessels, and filter paper is placed close to the incision. The filter paper is used to soak up dripping blood, but care must be taken not to disturb the clot as it forms. Cats are expected to stop bleeding within 2.5 minutes, and most dogs stop between 3 and 4 minutes. Prolonged bleeding times suggest platelet dysfunction provided platelet counts are normal. An alternative strategy providing similar information to the BMBT is measuring the platelet closure time using an automated machine (PFA-100, PFA-200). If an abnormal BMBT or platelet closure time is identified, further tests to characterize the reason for this dysfunction may be pursued (e.g., VWD testing). This requires measurement of VWF antigen at a specialist laboratory on blood collected prior to significant bleeding or transfusion of plasma products. The VWF antigen is expressed as percentage between 0% and 180%, with VWF antigen <50% representing dogs that are abnormal carriers of VWD and at higher risk of bleeding. Animals with VWF antigen >70% are unlikely to be VWD carriers or to be at risk of bleeding. In situations where intrinsic platelet pathology is suspected, other tests (e.g., aggregometry, flow cytometry) may be used but are usually available at specialist centers only. Platelet function may also be assessed in animals receiving antiplatelet drugs for therapeutic monitoring. This may be considered to ensure an antiplatelet effect has been achieved or to assess bleeding risk. The latter may be needed in animals receiving antiplatelet drugs that require an invasive procedure (e.g., dental extractions, feeding tube placement). Monitoring options include modified viscoelastic tests (thromboelastography (TEG) platelet mapping) and platelet aggregometry. Ideally, the patient's platelet function will be compared relative to their own baseline function, with reasonable therapeutic goals of >80%–90% platelet inhibition.



FIGURE 17.10 A proprietary lancet used to perform a buccal mucosal bleeding time.

Management

Specific interventions are dictated by whether bleeding is present. If bleeding is present, then transfusion products may be necessary. The exact type of blood product is situation specific but could include fresh whole blood (containing platelets, red cells, and clotting factors) in animals with acute hemorrhage and anemia, while nonanemic patients may benefit from the transfusion of platelets and/or coagulation proteins without red blood cells. For animals with acquired dysfunction without active bleeding, recommendations may consist entirely of avoiding invasive procedures and treating underlying disease. Pre-emptive administration of blood products may be used in animals with platelet dysfunction without active bleeding undergoing elective procedures. For example, a Dobermann with type 1 VWD undergoing routine ovariohysterectomy would benefit from pre-emptive administration of VWF via cryoprecipitate (1 unit per 10 kg), fresh frozen plasma (10 mL per 10kg), or fresh whole blood (1 unit per 15 kg). Desmopressin, a synthetic analog of vasopressin, is also commonly used



FIGURE 17.11 Nasal formulation of desmopressin that can be administered subcutaneously to augment hemostatic function via release of stored von Willebrand factor in the endothelium.

for dogs with VWD. Desmopressin activates vasopressin receptors on the endothelium, leading to release of stored VWF. In practice, this requires subcutaneous injection of the intranasal desmopressin product typically used for the management of diabetes insipidus. A previously unopened desmopressin product should be used at a dose of 1–4 µg/kg about 30 minutes before the elective procedure (Figure 17.11). Desmopressin could also be used in patients with active bleeding associated with platelet dysfunction, although it can only be given once or twice given the finite VWF stores in the endothelium. Desmopressin can also be administered to dogs prior to donating blood to boost the amount of VWF in the collected unit before administration.

Prognosis

Prognosis is mainly determined by the presence or absence of bleeding, as well as any underlying disease processes present. Bleeding can be severe, especially in the postoperative setting, and blood products are the key to successful management.

CLOTTING FACTOR DEFICIENCY OR DYSFUNCTION

Definition/Overview

Secondary hemostatic disorders are associated with reduced numbers or activity of clotting factors. These conditions may result in overt bleeding but may also be considered in certain situations prior to bleeding (e.g., liver disease).

Etiology

Several inherited clotting factor deficiencies have been described in dogs and cats, although they vary in terms of their prevalence. Hemophilia A (FVIII deficiency) is the most common inherited clotting factor disorder in dogs. Acquired secondary hemostatic deficiencies can occur associated with several underlying diseases, including DIC, vitamin K antagonism (e.g., anticoagulant rodenticide toxicity), severe liver disease, neoplasia, heatstroke, angiostrongylosis, and severe trauma. Iatrogenic coagulopathy may be appreciated secondary to anticoagulant overdosing, excessive synthetic fluid administration leading to dilution, severe acidemia, and severe hypothermia.

Pathophysiology

Although specifics may vary between individual diseases, thrombus formation is prevented if clotting factors or cofactors are absent. Clotting factor deficiency underpins the bleeding noted in animals with inherited disorders, as well as synthetic liver disease. In the case of Coumadin-derived vitamin K antagonist anticoagulant rodenticide toxicity, clotting factor numbers are initially preserved, but activation is impaired. These rodenticides inhibit the enzyme vitamin K epoxide reductase, preventing vitamin K recycling. In its absence, vitamin K dependent clotting factors (FII, FVII, FIX, FX) remain inactive and cannot exert their biological activity.

Clinical Presentation

Animals may present with symptomatic bleeding as outlined in Table 17.1. Historical clues (e.g., patient age) may be helpful in prioritizing certain differentials, for example dogs with hemophilia A (FVIIIa deficiency) may develop overt bleeding when deciduous teeth are lost or after initial vaccinations. Older animals with signs of secondary hemostatic dysfunction would be more likely to have rodenticide toxicity, liver disease, and neoplasia. Some animals may be seen that are currently asymptomatic but with an increased risk of bleeding. This includes that have recently ingested anticoagulant rodenticides, since evidence of bleeding usually occurs 3–5 days later. Dogs with severe hepatopathy also tend not to exhibit spontaneous bleeding even in the face of abnormal hemostatic tests but can bleed considerably after biopsy.

Differential Diagnosis

Hyperfibrinolysis, VWD.

Diagnosis

In symptomatic animals, an initial diagnostic step would be to perform the traditional hemostatic tests PT and aPTT. The PT gives insight into the extrinsic (FVII) and common pathways, while the aPTT provides insight into intrinsic (FXII, FXI, FIX, FVIII) and common pathways. Interpreting PT and aPTT together provides useful insight into the specific issues at play in an individual animal. For example, a patient with an extrinsic pathway defect will have prolonged PT relative to aPTT, while aPTT prolongation in the face of normal or minimally prolonged PT is suggestive of intrinsic

pathway dysfunction. The most common reason for extrinsic pathway abnormalities is vitamin K antagonism, since FVII has the shortest half-life of the vitamin K dependent factors. Anticoagulant rodenticide toxicity is the most common reason for vitamin K antagonism but may also occur in severe hepatic disease and malabsorptive conditions (e.g., severe inflammatory bowel disease). Intrinsic pathway defects, characterized by aPTT prolongation in excess of PT, can be a helpful clue toward hereditary factor deficiencies (e.g., hemophilia A [FVIII], hemophilia B [FIX]). This pattern is also appreciated in cases of consumption, as well as in proinflammatory states (e.g., immune-mediated hemolytic anemia [IMHA]). If inherited factor deficiencies are suspected, individual factor analysis can be performed at specialist laboratories but should be performed prior to administration of plasma products. The clinician should be mindful of the potential pitfalls of PT/aPTT measurement, especially if point-of-care devices are used, since they are more prone to error than specialist laboratory tests (**Figure 17.12a, b**). The activated clotting time (ACT) is a whole blood alternative to aPTT. While the ACT will provide similar information to the aPTT, it can be affected by anemia and thrombocytopenia. It has particular utility in situations where the effects of high concentrations of heparin are being monitored (e.g., dialysis circuits). Viscoelastic indicators of clot strength (e.g., maximum amplitude on TEG) are largely determined by fibrinogen content and, therefore, could be utilized in understanding hemostatic competence of dogs with secondary hemostatic dysfunction but would do little to help identify the reason for bleeding

Management

Therapeutic strategies will be based on (1) clotting factor replacement, (2) cofactor administration, and/or (3) pharmacological hemostatic agents. Clotting factor replacement involves transfusion of plasma containing blood products. Labile clotting factors (FV, FVIII) persist for a shorter period of time than others. Fresh frozen plasma refers to a plasma product collected from a dog, promptly spun and separated, and stored for up to 12 months. Beyond 12 months, the product is termed frozen plasma since the labile factor activities are decreased. If the clinician intends to transfuse FVIII to a dog with hemophilia A, for example, it will be necessary to transfuse either fresh whole blood, fresh frozen plasma, or cryoprecipitate. In contrast, a dog that has vitamin K antagonism secondary to rodenticide toxicity in need of FII, FVII, FIX, and FX could be administered fresh whole blood, fresh frozen plasma, or frozen plasma.

Cofactor administration most commonly consists of providing vitamin K in situations of suspected or confirmed vitamin K antagonism. Injectable vitamin K is usually given subcutaneously in symptomatic patients with bleeding or if there is concern for malabsorptive disease. Intravenous injection of vitamin K has been associated with anaphylaxis, and intramuscular injection could lead to intramuscular bleeding. Once stabilized, oral vitamin K can be administered instead. The dose and duration of therapy will vary depending on the disease state in question. For example, physiological doses of vitamin K (1 mg/kg per day) are usually given to animals with hepatopathy undergoing liver biopsy for 1–2 days prior to surgery and for 1–2 days postoperatively. In contrast, animals that were symptomatic for anticoagulant rodenticide intoxication are given higher doses (5 mg/kg per day) for 30 days given the persistence of toxicant. It is then typical for PT to be rechecked 48 hours after cessation of vitamin K to verify no residual coagulopathy is present. An alternative approach is employed when dealing with animals that have just ingested rodenticide that are not yet symptomatic. Prompt gastrointestinal decontamination (emesis and activated charcoal) should be employed, and then two options exist for management. Given the success of decontamination, vitamin K can be held initially, and a PT is checked 48 hours later. If the PT is normal, then no further treatment is needed, while vitamin K (5 mg/kg per day for 30 days) is instituted as for symptomatic cases if the PT is prolonged.

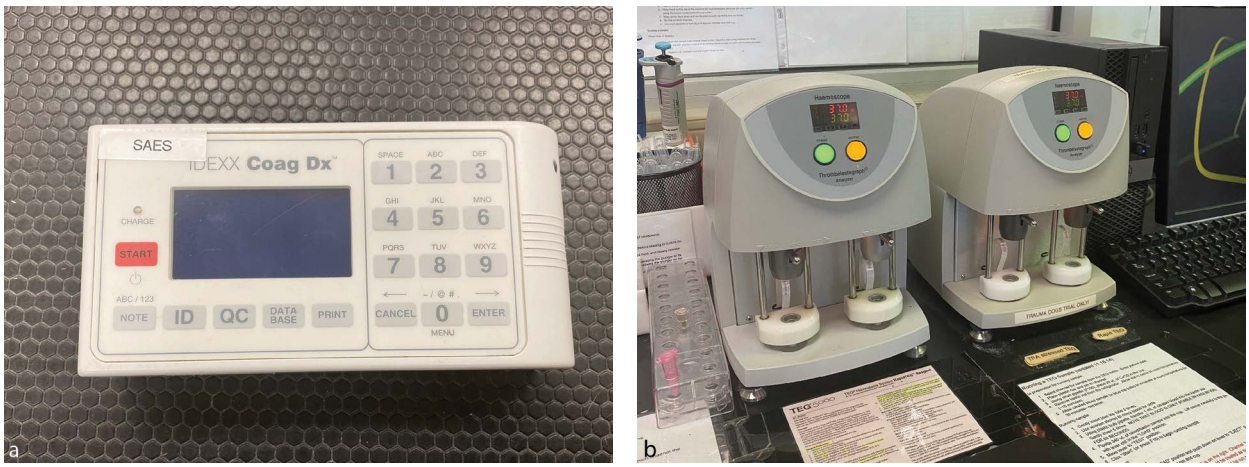


FIGURE 17.12 (a) Point-of-care device for patient-side measurement of prothrombin time and activated partial thromboplastin time and **(b)** thromboelastography machines.

Alternatively, vitamin K could be started after decontamination and given for 30 days, then rechecking PT 48 hours after cessation as for asymptomatic cases.

Finally, protamine is a specific antidote used in cases of iatrogenic bleeding secondary to heparin overdose but can prove difficult to dose effectively. Gene therapies are also emerging as potential therapeutic strategies for certain hereditary coagulopathies. Nonspecific hemostatic drugs (e.g., antifibrinolytics) may be considered for their adjunctive hemostatic effects.

Prognosis

Prognosis will be heavily influenced by the presence or absence of bleeding, as well as the reason for bleeding. Prompt and appropriate therapies for rodenticide toxicity, for example, are associated with excellent clinical outcomes, while hemostatic dysfunction secondary to severe underlying diseases (e.g., liver disease, heatstroke) will be determined by the severity of that issue. Animals with hereditary coagulopathies that receive repeated transfusions in light of bleeding events can survive long term, but this can prove to be both financially and emotionally taxing for owners.

HYPERFIBRINOLYSIS

Definition/Overview

Hyperfibrinolytic disorders describe enhanced plasmin-mediated clot breakdown.

Etiology

Hyperfibrinolysis is thought to occur in some Greyhounds that experience delayed postoperative hemorrhage secondary to decreased alpha-2 antiplasmin. Fibrinolytic disorders have also been identified as a secondary component of some hereditary coagulopathies in people (e.g., hemophilia A), but this has not been reported in dogs. Acquired hyperfibrinolysis has been reported in the setting of acute hemorrhage and shock (e.g., severe trauma, spontaneous hemoperitoneum), as well as acute liver disease and angiostrongylosis.

Pathophysiology

Simplistically, enhanced plasmin-mediated clot removal risks excessive blood loss, which could, in fact, lead to a consumptive coagulopathy through platelet and clotting factor use. The exact mechanisms at play in individual dogs have not been well characterized. Primary (hereditary) disorders represent abnormal regulation of fibrinolysis, while secondary (acquired) disorders describe increased activity of fibrinolysis. Hyperfibrinolysis associated with severe trauma and shock is well characterized in people and is thought to reflect the downstream effects of endothelial dysfunction (e.g., massive tPA release, inhibition of plasminogen activator inhibitor 1).

Clinical Presentation

Hyperfibrinolytic disorders should be considered in patients with acute, severe, large-volume hemorrhage, especially if shock or trauma is concurrently present. It is possible for hyperfibrinolysis to occur in conjunction with signs of other indicators consumptive coagulopathy (e.g., moderate thrombocytopenia, moderate PT, and aPTT prolongation).

Differential Diagnosis

Secondary hemostatic disorders, VWD.

Diagnosis

Until recently, D-dimers provided the best insight into fibrinolytic function in an individual patient. The more widespread availability of viscoelastic testing has provided an increased opportunity to identify hyperfibrinolysis (recognized as increased clot lysis) in dogs. The ability to recognize hyperfibrinolysis may be optimized by adding tPA to the TEG (tPA stressed TEG) (Figure 17.13).

Management

Antifibrinolytic drugs are a specific option for managing hyperfibrinolysis. Lysine analogs, including tranexamic acid and epsilon aminocaproic acid, are used for this purpose. Lysine analogs prevent the binding of plasminogen to lysine residues on the fibrin clot, thereby preventing plasmin-mediated clot removal (Figure 17.14). Management of hypoperfusion, especially if resuscitation is performed with plasma rather than large volumes of synthetic fluids, may play an important role in correcting hyperfibrinolysis in patients with states of shock.

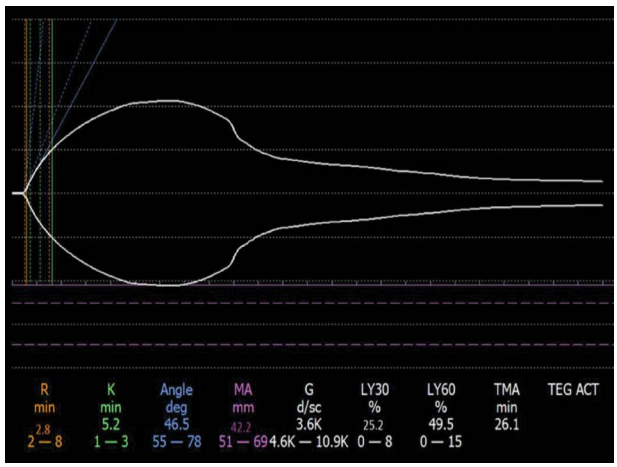


FIGURE 17.13 Thromboelastogram from a dog that sustained severe hemorrhage and hypovolemia following a thoracic stick impalement. The tracing is narrowed, consistent with hypocoagulability, and collapses prematurely, consistent with hyperfibrinolysis.

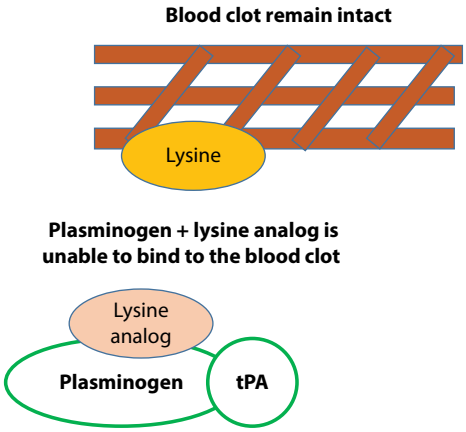


FIGURE 17.14 Lysine analogs prevent plasminogen binding to lysine residues on the surface of the fibrin clot, therefore supporting clot persistence.

Prognosis

Prognosis will be determined by the extent and severity of bleeding, especially in animals that suffered serious traumatic injuries. Bleeding in Greyhounds is unlikely to impact mortality but can be associated with longer hospitalization and more expensive treatments (e.g., blood product administration).

THROMBOTIC DISORDERS

Clinicians may be faced with animals that have (1) overt evidence of thrombosis, (2) a high suspicion of thrombosis not confirmed definitively, or (3) a disease associated with increased risk of thrombosis. Thrombosis can contribute to significant morbidity and mortality in affected animals. Thrombosis is used to describe blood clots that are localized to their blood vessel of origin, whereas thromboembolism describes the movement of a blood clot from its original location to a distant site. Risk factors for thrombosis development are described by Virchow's triad: (1) Hypercoagulability, (2) blood stasis, and (3) endothelial dysfunction. It is likely that several components of the triad must be present in order for thrombosis to occur. Hypercoagulability is the most readily investigated aspect of the triad. Viscoelastic tests provide a clinical correlate to hypercoagulability (e.g., increased maximum amplitude on thromboelastography). Hypercoagulability can occur associated with prothrombotic factor excess (e.g., increased fibrinogen, platelet hyperactivity) or antithrombotic factor deficiency (e.g., antithrombin loss). Blood stasis is harder to assess in individual patients, but ultrasound can be used to assess blood flow. Lastly, endothelial dysfunction is most difficult to assess and, therefore, is hard to assess its importance in individual patients. Patients tend to have either arterial thrombosis or venous thrombosis, suggesting different risk factors likely exist for their development, and will be considered separately in further sections.

ARTERIAL THROMBOSIS

Definition/Overview

Blood clots in the terminal aorta are common in cats (aortic thromboembolism [ATE]) and occasionally seen in dogs (aortic thrombosis). Other arteries may be affected leading to variable symptoms (e.g., cerebellar artery in a dog with acute cerebellar ataxia, main pulmonary artery thrombosis in a dog with pulmonary hypertension).

Etiology

ATE is most commonly seen in cats with cardiomyopathy (Figure 17.15) but may also occur secondary to lung (Figure 17.16a, b) tumors. Aortic thrombosis is less common in dogs but can occur due to a variety of diseases (e.g., protein-losing nephropathy, neoplasia, steroid administration, endocrinopathies, infections). No apparent cause is identified in some dogs with AT, however, despite extensive workup (i.e., cryptogenic disease).

Pathophysiology

Virchow's triad can be applied to understand the mechanisms underpinning arterial thrombosis. All aspects of the triad are potentially abnormal in cats with cardiomyopathy, for example. These cats are known to have prothrombotic factor excess, evidence of blood stasis when there is left atrial enlargement (evidenced by spontaneous echocardiographic contrast [smoke] and reduced atrial flow), and evidence of endothelial dysfunction on necropsy. Hypercoagulability may be recognized in other patients with arterial thrombosis (e.g., hypercoagulability on TEG, antithrombin deficiency), but blood stasis and endothelial dysfunction are harder to assess. Blood clots identified in arteries may represent true thrombosis or thromboembolism. Blood clots forming in the left ventricle (Figure 17.16c), for example, in cats with ATE break off then travel to the distal aorta, leading to significantly compromised blood flow to distal tissues.



FIGURE 17.15 Distal aortic ("saddle") thrombus in a cat with hypertrophic cardiomyopathy. (*Courtesy of M. Schaer.*)

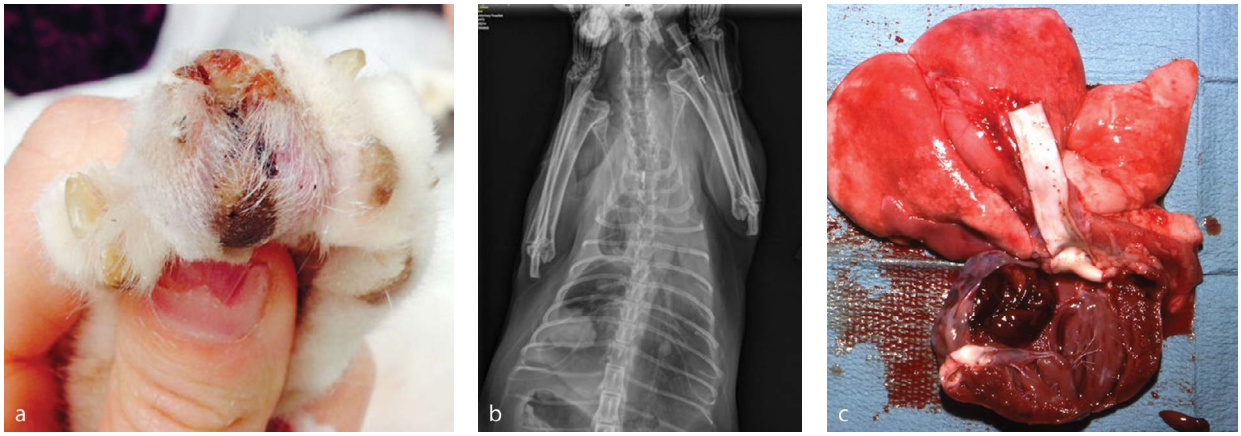


FIGURE 17.16 (a) A cat's paw showing the effects of a lung tumor thromboembolus; **(b)** ventral-dorsal radiograph of the same cat from (a) showing lung tumors with a prominent lesion in the right caudal lung lobe; **(c)** a postmortem view of a cat with cardiomyopathy and a large left atrial mural thrombus.

Clinical Presentation

Cats with ATE often present with an acute onset of bilateral pelvic limb paresis or plegia, with associated pain and distress recognized by marked tachypnea and vocalizing. Some cats may present with thoracic limb involvement and/or one pelvic limb instead. For cats with bilateral pelvic limb involvement, physical examination usually fulfils the five Ps: Paresis/plegia, pain, pallor, pulse absence, and poikilothermia (cold limbs) (Figure 17.17a). ATE may be the first indication of heart disease in some cats since there is often a long preclinical asymptomatic phase. The stress of the acute ATE event may push cats into congestive heart failure, so pulmonary edema and hypoxemia may also be identified. A similar presentation may be noted in dogs with aortic thrombosis, but more chronic and less dramatic presentations are also appreciated. Signs of arterial thrombosis will vary if other tissues are affected. Large blood clots in the pulmonary artery (Figure 17.17b) may lead to an acute onset of respiratory distress and hypoxemia or cardiovascular dysfunction. In the latter scenario, obstruction of blood flow from the right side of the heart will translate into poor left-sided cardiac output and signs of hypoperfusion.

Differential Diagnosis

Varies depending on the clinical presentation, for example, differential diagnoses for paresis include spinal cord injury, neoplasia, and muscle injury.

Diagnosis

Blood clots may be visualized with diagnostic imaging (e.g., ultrasound, computed tomography) but do require specialized equipment. For cats with ATE, a glucose and lactate differential can be considered. A blood sample obtained from an affected limb would be expected to have lower glucose and higher lactate compared to a sample obtained from an unaffected limb or jugular blood sample due to differences in perfusion. In many instances, confirmation of a blood clot with imaging or performing a glucose-lactate differential are not needed, since the presenting clinical signs are so compelling. For cats with signs of ATE, diagnostic workup should

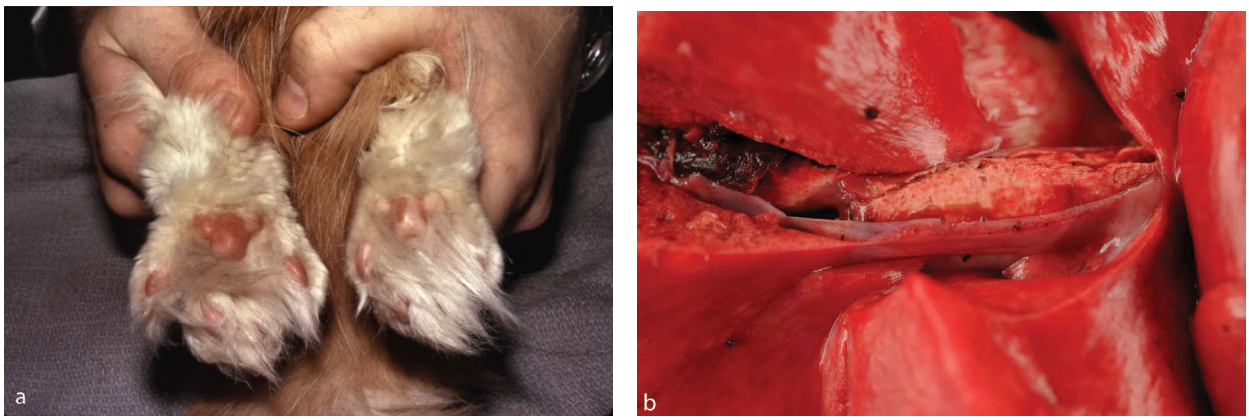


FIGURE 17.17 (a) Paw pads from a cat with aortic thromboembolism. Note the difference in color between the pads, the pad on the right showing acrocyanosis compared with the pad on the left. **(b)** A postmortem view of a Cushing's dog that formed a large thrombus in the pulmonary artery. (*Courtesy of M. Schaer.*)

consist of thoracic radiographs (to check for pulmonary edema and rule out lung masses) and ideally would involve characterization of underlying heart disease (e.g., echocardiography). For dogs with arterial thrombosis, a minimum diagnostic workup to include complete blood count, serum biochemistry, urinalysis, thoracic and abdominal imaging, and blood pressure measurement would be reasonable. Based on initial results, additional diagnostic testing may be considered (e.g., endocrine testing, advanced imaging). It is also noteworthy for the clinician that submits a pet with suspected blood clots for postmortem examination that blood clots may lyse quickly after death and, therefore, not be seen.

Management

Clinical management may encompass specific antithrombotic medications, as well as supportive measurements (e.g., analgesia, care of the recumbent animal) and treatment of underlying disease (e.g., heart failure management). Antithrombotic drugs refer to any drug that prevents blood clot formation. Antiplatelet drugs interfere with platelet function specifically, while anticoagulants interfere with clotting factors. The two situations when these drugs are used are preventing existing blood clots from getting bigger (i.e., treatment) or preventing new blood clots from forming (i.e., prevention or thromboprophylaxis). Histologically, arterial clots are platelet rich, and, therefore, antiplatelet drugs are often considered as the go-to option. The drug options most commonly used are aspirin and clopidogrel. Aspirin is a nonselective COX inhibitor that prevents the synthesis of thromboxane within the platelet. Thromboxane is, therefore, unable to bind to its specific platelet agonist receptor (TXA_2 receptor) and leads to irreversible platelet inhibition. Clopidogrel, in contrast, competes with ADP and prevents it binding to the specific ADP agonist receptor (P2Y12). Clopidogrel is considered to be superior to aspirin and is used more often in dogs and cats. Anticoagulant drugs (e.g., heparin, rivaroxaban) (Table 17.2) are still used with some frequency in animals with arterial thrombosis, since thrombin generation involves the assembly of clotting factors on the surface of activated platelets. For cats with cardiomyopathy, clopidogrel is often started if left atrial enlargement is noted prior to the onset of overt thrombosis, while dual therapy with clopidogrel and anticoagulants tend to be used after an acute crisis (Figure 17.18). If the patient stabilizes, anticoagulants are generally stopped after a few weeks, with clopidogrel maintained for the life of the patient. Thrombolytic drugs (e.g., tPA) may be considered in cases of acute thrombosis, since they accelerate

TABLE 17.2 Summary of anticoagulants

Drug category	Specific examples	Mechanism of action	Route of admin	Notes
Vitamin K_1 antagonist	Warfarin	– Inhibits the enzyme vitamin K epoxide reductase – Prevents vitamin K recycling needed for the activation of the clotting factors IIa, VIIa, IXa, and Xa – Also prevents activation of the anticoagulants protein C and protein S	p.o.	– Rarely used now – Cheap – Requires frequent therapeutic monitoring – Monitoring test = PT – Takes ≅ 3 days to take effect – Must give heparin during the first 3 days to prevent risk of thrombosis due to inhibition of protein C and protein S

Heparins	Unfractionated heparin	– Composed of a mixture of heparin chain lengths
		– Indirect anticoagulant
		  – Increases the activity of the endogenous anticoagulant antithrombin
		  – Antithrombin inhibits the effects of factors IIa and factors Xa
			IV
			SC
				– Cheap
				– Given by intermittent injection or as constant rate infusion
				– Frequent therapeutic monitoring is recommended
				– Monitoring tests: Anti-Xa activity, aPTT, activated clotting time (ACT), rapid-TEG
				– Avoid in patients with antithrombin deficiency

Low-molecular-weight heparins	Dalteparin (Fragmin®) Enoxaparin (Lovenox®)	– Standardized product containing short-chain lengths – Indirect anticoagulant – Different interaction with antithrombin compared to unfractionated heparin, meaning anticoagulant activity arises predominantly from inhibition of factor Xa	SC	– Expensive – Given by intermittent injection – Therapeutic monitoring is uncommonly available – Monitoring test–Anti-Xa activity – Avoid in patients with antithrombin deficiency
Direct oral anticoagulants	Rivaroxaban	– Direct inhibition of factor Xa – Does not rely on antithrombin to achieve effect	p.o.	– Expensive – Therapeutic monitoring is uncommonly available – Monitoring test–Anti-Xa activity, maybe PT

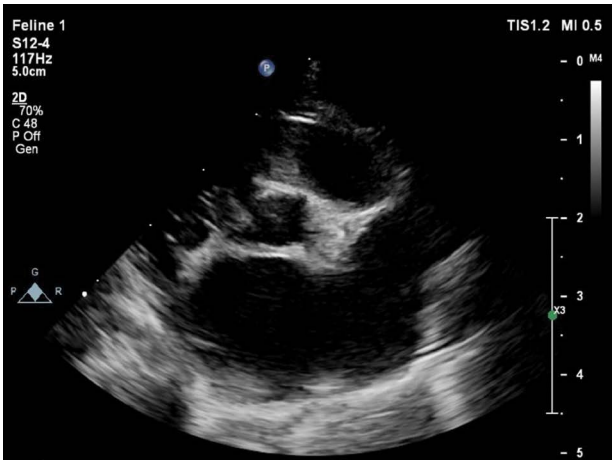


FIGURE 17.18 Right parasternal short-axis echocardiographic view of a cat with asymptomatic hypertrophic cardiomyopathy showing signs of left atrial enlargement for which prophylactic clopidogrel would be recommended.

plasmin-mediated clot breakdown and could be used alongside antithrombotic drugs. The use of thrombolytic drugs in the management of ATE in cats is controversial, however, since serious adverse effects have been encountered (bleeding, reperfusion injury), and outcome is not clearly improved with their usage.

Prognosis

Prognosis for cats with ATE is guarded, since about two-thirds of cats affected will not survive the acute crisis, and survivors have a high risk of recurrent episodes. Another challenge of acute arterial thrombosis is reperfusion injury, where severe metabolic derangements (e.g., electrolyte and acid–base abnormalities, acute azotemia) may occur when perfusion is restored. The prognosis for dogs with aortic thrombosis is largely governed by their ambulatory status at presentation, with nonambulatory dogs being more likely to die or be euthanized. The prognosis for other anatomical sites is variable (e.g., central nervous system signs are often short lived and nonprogressive).

VENOUS THROMBOSIS

Definition/Overview

Blood clots that form in veins are commonly seen in dogs and to a lesser extent in cats.

Etiology

Venous clots are associated with several diseases in dogs, leading to disturbances in Virchow's triad and pathological thrombosis. Associated diseases vary in importance depending on the location of the clot and include, but are not limited to, immune-mediated hemolytic anemia and heartworm disease (pulmonary thromboembolism), hepatobiliary disease and splenectomy (portal vein thrombosis), and central venous catheters (femoral vein, jugular vein). Venous clots are seen less often in cats.

Pathophysiology

Virchow's triad can again be applied to understand the mechanisms underpinning venous thrombosis. Hypercoagulability is most easily identified. Prothrombotic factor excess (e.g., hyperfibrinogenemia) may be observed in animals with systemic inflammatory diseases (e.g., IMHA, sepsis, acute necrotizing pancreatitis). Other mechanisms that may be implicated include abnormal tissue factor expression on cells (e.g., neoplastic cells) triggering the initiation phase of the cell-based model of hemostasis. In IMHA, hemolysis leads to the circulation of free hemoglobin that scavenges nitric oxide. Nitric oxide is a platelet inhibitor released by the endothelium; therefore, dogs with IMHA may also have uninhibited platelet activation. Immobility and recumbency is an important risk factor for venous thrombosis in people (e.g., long-haul flights, immobility after surgery) but is less well described in animals. Endothelial dysfunction may contribute to thrombosis also (e.g., central venous catheters) but are harder to investigate.

Clinical Presentation

The clinical consequences of venous thrombosis will depend on the tissues affected, the amount of vessel occlusion, and the chronicity of the problem. Acute thrombosis can lead to a rapid onset of severe, potentially devastating symptoms. For example, recent splenectomy has been associated with acute portal vein thrombosis that leads to a devastating syndrome of acute-onset hypovolemia secondary to massive gastrointestinal fluid losses and hemorrhage, widespread intestinal ischemia, gastrointestinal edema, and acute abdominal effusion (Figure 17.19). Other situations may risk morbidity but less likely to be associated with mortality (e.g., catheter-associated thrombosis).



FIGURE 17.19 Postmortem image of a dog with massive mesenteric ischemia secondary to an acute portal vein thrombus following splenectomy.

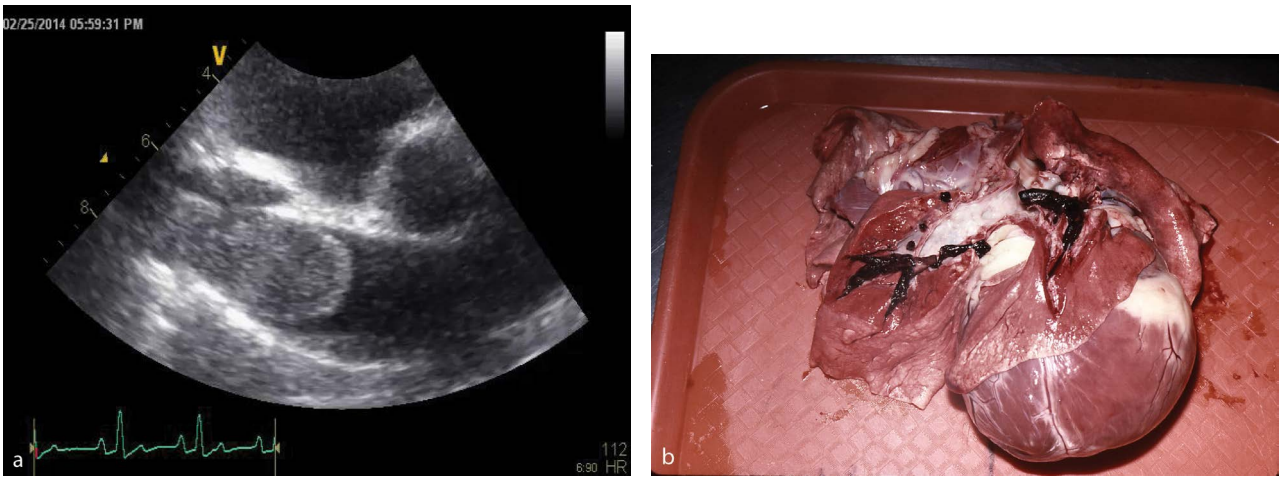


FIGURE 17.20 **(a)** Echocardiographic image of a dog with glomerulonephritis that developed acute tachypnea. A large thrombus is seen in the main pulmonary artery. **(b)** Postmortem lung dissection from a dog with immune-mediated hemolytic anemia that formed many pulmonary thrombi. (b, *Courtesy of M. Schaer.*)

Diagnosis

Similar to arterial clots, diagnostic imaging may allow visualization of venous thrombosis (e.g., ultrasound, computed tomography) (Figure 17.20a). Whether imaging is successful in identifying clots may be influenced by the skill of the operator. Patient stability may prevent imaging from being done, and a presumptive diagnosis may be made instead (e.g., acute onset of tachypnea and hypoxemia in a dog with IMHA suggestive of pulmonary thromboembolism; Figure 17.20b). Venous clots may also be recognized incidentally and may reflect the presence of disease rather than driving the process. As for arterial clots, a systemic diagnostic workup to include complete blood count, serum biochemistry, urinalysis, and thoracic and abdominal imaging would be reasonable. Venous clots may also be lysed prior to visualization in animals undergoing postmortem examination as for arterial thrombosis (Figure 17.21).

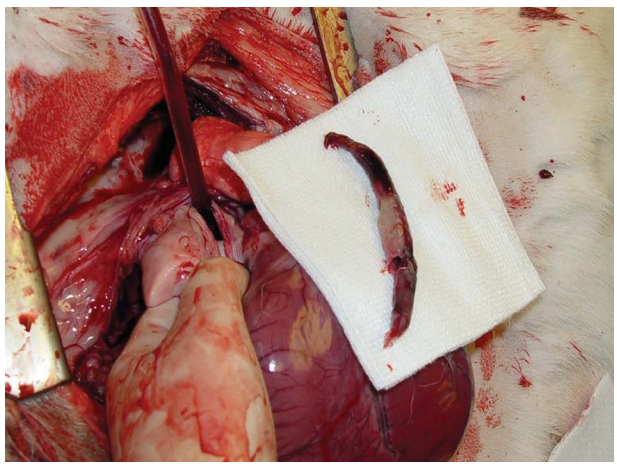


FIGURE 17.21 Large pulmonary artery clot identified during a postmortem examination.

Differential Diagnosis

Differential diagnosis will depend on clinical presentation, for example, acute onset of tachypnea and hypoxemia in a dog with IMHA could be secondary to pulmonary thromboembolism, but alternative differential diagnoses would include aspiration pneumonia, acute respiratory distress syndrome, volume overload, or heart failure.

Management

Clinical management will again encompass specific antithrombotic medications, as well as supportive measurements (e.g., supplemental oxygen) and situation-specific recommendations (e.g., removal of central venous catheter). Antithrombotic drugs will again be considered for the treatment or prevention of thrombosis. Histologically, venous clots are fibrin rich, and anticoagulant drugs interfering with fibrin formation are usually preferred. Several anticoagulant options are available (Table 17.2). Heparin drugs are commonly used, but there is growing interest in rivaroxaban. Several factors should be considered when choosing an anticoagulant drug. These include the cost of the drug, the frequency of dosing, the route of administration, and the requirement for therapeutic monitoring. For example, unfractionated heparin is a cheap drug given by injection multiple times per day, which benefits from therapeutic monitoring. In contrast, rivaroxaban is an expensive drug given orally once per day for which therapeutic monitoring may not be needed. As for arterial thrombosis, dual therapy (antithrombotic and antiplatelet drug) is often considered based on the cell-based model of hemostasis. The duration of therapy is often disease specific. For example, anticoagulants are likely used for a short period only in dogs with central venous catheter-related thrombosis yet may be considered for longer in dogs with IMHA. Thrombolytic drugs are used quite uncommonly for venous thrombosis and

are not suited for incidentally identified or chronic thrombosis.

Prognosis

Prognosis is variable, since a better prognosis is associated with incidentally identified thrombosis, while acute thrombosis can be devastating. Antithrombotic drugs have been associated with an improved outcome in certain disease states (e.g., IMHA). Consequently, thromboprophylaxis is recommended for animals with diseases associated with thrombosis.

COMPLEX HEMOSTATIC DISORDERS

Some animals acquire hemostatic dysfunction that has features of both hypercoagulability and hypocoagulability. These complex disorders are challenging both from a diagnostic and therapeutic perspective and are associated with a guarded or grave prognosis.

DISSEMINATED INTRAVASCULAR COAGULATION

Definition/Overview

Disseminated intravascular coagulation (DIC) is characterized by widespread thrombosis within blood vessels, which may lead to overt hemorrhage.

Etiology

DIC occurs secondary to an underlying disease process. Several disease states have been implicated in DIC, including systemic inflammation, sepsis, pancreatitis, neoplasia, heatstroke, and envenomation.

Pathophysiology

The precipitating trigger incites systemic activation of coagulation, resulting in massive thrombin generation and widespread clot formation. Extensive thrombosis has two major detrimental effects. First, microthrombosis may lead to tissue hypoperfusion and resultant tissue dysfunction. Second, massive thrombosis leads to clotting factor consumption and fibrinolysis activation, leading to a bleeding tendency.

Clinical Presentation

Obvious signs of bleeding develop later in the syndrome. In the nonovert, prothrombotic phase, signs of organ failure may be noted. This could include hypoxemia, arrhythmia, acute azotemia, icterus, and neurological deficits. One first helpful clue in hospitalized animals would be the appreciation of petechiation or ecchymoses and excessive bruising around venipuncture and IV catheter insertion sites (Figure 17.22).



FIGURE 17.22 Hospitalized dog with multicentric lymphoma and aspiration pneumonia that developed extensive ecchymoses on the trunk. Multiple hemostatic disorders were noted suggestive of disseminated intravascular coagulopathy.

Differential Diagnosis

Multiple organ dysfunction syndrome, hepatic failure.

Diagnosis

Clinical confirmation of DIC may be challenging, since clinical signs and laboratory changes identified in individual patients can vary. Early in the disease course, hypercoagulability and DIC will be asymptomatic (nonovert) and may be missed by conventional laboratory diagnostic tests. At this point, potential laboratory abnormalities would include increased maximum amplitude on TEG, moderate thrombocytopenia, possibly shortened PT and aPTT, increased D-dimers, and increased thrombin–antithrombin complexes. As consumption continues, a bleeding tendency may develop (overt DIC). The bleeding characteristics may have features of both primary and secondary hemostatic dysfunction. No absolute definition for DIC in dogs and cats exists. Generally, several abnormal diagnostic results in animals with compatible clinical signs is necessary. Potential hemostatic abnormalities in overt DIC include thrombocytopenia, prolongation of PT and aPTT, hypofibrinogenemia, elevated D-dimers, and reduced antithrombin activity.

Management

Management is very challenging, since in theory antithrombotic medications would be indicated in the early stages of DIC, while anticoagulant replenishment through provision of plasma transfusions would be helpful during overt DIC. Since most animals with DIC are recognized once bleeding is evident, it is most likely that blood products will form the mainstay of therapy. Antifibrinolytic drugs (e.g., aminocaproic acid, tranexamic acid) are contraindicated in DIC, since blood clot persistence could lead to worsening consumption of clotting factors and platelets.

Prognosis

Prognosis is often considered guarded to grave, but a greater chance of success would be expected if the underlying disease process triggering DIC is managed effectively, along with intensive care supportive care.

HEPATOBILIARY DISEASE

Definition/Overview

Intrinsic liver disease, biliary tract disease, and portovascular diseases have been associated with variable hemostatic profiles.

Etiology

Severe intrinsic liver diseases can be either acute or chronic in nature. A variety of diseases could be encountered, including inflammatory, infectious, toxic, and neoplastic insults. Biliary tract disorders encompass inflammatory, infectious, neoplastic, and obstructive pathologies. Portovascular conditions include congenital and acquired portosystemic shunts.

Pathophysiology

The liver has influence on primary hemostatic function via thrombopoietin production by hepatocytes. The liver is the major site of procoagulant and anticoagulant protein synthesis; therefore, advanced synthetic liver failure can lead to disruption of several important proteins. The cross talk between inflammation and coagulation may also impart the overall hemostatic status of an individual patient.

Clinical Presentation

Spontaneous hemorrhage is rarely seen in animals with liver disease, although tolerance for invasive procedures (e.g., biopsy) may be lower, and bleeding could result (Figure 17.23a, b). Thrombosis may occur in advanced liver disease, which may lead to additional symptoms depending on the location of the thrombus (e.g., portal vein thrombus leading to ascites). Dogs with congenital portosystemic shunts that had evidence of hepatic encephalopathy are more likely to be hypercoagulable.

Differential Diagnosis

DIC.

Diagnosis

Since variable hemostatic profiles can be encountered, it is reasonable to obtain a platelet count and PT/aPTT at the bare minimum. More comprehensive characterization of hemostasis, for example by measuring fibrinogen, D-dimers, and viscoelastic testing, may provide greater insight into the status of an individual patient. Hyperfibrinolysis may be appreciated in some patients with acute hepatopathy.

Management

The therapeutic approach will vary between patients. Patients with hypocoagulability are treated in the event of bleeding occurring. That said, pretreatment with vitamin K_1 and/or clotting factor administration may be provided to animals undergoing invasive procedures. For animals with thrombosis, anticoagulation is recommended, although the exact duration of therapy can vary and should be determined by clinical progress (e.g., resolution of ascites, ultrasound evidence of clot resolution).

Prognosis

Prognosis will depend on the extent of the primary disease and if complications occur associated with invasive procedures.

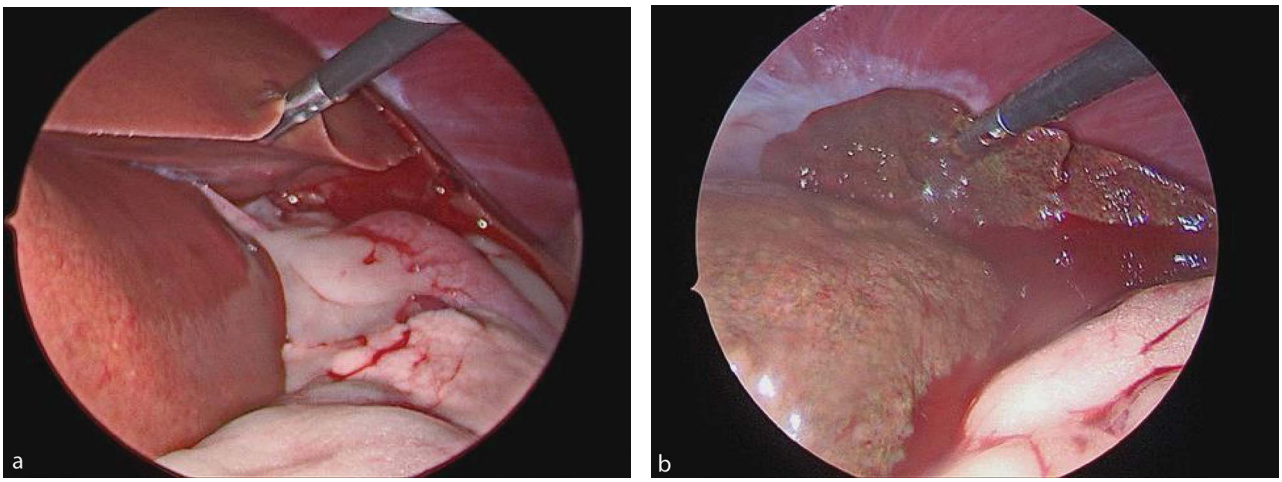


FIGURE 17.23 Intraoperative images obtained during laparoscopic liver biopsies indicating (a) mild hemorrhage and (b) severe hemorrhage. (*Photo credit Katharine Lunn, BVMS, DACVIM.*)

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CHAPTER
18

Dermatologic Disorders

Domenico Santoro and Amelia White

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PART 1: A PRACTICAL APPROACH TO THE DERMATOLOGICAL WORKUP

INTRODUCTION

Different dermatological diseases can have similar clinical features, which makes obtaining a definitive diagnosis challenging. This chapter will focus on the practical approach to any dermatological disorder as well as review some of the more common dermatological diseases. Use of a systematic approach to every dermatology case will aid in obtaining an accurate and timely diagnosis.

HISTORY

Obtaining a thorough and detailed medical history will be imperative when considering possible differential diagnoses contributing to the dermatosis. Many skin conditions are multifactorial with a complicated pathogenesis, so determining the overall health status of the animal is important as well.

When obtaining a history, important information includes signalment, age of onset, environmental and

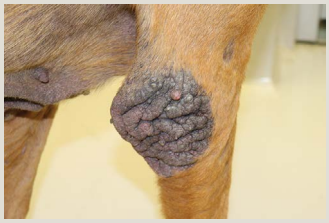
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lifestyle exposure, exposure to other animals, onset and distribution of clinical lesions, severity and distribution of pruritus, response to previous therapies, skin lesions present on other pets/people in the household, seasonal trends in disease occurrence, dietary history, and current medications and supplements. General demeanor, activity level, appetite, thirst level, urinary/defecation habits, body weight fluctuations, and changes in neurological status may all be necessary to understand the severity of disease and consider nonallergic causes such as endocrinopathies.

PHYSICAL EXAMINATION

The skin is an external and easily accessible organ for examination; however, the value of a complete physical exam cannot be overlooked. The particular types of skin pathology are illustrated and described in Table 18.1. Some dermatoses are a manifestation of systemic diseases, and evaluation of every body system will aid in making the correct diagnosis (Table 18.2). This includes thorough evaluation of the eyes and oral cavity, thoracic auscultation, abdominal palpation, lymph

TABLE 18.1 Common secondary skin lesions

Alopecia		Partial or complete loss of hair
Callus		Thickening and hardening of the skin with alopecia and hyperpigmentation, commonly located over a bone prominence such as an elbow or tarsus
Comedone		Dilated hair follicles filled with keratinous and sebaceous material creating small white and black raised lesions on the dorsum
Crust		Dried accumulations of scale, cells, blood, wound exudate, and medications on the skin surface
Epidermal collarette		Annual rim of scale representing the remnants of a pustule, vesicle, or bulla

(*Continued*)

TABLE 18.1 Common secondary skin lesions (*Continued*)

Erosion		Partial epidermal loss or defect that does not cross the basement membrane
Fissure		Cracking or linear cleavage of the epidermis that may cross into the dermis
Follicle casts		Excessive scale (keratin) and hair fragments accumulating around hair shafts
Hemorrhagic vesicle		Small, circumscribed, elevated lesion filled with fluid (blood) measuring <1 cm in size
Lichenification		Thickening and hardening of skin as a response to chronic dermatitis
Macule		Circumscribed, flat skin color change measuring <1 cm in size

(*Continued*)

TABLE 18.1 Common secondary skin lesions (*Continued*)

Necrosis		Ischemia or toxin-induced skin death
Nodule		Circumscribed, raised, firm elevation measuring >1 cm in size
Papule		Small, firm mass <1 cm in size
Patch		Circumscribed, flat skin color change measuring >1 cm in size
Pigment abnormalities		Changes in pigmentation (increased or decreased) of skin or hair in response to inflammation
Plaque		Large, flat-topped, raised lesion >1 cm in size (representing coalescing papules)

(*Continued*)

TABLE 18.1 Common secondary skin lesions (*Continued*)

Pustule		Small, circumscribed, elevated lesion filled with purulent exudate
Scale		Accumulation of loose stratum corneum appearing as fine, white material
Scar		Alopecic, depigmented fibrous tissue
Ulcer		Complete defect in the epidermis that crosses the basement membrane
Wheals		Rapidly developing and resolving circumscribed, elevated, edematous lesion

node palpation, rectal evaluation, complete neurological evaluation, and assessment of vital signs.

There are several goals to keep in mind when examining the skin, ears, claws, mucocutaneous regions, and appendages. The distribution of dermatological lesions provides information about the cause of the lesions. Typically, immune-mediated diseases cause a symmetrical pattern of lesion distribution, whereas infectious and neoplastic diseases cause asymmetrical patterns. Additionally, some immune-mediated conditions have consistent distribution patterns. For example, flea allergy dermatitis typically presents on the caudodorsal lumbar region, and discoid lupus erythematosus typically presents on the rostral muzzle and nose. Knowledge and recognition of distribution patterns can quickly narrow the differential diagnosis list.

When evaluating the skin, take note of the types of dermatological lesions present, as this can indicate the type of disease. Lesion are classified as primary and secondary. Primary lesions are present at the onset of disease and develop as a direct (de novo) cause of the pathogenesis, making them the most characteristic of the disease process. These include macules, papules, pustules, vesicles, bullae, wheals, and nodules. Contrarily, secondary lesions develop as the disease progresses over time and result from the primary lesions or from self-trauma. These include erosions, ulcers, fistulae, crusts, scale, lichenification, and alopecia (Table 18.2).

TABLE 18.2 Common skin conditions: Disease, etiology, clinical signs, diagnosis, and treatment

Common neoplastic and nonneoplastic skin tumors

Tumor	Characteristic lesion	Location	Diagnosis	Treatment
Apocrine gland tumors of the anal sac	Nodule, fistula, or ulceration	Perianal area	Histopathology, cytology	C, Ch, L, R, Sx
Basal cell tumor / carcinoma	Nodule, ulcer, cyst	Head, pinnae, neck, extremities for basal cell tumor, any for carcinoma	Histopathology, cytology	C, Ch, L, R, Sx
Collagenous nevus	Nodule, plaque, polyp	Extremities, head, neck, trunk, ventrum	Histopathology	None, C, L, Sx
Cutaneous T-cell lymphoma	Depigmentation, erosion, ulceration, papule, nodule, plaque, gingivitis, crusts	Nose, oral cavity, periocular, footpads, trunk	Histopathology	CCS, CHOP, Is, Lo, Le, R, Sx
Dermatofibromas, multiple	Nodule, mass	Any	Histopathology, abdominal ultrasound to assess kidney tumor	None
Fibropruritic nodule	Nodule	Rump	Histopathology	Flea eradication, CCS
Epidermal hamartoma	Hyperpigmented papule, nodule, plaque with linear orientation	Any	Histopathology	C, Is, L, Sx
Cutaneous hemangioma	Erythematous to black macules or papules	Ventral abdomen, trunk, extremities	Histopathology	C, L, Sx
Hair follicle tumors	Nodule, mass, cyst	Head, trunk, any	Histopathology	C, L, Is, Sx Ch for malignant forms
Histiocytoma	Nodule	Face, paw, trunk	Histopathology, cytology	None, C, L, Sx
Bowenoid in situ carcinoma (Bowen disease)	Pigmented plaque, scale	Trunk	Histopathology	C, Im, L, PDT, R, Sx
Keratoacanthoma	Nodule, cyst, cutaneous horn	Dorsum, tail, extremities, any	Histopathology	C, Is, L, Sx
Mast cell tumor	Nodule, papule, edema	Any, especially limbs, abdomen, chest	Histopathology, cytology	C, CCS, Ch, H1, H2, R, Sx
Melanoma	Hyperpigmented to nonpigmented nodule, mass, macule	Digit, claw bed, extremities, head, abdomen, scrotum	Histopathology, cytology	C, L, Sx R, Ch, and vaccine with malignant melanoma
Papilloma	Papule, nodule, wart-like	Face, lip margins, oral mucosa, paws, footpads, extremities, ventral abdomen	Histopathology, cytology	None, A, C, In, L, Sx
Plasmacytoma	Nodule	Head, pinnae, perioral, extremities	Histopathology, cytology	C, L, Sx R and Ch for multiple tumors
Perianal gland adenoma	Nodule	Perianal region	Histopathology, cytology	C, L, R, Sx, neuter
Sebaceous adenoma	Nodule (wart-like)	Trunk, head, extremities	Histopathology	None, C, L, Sx, vit A

(*Continued*)

TABLE 18.2 Common skin conditions: Disease, etiology, clinical signs, diagnosis, and treatment (*Continued*)

Common neoplastic and nonneoplastic skin tumors

Tumor	Characteristic lesion	Location	Diagnosis	Treatment
Squamous cell carcinoma	Erosion, ulceration, erythema, nodule, plaque	Pinnae, external ear canal, periocular, nose, trunk, claw bed, ventral abdomen	Histopathology	C, Ch, Im, L, R, Sx

A, azithromycin; C, cryosurgery; CCS, corticosteroids; Ch, chemotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; H1, H1 blocker; H2, H2 blocker; Im, imiquimod; In, interferon; Is, isotretinoin; L, CO2 laser ablation; Le, leflunomide; Lo, lomustine; PDT, photodynamic therapy; R, radiation; Sx, surgical excision; vit A, vitamin A.

Common keratinization disorders

Disease	Etiology	Dermatologic signs	Diagnosis	Treatment
Canine ear margin dermatosis	Unknown, Dachshunds overrepresented	Scaling, crusting, follicular casts, alopecia, and lichenification of ear margins Fissures in chronic cases	Clinical appearance, histopathology	Antiseborrheic topical agents: Sulfur, salicylic acid, benzoyl peroxide, petroleum Moisturizers
Nasodigital hyperkeratosis	*Unknown:* Idiopathic, senile change, hereditary (e.g., Labrador Retriever), anatomical (e.g., Boxer, Bulldog), or secondary to other disease	Irregular, fine, papillated keratinous fronds on dorsal nasal planum and paw pads	Clinical appearance, histopathology, rule out other diseases	Filing/trimming excessive growth Topical moisturizers Topical antiseborrheic agents
Feline acne	Idiopathic, secondary to allergic dermatitis	Alopecia, erythema, papules, nodules, comedones, crusts of ventral rostral mandible	Clinical appearance, histopathology	Topical antiseptics, antibiotics, and/or antiseborrheics Systemic antibiotics Systemic steroids
Zinc-responsive dermatosis	*Syndrome I:* Defective intestinal absorption of zinc (e.g., Siberian Husky, Alaskan Malamute) *Syndrome II:* Rapidly growing animals fed zinc-deficient diet	Crusting and alopecia of pinnae, pressure points, periocular and perioral areas, muzzle, and ventral mandible	Clinical appearance, histopathology confirmatory	*Syndrome I:* Zinc supplementation *Syndrome II:* Zinc supplementation and dietary modification

Common metabolic disorders

Disease	Etiology	Dermatologic signs	Diagnosis	Treatment
Necrolytic migratory erythema / superficial necrolytic dermatitis / metabolic epidermal necrosis / hepatocutaneous syndrome	Liver failure or hepatopathy, pancreatic neoplasia, diabetes	Erythema, alopecia, crusts, erosions, ulcerations of rostral muzzle, perioral and perianal areas, axillae and inguinal areas, pinnae, elbows, and hocks Severe crusting of paw pads	Histopathology, abdominal ultrasound, serum chemistry	Grave prognosis (supportive care) IV amino acid supplementation Dietary amino acid, zinc, and essential fatty acid supplementation Antibiotics Topical antiseptics

(*Continued*)

TABLE 18.2 Common skin conditions: Disease, etiology, clinical signs, diagnosis, and treatment (*Continued*)

Common metabolic disorders				
Disease	**Etiology**	**Dermatologic signs**	**Diagnosis**	**Treatment**
Canine hypothyroidism	Lymphocytic thyroiditis (most commonly)	Myxedema (tragic face), symmetrical truncal alopecia, alopecia dorsal muzzle and tail, seborrhea, hyperpigmentation, secondary bacterial and yeast infection	Canine thyroid panel TSH (normal to high), total T4 (low), and fT4 (low) Hypercholesterolemia, mild nonregenerative anemia	Levothyroxine supplementation
Feline hyperthyroidism	Functional thyroid hyperplasia Thyroid adenoma	Palpable thyroid slip, excessive shedding, truncal alopecia, unkept/matted haircoat, seborrhea sicca, skin atrophy, increased nail growth	Total T4 (normal to high), fT4 (high) Ultrasound, radioactive thyroid scintigraphy	Iodine-restricted diet, methimazole, carbimazole, surgical removal, radioactive iodine therapy
Canine hyperadrenocorticism	Pituitary adenoma (80%) Adrenal neoplasia (15%–20%) Iatrogenic	Truncal alopecia, skin atrophy, seborrhea sicca, secondary infections, comedones, calcinosis cutis, hyperpigmentation, bruising	Physical exam, stress leukogram, elevated alkaline phosphatase, urine cortisol-to-creatinine ratio, ultrasound, ACTH stimulation test, resting ACTH, low-dose dexamethasone suppression test	Trilostane, mitotane, surgery Ketoconazole, selegiline, cabergoline
Feline hyperadrenocorticism	Pituitary adenoma (80%) Adrenal neoplasia (15%–20%) Iatrogenic	Truncal alopecia, skin atrophy, seborrhea sicca, secondary infections, comedones, calcinosis cutis, hyperpigmentation, skin fragility, bruising	Physical exam, stress leukogram, hyperglycemia, urine cortisol-to-creatinine ratio, ultrasound, ACTH stimulation test, resting ACTH, low-dose dexamethasone suppression test	Trilostane, surgery Metyrapone, radiation therapy
Alopecia X	Unknown Many proposed mechanisms, including sex hormone imbalance Chow Chow, Pomeranian, Poodle, and Keeshond overrepresented	Bilaterally symmetrical alopecia sparing head and legs Hyperpigmentation	Rule out other causes of alopecia Histopathology	None Microneedling, trilostane
Hyperestrogenism	Exogenous exposure from owners or other supplementation Intact female: Ovarian cyst Intact male: Sertoli cell tumor	Non inflammatory alopecia spreading from perineal area diffusely, gynecomastia, estrus behavior, pendulous prepuce, linear preputial erythema, comedones	Elevated estrogen levels, ultrasound, history	Remove exogenous exposure Ovariohysterectomy Castration
Xanthoma	Abnormal lipid metabolism (hyperlipoproteinemia) High-fat diets Megestrol acetate use in cats-induced diabetes mellitus	White-yellow papules, nodules or plaques, ulcer, erythema on head, extremities, paw, or bony prominences	Histopathology	Correct underlying cause and will spontaneously resolve Surgical removal

(*Continued*)

TABLE 18.2 Common skin conditions: Disease, etiology, clinical signs, diagnosis, and treatment (*Continued*)

Miscellaneous dermatological disorders				
Disease	**Etiology**	**Clinical signs**	**Diagnosis**	**Treatment**
Canine acral lick dermatitis/granuloma	Allergic dermatitis, osteoarthritis, neuropathy, behavioral	Well-demarcated alopecia, erythema, exudate, erosion, ulcer, crust, lichenification	Clinical appearance, histopathology	Barrier (e.g., E-collar, wrap), topical antiseptics, topical steroids, pain medications, systemic antibiotics, systemic anti-inflammatory drugs, gabapentin +/– amantadine, anxiolytics, address the underlying cause
Canine actinic (solar) dermatitis	Excessive UV radiation exposure	Alopecia, erythema, papule, nodules, crusts, ulcers, hemorrhagic bullae on sun-exposed skin	Clinical appearance and history Histopathology	UV radiation avoidance, protective clothing, firocoxib, retinoids (topical, systemic), vitamin A, carotenoids with glucocorticoids, topical diclofenac, topical imiquimod, sunscreen
Canine calcinosis cutis	Dystrophic calcification usually secondary to excessive cortisol levels (e.g., glucocorticoid use or hyperadrenocorticism)	Alopecic, firm, erythematous to salmon color papules and plaques Head, preauricular, dorsum, ventrum, perianal, or frictional areas	Clinical appearance, histopathology	Treat underlying cause of excessive cortisol, topical antiseptics to prevent infection, topical DMSO gel to resorb calcium, surgical removal focal lesions
Feline idiopathic ulcerative dermatitis	Unknown	Crusted ulcers with alopecia, lichenification, and variable pain and pruritus Localized to dorsal neck and shoulder area	Histopathology	Systemic glucocorticoids, topical antiseptics, surgical removal
Feline plasma cell pododermatitis	Unknown	Soft, flaccid, swollen paw pads with erythema, scaling, scaling striae, fissure, depigmentation, and ulcer	Histopathology	Doxycycline, cyclosporine, glucocorticoids
Canine dermatomyositis/ ischemic dermatopathy	Hereditary—Collie, Shetland Sheepdog, Beauceron Shepherd, Belgian Tervuren, Portuguese Water Dog, and others	Early-age onset (6 months) Lesions on areas with mechanical trauma or friction (face, muzzle, paws, extremities) Alopecia, erythema, scaling, crusting, ulceration	Histopathology, EMG	None; vitamin E, pentoxifylline
Postrabies vaccine vasculitis +/- panniculitis	Idiopathic with Poodle, Yorkshire Terrier, and Silky Terrier overrepresented	Well-demarcated, annular area of alopecia, erythema, hyperpigmentation, scaling, ulcer, and scarring at injection site	Histopathology	None, pentoxifylline, avoid vaccination in future

(*Continued*)

TABLE 18.2 Common skin conditions: Disease, etiology, clinical signs, diagnosis, and treatment (*Continued*)

Miscellaneous dermatological disorders				
Disease	**Etiology**	**Clinical signs**	**Diagnosis**	**Treatment**
Cutaneous adverse drug reaction	Idiosyncratic (unpredictable—any medication, supplement, vaccination, or antiparasitic treatment possible)	Variable clinical lesions and severity Erythema, alopecia, scaling, crusting, erosion, ulceration, hyperpigmentation, and tissue necrosis	Drug history, histopathology, response to drug withdrawal (drug provocation not recommended)	Supportive care
Common alopecia dermatoses				
Disease	**Etiology**	**Clinical signs**	**Diagnosis**	**Treatment**
Canine pattern alopecia/ baldness	Unknown with breed predilection (Boston Terrier, Boxer, Chihuahua, Dachshund, Italian Greyhound, Manchester Terrier, Miniature Pinscher, Whippet)	Noninflammatory, nonpruritic follicular miniaturization and alopecia of pinnae, dorsal head, ventral neck, ventral trunk, caudomedial pelvic limbs	Clinical presentation	None
Color dilution alopecia	Mutation in MLPH gene resulting in abnormal melanin deposition within hair shaft	Alopecia, papules, crusts, scaling, broken hairs, dull haircoat starting along dorsum and extending diffusely	Histopathology and clinical appearance	None
Anagen/telogen effluvium/ defluxion	Stress, disease, or drug-induced hair cycle arrest	Abrupt hair cycle arrest and rapid, noninflammatory alopecia diffusely occurring with days (anagen) or months (telogen) after inducing event	History, trichogram	None
Postclipping alopecia	Unknown—plush-coated breeds high risk	Lack of hair regrowth months after close clipping of hair	History	None Rule out other causes, melatonin
Canine recurrent/seasonal flank alopecia	Unknown cyclical follicular dysplasia Boxer, English Bulldog, Airedale Terrier, Schnauzer overrepresented	Cyclic well-demarcated, noninflammatory alopecia and hyperpigmentation on lateral trunk	History, histopathology	None Melatonin, microneedling
Feline paraneoplastic alopecia	Unknown pathophysiology Associated with pancreatic and hepatic neoplasms	Rapidly developing complete, noninflammatory alopecia of ventrum and extremities Shiny skin	History, histopathology, abdominal ultrasound, necropsy	None Grave prognosis
Common pigmentary dermatoses				
Disease	**Etiology**	**Clinical Signs**	**Diagnosis**	**Treatment**
Lentigo	Unknown Hereditary in Pugs and orange cats	Well-demarcated, flat, hyperpigmented macules Cats—mucocutaneous areas Dogs—diffusely on ventrum	Clinical appearance, histopathology	None Differentiate from pigmented viral plaques, pigmented nevi, and melanoma (these are raised lesions)
Vitiligo	Acquired melanocyte destruction Hereditary in Belgian Tervuren dogs, Rottweilers, and Old English Sheepdogs Idiopathic cases reported in Collie, Dobermann Pinscher, Giant Schnauzer, Bullmastiff, Newfoundland, German Shepherd Dog, Dachshund, and Siamese cat	Symmetrical macular depigmentation, leukoderma, and leukotrichia of nose, lips, buccal mucosa, face, footpads, claws May spread diffusely Periocular leukotrichia in Siamese cat	Clinical appearance, histopathology	None May spontaneously improve Attempted therapies include calcineurin inhibitors, vitamin D, antioxidants, narrow-band UVB light, L-phenylalanine

OTOSCOPY

Thorough evaluation of the ears includes evaluation of the periauricular skin, pinnae, and ear canals. Palpation of the ear canals is an important tool capable of indicating the severity of ear disease. Normal, noninflamed ear canals are pliable on palpation. Ear canals with severe inflammation are larger and firmer on palpation with decreased pliability (Figures 18.1 and 18.2a).

To access the ear canal with ease, first locate the tragus. This is the plateau-like outermost piece of cartilage at the ear canal opening. Find the intertragic incisure just caudal to the tragus, and gently insert the otoscope cone into this space with the otoscope cone pointed ventral and slightly rostral while gently lifting the ear pinna dorsally. Maneuvering the ear pinna will help to straighten out the vertical ear canal. Once at the proximal portion of the vertical ear canal, turn the otoscope cone medially while maneuvering the ear pinna lateroventrally. This will allow access to the horizontal ear canal for visualization of the tympanic membrane.

While evaluating the ear canal, observe for changes in wall thickness, erosions/ulcerations, masses, foreign body, otic debris, hair, and the tympanic membrane. Be mindful of the patient's comfort level during this process and use sedation if the animal is moderately painful. Assess the tympanic membrane for normal structures and position. Changes in architecture or presence of fluid/masses behind the tympanic membrane may cause bulging or rupture. Sometimes a tear or complete loss of the tympanic membrane is present.

Video otoscopy is another tool sometimes available for use during awake or sedated ear examination. Benefits of this equipment include image and video capture software, enhanced magnification and visualization of the ear canal, and access for otic procedures, including deep ear flush, myringotomy, and tissue extraction (Figure 18.2b, c).

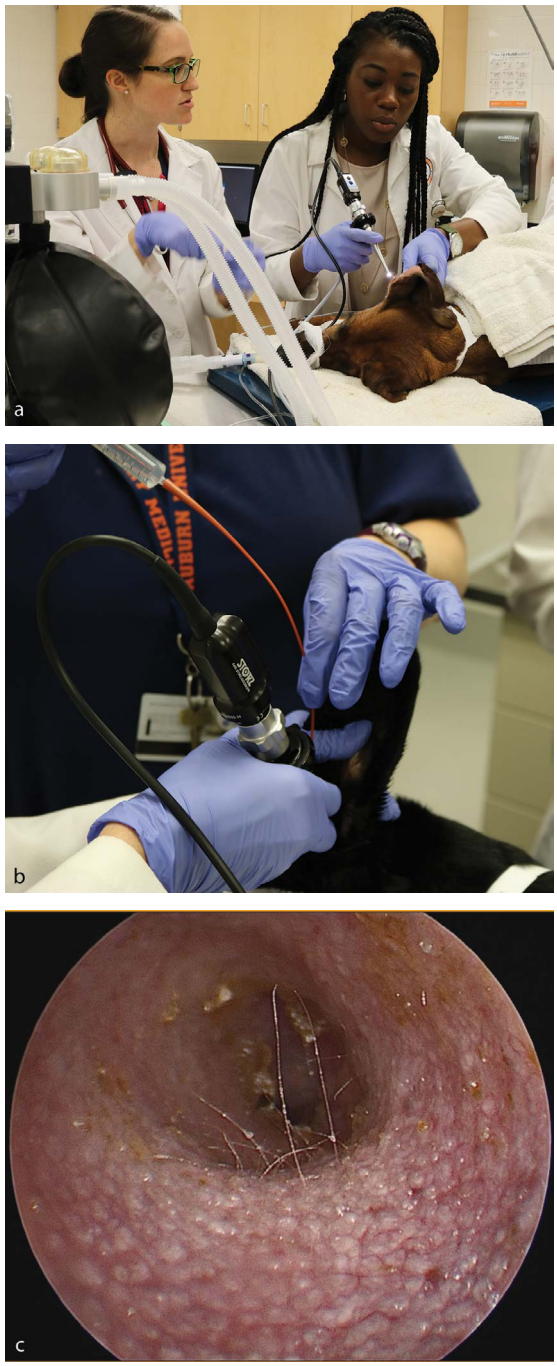


FIGURE 18.2 (a) Storz video otoscope is used to evaluate the external ear canal. (b) A red rubber catheter is passed through the instrument port to perform deep ear flushing with saline. (c) Severe glandular hyperplasia of vertical and horizontal external ear canal in a Cocker Spaniel with severe, chronic otitis externa.

CYTOLOGY

Cytology is a quick and easy diagnostic to perform in the clinic. Diff-Quik® is used to stain cytology slides for evaluation (Figure 18.3a, b) using a 40× or 100× oil objective for bacteria, yeast, inflammatory cells, acantholytic keratinocytes, and neoplastic cells.

The collection technique for cytology is dependent on the nature of the lesion. For exudative lesions, use direct impression smear of the exudate by placing a glass slide directly over the lesion and gently rotating in a circular

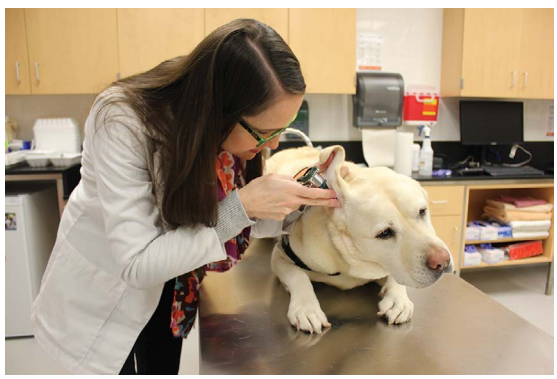


FIGURE 18.1 A handheld otoscope with ear cone.



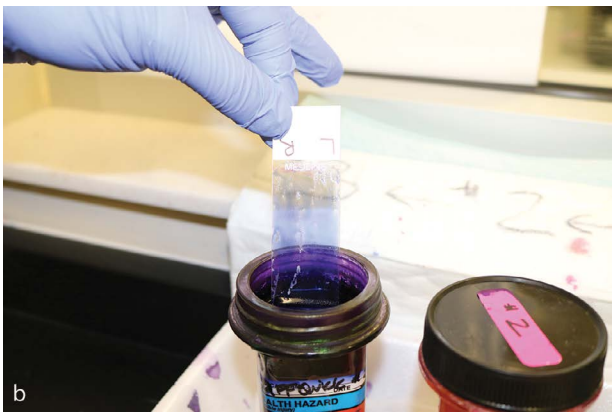


FIGURE 18.3 (a) Diff-Quik stain is a modified Romanowsky stain that includes a fixative (light blue), eosinophilic (red), and basophilic (dark blue) stain. **(b)** The slide is tinctured into each stain 5–10 times in each stain before rinsing with distilled water and air drying.

motion (Figure 18.4). Sampling from under a crust, along the edge of an epidermal collarette, or rupturing a pustule improves the diagnostic accuracy of the sample.

Direct impression provides reliable results from less exudative lesions as well; however, acetate tape cytology is helpful in areas that are difficult to fit a glass slide (e.g., interdigital skin) (Figure 18.5). One challenge of acetate tape cytology is the amount of sample obtained, which makes it difficult to see organisms present in low numbers (Figure 18.6).



FIGURE 18.4 Direct impression cytology of a skin lesion on the ventral abdomen of a dog.



FIGURE 18.5 Tape cytology of a skin lesion on the medial stifle of a dog.

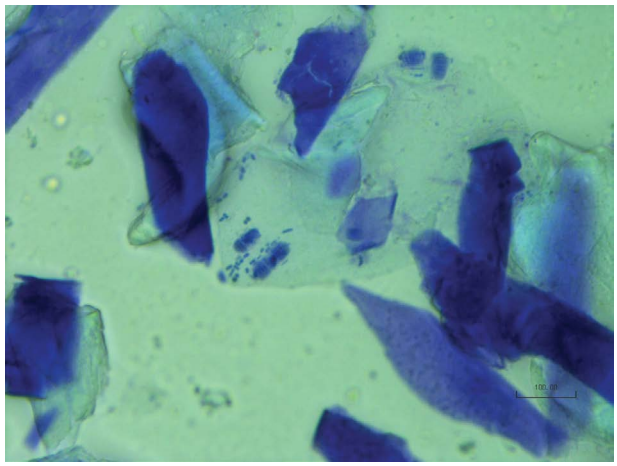


FIGURE 18.6 Tape cytology identifies large scrolls of corneocytes along with *Conchiformibius* spp. bacteria (oral contaminant), as well as cocci- and rod-shaped bacteria.

Sample claw bed debris using a blunt metal spatula or wooden tip of a cotton-tipped applicator. Roll or touch the sample to a glass slide for evaluation (Figure 18.7a, b).

For nodular lesions, especially nondraining nodules, fine-needle aspirate of the lesion using a 22- to 25-gauge needle (Figure 18.8) and 5 mL syringe to express contents onto a glass slide is more accurate than surface cytology alone.

Obtain otic cytology swab samples from both external ear canals using cotton-tipped applicators in cases of otitis. Roll the samples gently onto a glass slide, heat fix using a match or lighter, and then stain using Diff-Quik and/or Gram stain (Figure 18.9a–d). Evaluate otic samples for parasites by placing the otic debris into mineral oil on a glass slide, then apply a glass coverslip. Lower the microscope light source (condenser) and the light power when evaluating for parasites with the less powerful objectives (4× or 10×) (Figure 18.10a, b). Mites and other parasites are much larger than bacteria and yeast, so less power is required. Also, these organisms may be very translucent, so use of less light power enhances visualization of these parasites.

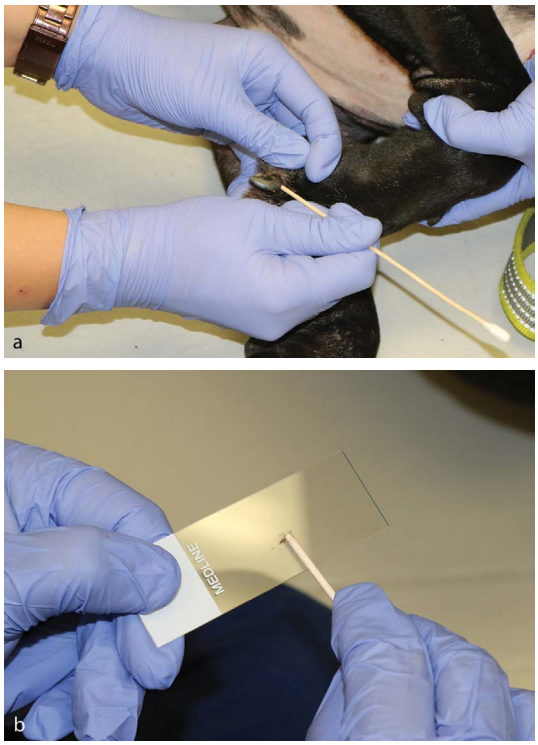


FIGURE 18.7 Claw bed cytology. **(a)** The blunt end of a metal spatula or cotton-tipped applicator is used to pull keratinous debris away from claw bed. **(b)** Sample is rolled onto center of glass slide, heat fixed, and stained for microscopic evaluation.



FIGURE 18.8 Fine-needle aspiration of digital mass on digital paw pad of a Great Dane.

SKIN SCRAPING

Skin scraping allows for visualization of parasites in the superficial and deep layers of the skin, and the technique varies slightly depending on the parasite of interest. In animals with pruritic dermatoses suspected to be caused by *Sarcoptes* spp. mites, superficial skin scraping over larger areas of the ventrum, elbows, hocks, and pinnae margins is preferred. Scrape the skin superficially without creating bleeding using wide swipes and a #10 scalpel blade or blunt metal spatula. Apply mineral oil to the blade/spatula or directly to the skin during scraping (Figure 18.11a, b). Deep skin scraping technique allows

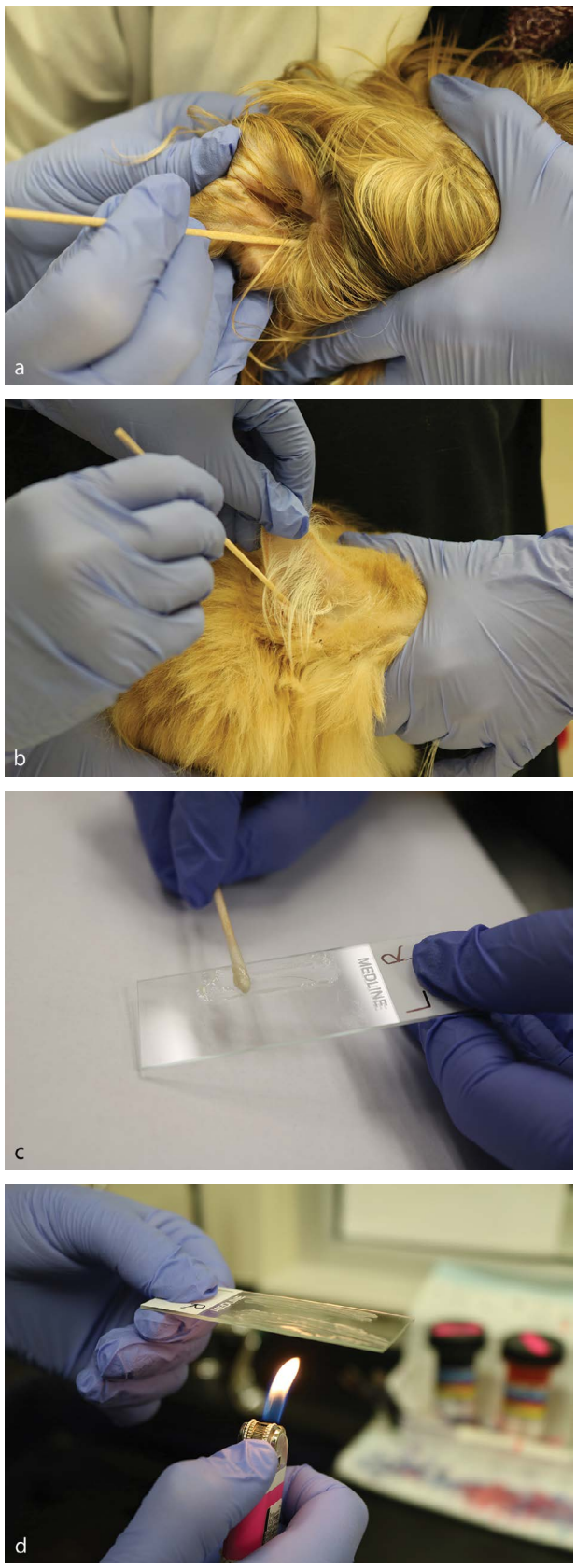


FIGURE 18.9 Ear cytology. **(a)** A cotton-tipped applicator is used to collect a sample from the vertical external ear canal of a dog and **(b)** in a cat. **(c)** The sample is rolled gently onto a glass slide and **(d)** heat fixed prior to staining with Diff-Quik.

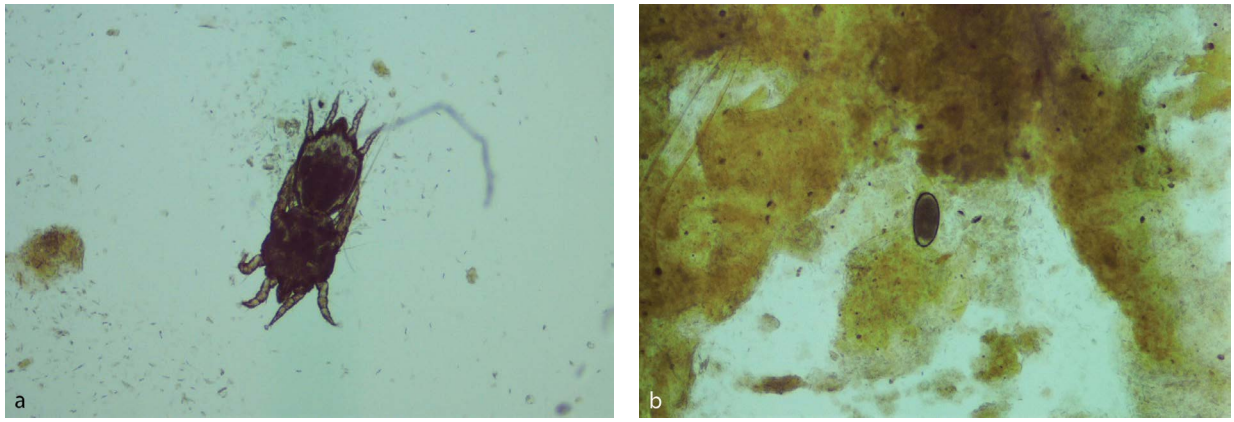


FIGURE 18.10 Ear cytology mite preparation in mineral oil reveals copulating *Otodectes* spp. mites from **(a)** dog and **(b)** ova.

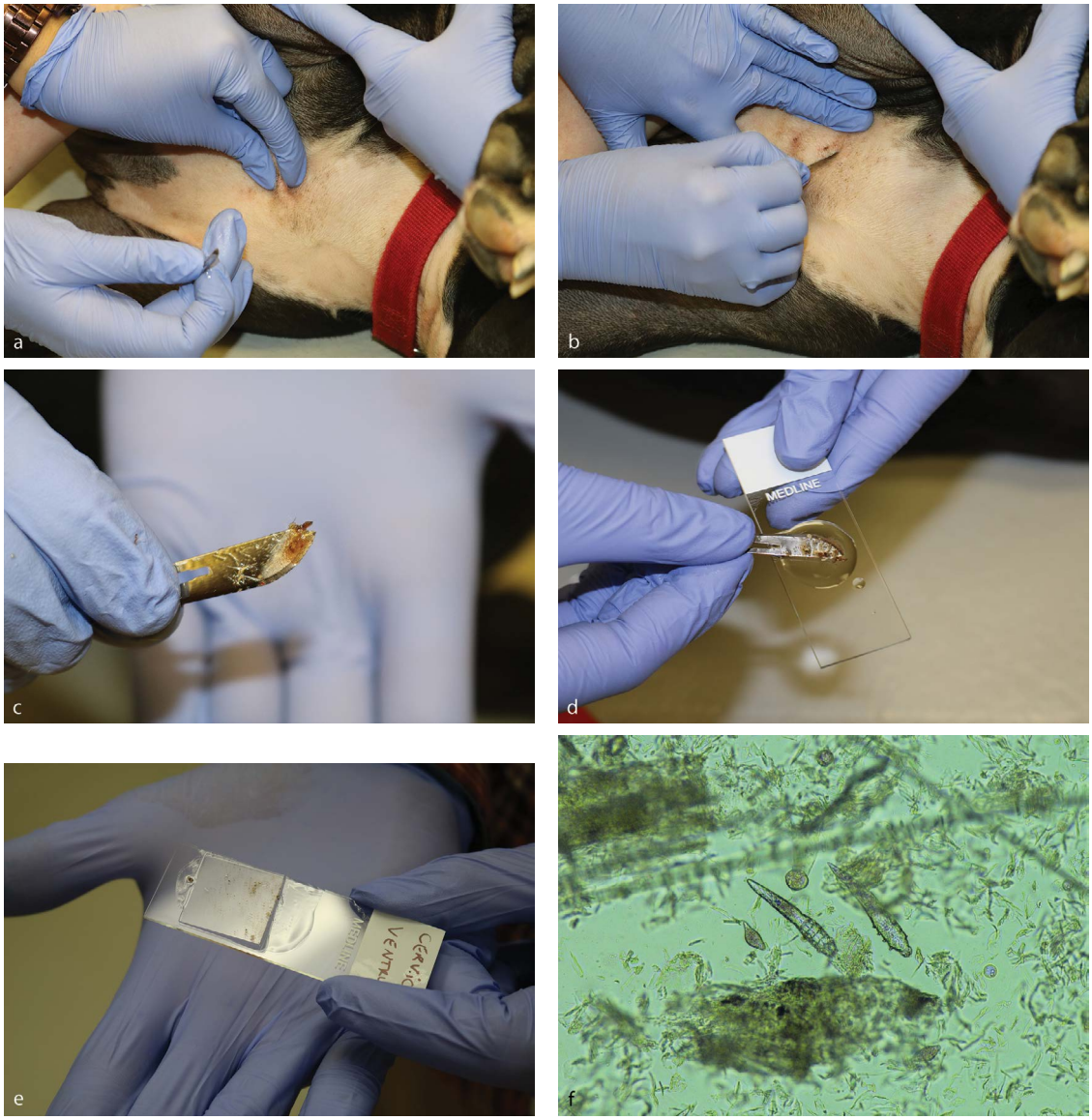


FIGURE 18.11 Deep skin scraping. **(a)** The skin is pinched gently between the fingers to help extrude mites to the skin surface prior to **(b)** scraping the area with a blade lubricated in mineral oil. **(c)** Skin scraping sample is collected on the distal end of the #10 blade, **(d)** placed on a glass slide in mineral oil, **(e)** and a glass coverslip applied. **(f)** *Demodex canis* mites observed at 10× objective power in low light from skin scraping.

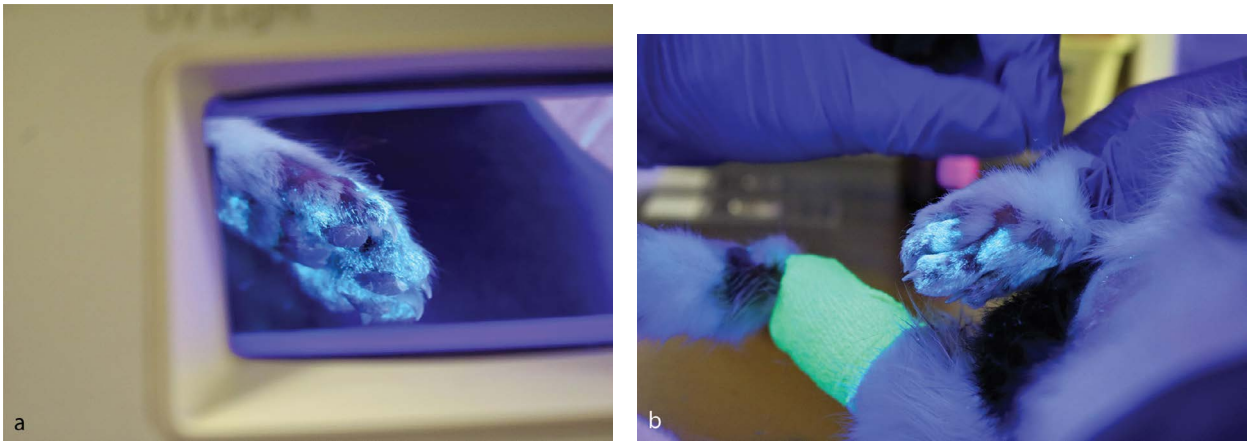


FIGURE 18.12 **(a)** Wood's lamp demonstrates green fluorescence of hairs on a cat paw with and **(b)** without magnification.

for visualization of *Demodex* spp. mites that live deeper in the hair follicle, and for this reason, a light squeezing of the skin to facilitate the extrusion of the mites may be indicated. Use the same instruments and mineral oil; however, select several focal areas of dermatitis and scrape repeatedly over the area until bleeding occurs (Figure 18.11c–e). Place a glass coverslip over the sample and evaluate as described earlier for otic parasites (Figure 18.11f).

WOOD'S LAMP

This is a screening test for dermatophytosis. Some species of dermatophyte fluoresce an apple-green/yellow-green color. The major dermatophyte positive to Wood's lamp is *Microsporum canis* (50%–80% of isolates); however, other less common fungi (*M. distortum*, *M. audouinii*, and *Trichophyton schoenleinii*) can also fluoresce (Figure 18.12a, b). The fluorescence is caused by a water-soluble chemical metabolite (pteridine) within the cortex or medulla of the hair. Keep in mind that other things can fluoresce to create a false-positive result, including medications, bacteria, scale/crust, soaps, petroleum, and fabric fibers. Wood's lamp is very helpful to make a diagnosis of dermatophytosis and select the best hairs to sample for culture or polymerase chain reaction (PCR). However, lack of fluorescence does not rule out dermatophytosis, so perform fungal culture or PCR to obtain a definitive diagnosis.

TRICHOGRAPHY

Microscopic evaluation of hairs (trichography) can be helpful to look for changes in the normal anatomy of hair shafts, evaluate for self-trauma (overgrooming/hair plucking), screen for parasites, and observe invasion of fungal hyphae or spores. Potassium hydroxide (KOH) 10%–20% with heat helps to dissolve keratinous buildup around hair shafts to improve visibility for trichography; however, it is not required to properly evaluate most animal hairs for changes. Pluck hairs from characteristic lesions, place in mineral oil, apply a coverslip, and evaluate at low and high power (Figure 18.13a, b).

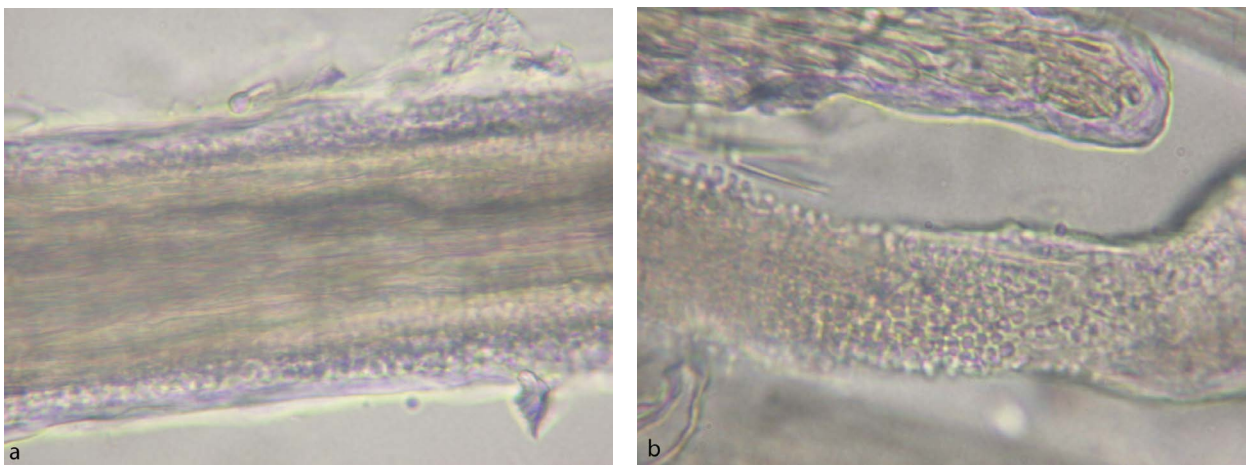


FIGURE 18.13 Hair shaft affected by dermatophytosis. **(a)** Note multiple hyphae running into the cortex of the hair shaft surrounded by arthrospores. **(b)** Note the large amount of arthrospores evident outside the hair shaft at the level of the bulb.

CULTURE

Fungal Culture

There are many fungal culture media available on the market. However, the most common used ones include the dermatophyte test medium (DTM) and Sabouraud-based media (Figure 18.14). The dermatophyte test medium is a specialized agar for culturing dermatophytes from hair and skin samples collected from peripheral lesion margins. The DTM is the most commonly used medium. Several types of fungal media exist with variable additives for rapid fungal sporulation or inhibition of saprophytic and bacterial overgrowth; however, many DTMs contain phenol red as a pH indicator. When dermatophytes consume protein in the media and release alkaline metabolites, the pH increases and causes a color change from yellow to red. After dermatophytes have consumed all of the protein, they will use the remaining carbohydrates, producing acid metabolites that cause the medium to change color from red back to yellow. The majority of other fungi (nondermatophytic) consume carbohydrate metabolites first so that no red color change occurs initially if they are the only fungal organisms present; however, after about 10–14 days, red color change occurs as they begin to utilize the remaining proteins. Ideally, evaluate DTMs daily for concurrent colony growth and color change. Examine growing colonies microscopically to confirm the most likely organism(s) present by evaluating the morphology of fungal reproductive structures. Macroscopic colony features, including color and texture, can aid in fungal identification as well. When growing the in-house DTMs, keep in mind that dermatophytes prefer to grow in the dark at 30°C with 30% humidity. False-negative growth may occur if culture environments are suboptimal.

Bacterial Culture Technique

Swab technique is a cheap and easy technique to perform; however, proper technique is important to prevent overgrowth of contaminants in culture. Reserve swab culture technique for aerobic bacteria collected from superficial skin lesions, including papules, pustules, crusts, and epidermal collarettes. Do not collect samples near mucocutaneous junctions due to the abundant flora at these sites. Avoid collecting samples from draining tracts and ventral paws due to the high risk for contamination of environmental organisms. This technique is not feasible for nodular lesions, so perform biopsy for tissue culture for nodular dermatitis (Figure 18.15a–e).



FIGURE 18.14 An example of dermatophyte testing medium (right side, lighter/clear) and rapid sporulating medium (left side, darker/opaque) dual plate (Derm-Duet II) for dermatophyte culture.

Macerated Tissue Culture

This technique is the gold standard for sample collection for all types of culture; however, it is more invasive and expensive than swab technique because it requires biopsy. Additionally, some animals may require sedation when collecting samples from the face, pinnae, paws, or perineal area, especially if they are overly fractious, stressed, or painful. This is the preferred collection technique for deep, nodular dermatitis, which may be caused by aerobic bacteria, anaerobic bacteria, opportunistic environmental bacteria (*Nocardia* spp., *Mycobacteria* spp.), dermatophyte, and opportunistic fungi.

Avoid performing a biopsy through a draining tract if possible (choose an intact nodule, papule, or pustule). Clean the area with chlorhexidine to remove any surface contaminants. Use 2% lidocaine injected beneath and/or around the lesion to be biopsied. Next, use a punch biopsy tool or scalpel blade to remove a tissue sample. When working up a nodular dermatoses case, include enough tissue for bacterial, fungal, and *Mycobacteria* spp. cultures to rule out infectious causes. You may need to take up to 4–5 punch biopsy samples when submitting several cultures (along with histopathology). Place samples in culture transport medium and submit to the laboratory as soon as possible (Figure 18.15a–e). Refrigeration preserves most bacteria and fungi in transit; however, some fungal and fungal-like organisms (e.g., *Pythium* spp., *Lagenidium* spp., *Paralagenidium* spp., *Aspergillus* spp., and Zygomycetes) die at cold temperatures. If you are not familiar with the handling of the specimen, it is always recommended to consult the laboratory submission guidelines or speak with a laboratory personnel for further guidance.

HISTOPATHOLOGY

Histopathology is helpful to evaluate changes in normal skin architecture induced by acute and chronic dermatoses. This technique provides a definitive diagnosis for autoimmune and neoplastic conditions, and it is useful to diagnose some inflammatory and infectious diseases. Biopsy selection site is critical when making an accurate diagnosis. Select primary lesions when possible, and

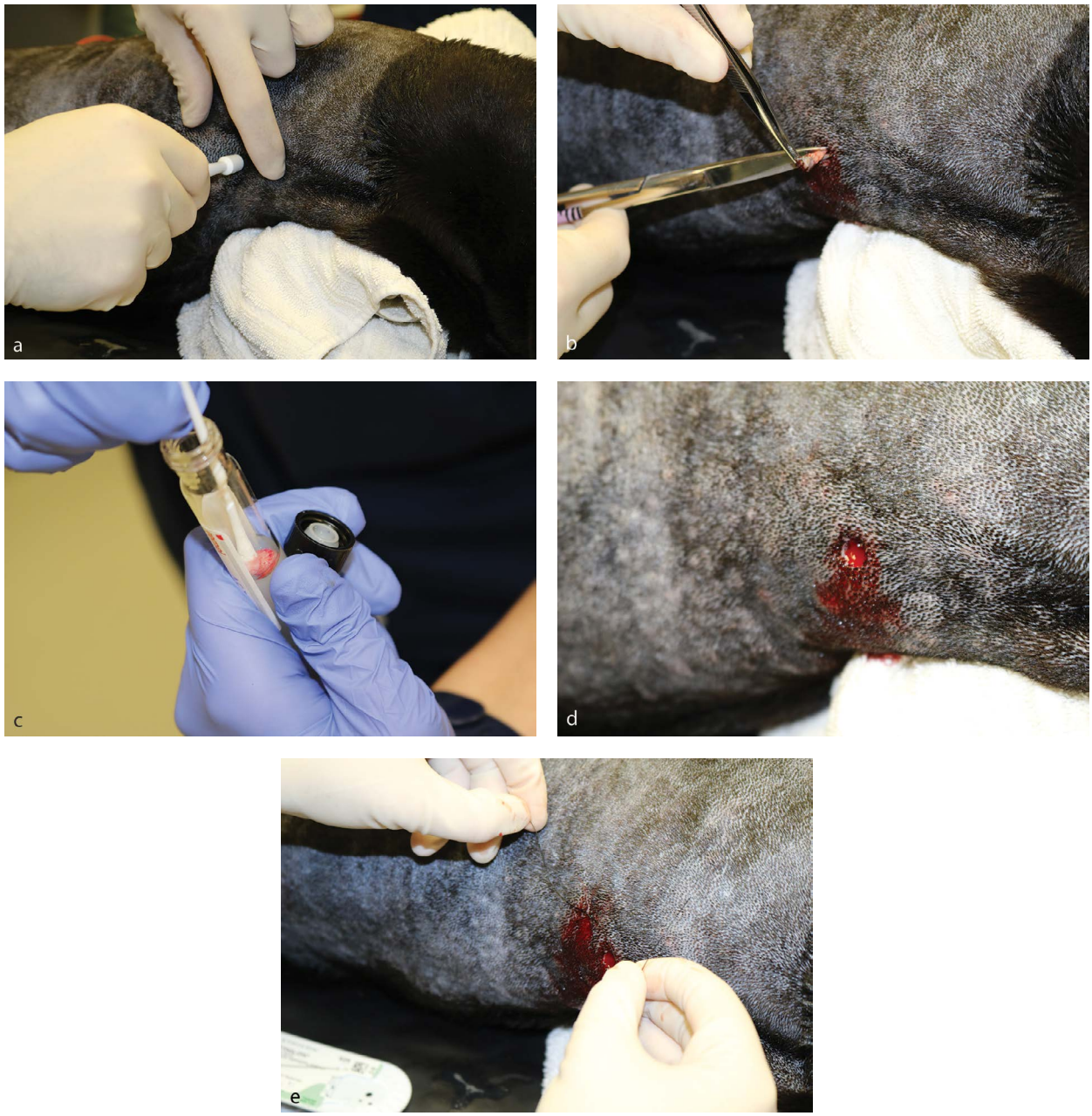


FIGURE 18.15 **(a)** Skin is injected with 2% lidocaine, and then an 8 mm punch biopsy tool is used to biopsy a representative sample. **(b)** The skin plug is removed with sterile scissors. **(c)** A punch biopsy sample is pressed deep into the culture media using a sterile swab prior to processing. **(d)** The biopsy site will hemorrhage slightly until **(e)** sutured using a single cruciate pattern.

always submit two to four pieces of tissue to improve diagnostic ability for the pathologist.

Preparation of the biopsy sites is different from that for tissue culture. The surface of skin collected for histopathology usually is not surgically prepared to avoid removing essential components necessary for making the diagnosis. Biopsy is performed as described earlier. Special stains provide better visualization of infectious organisms and include Gomori methenamine silver (GMS), periodic acid-Schiff (PAS), and acid-fast stains. Immunohistochemical stains may be helpful for identifying infectious and neoplastic cells.

ADVANCED IMAGING

Radiographs and advanced imagining modalities provide additional information about changes in deep soft tissues and bone. Radiographs of distal extremities provide evidence of chronic osteoarthritis, foreign body, or osteomyelitis as contributing factors to a dermatosis. Visualization of the tympanic cavity to assess for fluid, osteomyelitis, or neoplasms is preferred via advanced imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI) studies; however, these modalities are limited to referral centers.

IMMUNODIAGNOSTICS

With the growing accessibility to research and commercial laboratories, immunodiagnostic testing options are expanding. Numerous PCR, enzyme-linked immunosorbent assay (ELISA), immunohistochemical stains, flow cytometry, deoxyribonucleic acid (DNA) profiling, and even whole genomic sequencing testing options are now available for purchase. In particular, PCR is a modality growing in popularity for making a rapid diagnosis using a small sample size. PCR to confirm the presence of an infectious organism in tissue is performed from fresh or formalin-fixed paraffin-embedded tissue samples. This technique is very sensitive to pick up organism DNA in a sample; however, positive test results do not prove the organism is the cause of disease or that it is even alive! For example, nonviable dermatophyte DNA may reside on the haircoat of the animal, and some animals may be asymptomatic carriers of dermatophyte. The same is true for *Mycobacteria* spp. and numerous saprophytic fungi, so it is important to pair PCR results with histopathology to confirm the presence of the organism within tissue proving infection instead of contamination of the sample.

BACTERIAL DERMATITIS

INTRODUCTION

Bacterial skin infections occur commonly in veterinary dermatology and are most often secondary to some other disease process. Common primary causes include allergic dermatitis, parasites, endocrinopathies (e.g., hypothyroidism, hyperadrenocorticism, and sex hormone imbalances), autoimmune dermatoses, adverse drug reactions, immunosuppression, and neoplasia. Identifying and controlling these primary conditions is necessary in order to adequately treat and prevent recurrence of the bacterial infection. This is especially important when considering that repeated infections and repeated use of antibiotics will contribute to antibiotic resistance.

The term "pyoderma" means "pus in skin," and it most commonly refers to bacterial dermatitis in veterinary dermatology. Pyoderma can be classified into surface, superficial, and deep pyoderma based on the cutaneous layers involved in the infection. Bacterial pyoderma is common in dogs and less common in cats. The most common etiologic agent involved is *Staphylococcus pseudintermedius*, though other causative bacteria include other normal flora bacteria such as *S. schleiferi*, *S. delphini*, *S. epidermidis*, *Streptococcus canis*, *Escherichia coli*, *Pseudomonas* spp., *Bacillus* spp., *Corynebacterium* spp., *Micrococcus* spp., and *Proteus mirabilis* to name a few.

Clinical presentations of bacterial dermatitis vary, but the diagnostic workup and treatment approach is similar. This section will focus on a few common presentations of bacterial dermatitis. Treatment of bacterial infections involves topical antimicrobial therapy and, occasionally, antibiotic therapy. Common active ingredients present in topical products effective against Gram-positive and Gram-negative bacteria include chlorhexidine, benzoyl peroxide, malic and acetic acids, lime sulfur, ethyl lactate, diluted sodium hypochlorite (bleach), superoxidized hypochlorous solution (modified bleach solution), povidone iodine (betadine), and accelerated hydrogen peroxide. Specific recommendations for preferred antibiotics and their doses for canine pyoderma are provided in open-access guidelines provided by the International Society for Companion Animal Infectious Diseases (https://iscaid.org/).

SKIN FOLD PYODERMA—INTERTRIGO

Definition/Overview

Intertrigo is a type of surface inflammation and infection in areas where the skin is folded upon itself (e.g., facial and caudal folds in brachycephalic dogs).

Etiology

Bacteria typically colonize warm, humid areas of the skin, including places where the skin is folded or wrinkled. Examples include naso-ocular skin folds, lip folds, interdigital webbing, axillae, inguinal area, neck folds, vulvar folds, and tail folds. Because the bacterial load may be higher in these areas, the skin is more prone to develop bacterial overgrowth and subsequent dermatitis.

Pathophysiology

Factors contributing to bacterial overgrowth at these sites include frictional forces (skin rubbing), poor ventilation, trapping of tears/saliva/urine/feces, and abundant surface secretions. The bacteria and yeast living in these skin folds overgrow, and secondary inflammation develops. Certain breeds are more prone to anatomical variations causing excessive skin folds, including English Bulldog, Boston Terrier, French Bulldog, Shar Pei, and Mastiff. Obesity may also be a contributing factor to acquired skin fold dermatitis.

Clinical Presentation

The most common clinical signs include malodor, erythema, alopecia, exudate, keratinous debris, and crusting within skin folds (**Figure 18.16**). Be sure to carefully examine areas by lifting skin folds; otherwise, the lesions are missed easily.

Differential Diagnoses

Yeast (*Malassezia* spp.) and *Demodex* spp. mites commonly complicate inflammation along with bacteria. Occasionally, dermatophyte may complicate these lesions.



FIGURE 18.16 Erythema, lichenification, alopecia, and papules within the perivulvar and intramammary skin folds of a dog.

Allergic dermatoses (atopic dermatitis, adverse food reaction) exacerbate inflammation of skin. Obesity contributes to the depth of skin folds. Urine and/or fecal incontinence contribute to bacterial overgrowth within skin folds.

Diagnosis

Cytology using direct impression smear technique or using a cotton-tipped applicator to collect the sample and roll it onto the slide will reveal cocci- and/or rod-shaped bacteria along with neutrophils. Occasionally, yeast may be found as well. Skin scraping and fungal culture to rule out infection with *Demodex* spp. and dermatophytes, respectively, may be indicated.

Management

Treatment centers on controlling the bacterial overgrowth and inflammation, reducing the exudate, and reducing friction, especially considering intertrigo is a life-long issue. Topical agents containing chlorhexidine aid in reducing overgrowth of bacteria and yeast, malic acid or acetic acid reduce excess moisture and act in an antimicrobial fashion, and corticosteroids help to reduce inflammation. Wipes, shampoos, mousses, and creams are commonly used formulations. If the infection is severe or in an area difficult to apply topical therapy, such as the naso-ocular or tail folds, then systemic antibacterial therapy may be required. Cosmetic surgery to remove excessive skin folds and weight loss help to reduce continued frictional damage of the skin.

PYOTRAUMATIC DERMATITIS—ACUTE MOIST DERMATITIS—HOT SPOT

Definition/Overview

Pyotraumatic dermatitis is a type of surface pyoderma characterized by an acute onset of self-induced inflammation and infection of skin due to excessive licking, chewing, or scratching in an effort to relieve either pain or pruritus of the skin.

Etiology

Pyotraumatic dermatitis occurs commonly in dogs with allergic dermatitis, particularly flea bite hypersensitivity and atopic dermatitis, but also food allergy. Lesions may be more common in these dogs during warm, humid seasons and in dogs with dense haircoats. Other underlying diseases associated with this dermatosis include ectoparasites, contact hypersensitivity, anal sacculitis, otitis externa, poor hygiene, osteoarthritis, peripheral neuropathy, and psychological disorders.

Pathophysiology

The original pruritic or painful stimulus causes the dog to overgroom an area of skin. The excessive licking, chewing, and/or scratching creates trauma to the skin leading to erythema, excoriation, inflammation, and secondary infections. Lesions spread rapidly circumferentially from the initial site, especially with ongoing self-induced trauma.

Clinical Presentation

Lesions present as well-demarcated areas of erythema, hair loss, excoriation, and exudate. With chronicity, lesions may develop crusts, scales, papules, and pustules. Lesions tend to be much larger than they appear, so shaving the haircoat to assess the severity of dermatitis is important, especially in long-haired dogs (Figure 18.17). Lesions tend to spread rapidly if not treated.



FIGURE 18.17 Multifocal erythematous and exudative plaques and papules with lichenification and crusting on left thoracic limb of a dog.

Differential Diagnoses

Determining the underlying cause is important and includes allergic dermatitis (atopic dermatitis, flea bite hypersensitivity, food allergy, and contact allergy), thermal or chemical injury, clipper blade-induced injury, osteoarthritis, or other musculoskeletal disorder, ectoparasites, dermatophytosis, bacterial dermatitis, *Malassezia* spp. dermatitis, otitis externa, anal sacculitis, peripheral neuropathy, and psychological disorders.

Diagnosis

History of an acute-onset exudative dermatitis along with owner-observed pruritic behaviors, dermatological lesion appearance, and cytological evaluation provide a rapid diagnosis. Histopathology may help to confirm the diagnosis if needed.

Management

Haircoat must be clipped in order to assess the extent of the dermatitis, and improve the efficacy of the topical treatment. If the lesion is localized to a focal area, then topical antibacterial and anti-inflammatory therapy alone is effective. If the lesion is more extensive, and/or the patient is significantly immunocompromised, then systemic antibiotic therapy may be needed. Antipruritic and anti-inflammatory therapy may include topical or systemic glucocorticoids, oclacitinib (Apoquel) or lokivetmab (Cytopoint). An Elizabethan collar or other barrier devices prevent ongoing self-induced trauma to lesions. Another important component of management is the identification and treatment of the primary cause of the pain and/or pruritus.

SUPERFICIAL BACTERIAL DERMATITIS

Definition/Overview

Bacterial infection and inflammation involving the epidermis and the superficial follicular epithelium.

Etiology

The most common causative agent in the dog and cat is *S. pseudintermedius*; however, other normal flora bacteria may contribute as well (see the introduction section). There are many causes for colonization with bacteria, including trauma/traumatic inoculation, allergic dermatitis (atopic dermatitis, food allergy, flea bite hypersensitivity, and contact allergy), endocrinopathies (e.g., hypothyroidism, hyperadrenocorticism, and sex hormone imbalances), autoimmune dermatoses, neoplasia, ectoparasites, and thermal/chemical injury.

Pathophysiology

Bacteria may either be traumatically inoculated through scratching, biting, or other forms of trauma, or bacteria may act in an opportunistic fashion to colonize epidermal and follicular epithelium in immunocompromised hosts. Recognition of bacterial colonization by the host immune systemic leads to neutrophilic and granulomatous inflammatory infiltrates into the skin and hair follicle creating inflammation, and clinical lesions develop. Animals with bacterial infections of the skin and hair follicle have variable pruritus.

Clinical Presentation

Clinical lesions may develop in any skin location, and sometimes the distribution of lesions may be helpful when determining the primary cause of infection. For example, atopic dermatitis causes lesions to develop on the face, pinnae, paws, axillae, ventral abdomen, perineum, and other frictional areas, whereas flea bite hypersensitivity causes lesions to develop near and around the tail base, ventral abdomen, and distal extremities. Lesions consistent of erythematous papules, pustules, epidermal collarettes, crusting, scaling, and alopecia (Figure 18.18a, b). Hair shafts may be observed protruding through the center of papular and pustular lesions. Lesions may coalesce to form plaques and large epidermal collarettes and may be widespread in chronic infections.

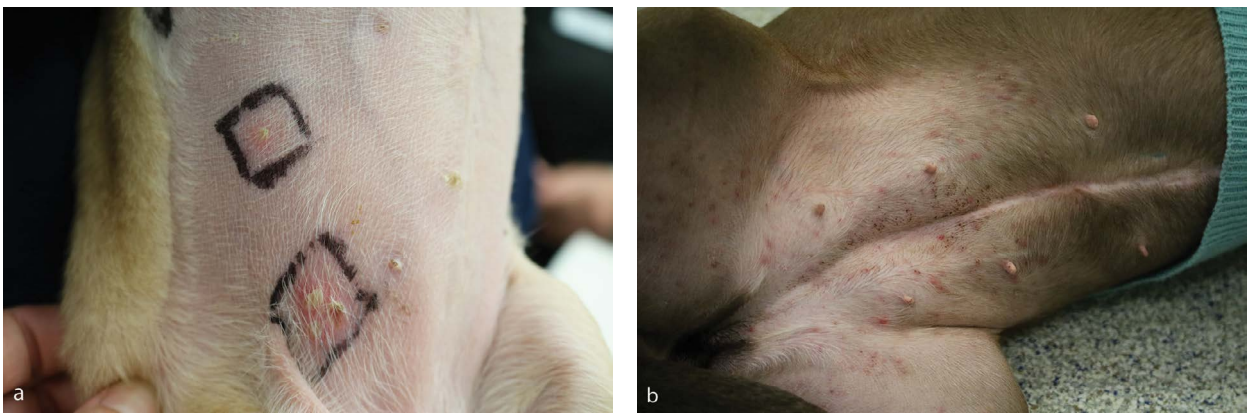


FIGURE 18.18 (a) Multifocal panfollicular pustules with circumferential erythema on ventral abdomen of a dog on chronic oral glucocorticoid therapy. (b) Numerous erythematous papules, epidermal collarettes, comedones, crusts, and alopecia on the ventral abdomen of an atopic dog.

Differential Diagnoses

The most likely differentials for superficial folliculitis include demodicosis and dermatophytosis. In fact, most of the clinical lesions are identical, which explains why superficial bacterial folliculitis is misdiagnosed as one of these diseases. Cytology, skin scrapings, Wood's lamp, trichography, and fungal culture can easily distinguish between these three differentials. Other differentials to consider include pemphigus foliaceus, dermatophilosis, *Malassezia* dermatitis, and epitheliotropic lymphoma.

Diagnosis

Clinical lesions combined with cytological evaluation is confirmatory for the majority of cases. Cytology collected from pustular contents, along the rim of an epidermal collarettes, or under a crust is most rewarding. Finding cocci-shaped bacteria inside of neutrophils in conjunction with examination findings is a confirmed diagnosis. Occasionally, bacterial load is low, and cytology does not yield a diagnostic sample. However, if highly degenerated neutrophils are present, these are highly suggestive of an active pyoderma. Swab or tissue aerobic culture and susceptibility testing is a more sensitive technique when bacterial folliculitis is suspected, but no bacteria are observed on cytological evaluation. Be sure to collect the sample from a pustule, under a crust, or along/under the rim of epidermal collarettes. Avoid culturing areas with high contamination, including perioral, paws, and perineal regions. Always perform aerobic culture and susceptibility testing when there is a suspicion of antibacterial resistance including animals/housemates with a history of antibiotic resistance, 50% reduction of skin lesions within 2 weeks of therapy, active lesions developing within the first 2 weeks of therapy, intracellular cocci after 6 weeks of therapy, and anytime there are rod-shaped bacteria on cytology.

Management

Topical therapy has the great advantage of preventing the formation of antibiotic resistance, since most topical therapies are antiseptics, not antibiotics. Current guidelines (https://iscaid.org/) suggest that topical therapy alone should be selected whenever possible. Treatment with topical therapy alone is sufficient to cure most cases of superficial bacterial folliculitis; however, owner and patient compliance will determine therapy success. If topical therapy is selected, daily to every-other-day application of sprays or mousses and weekly to biweekly (every 3 days) shampoo therapy is most effective to resolve the infection, especially with widespread lesions. Localized lesions can resolve with once- to twice-daily application of topical therapy using gel, cream, ointment, lotion, or wipe formulations. Owners need to understand the proper application techniques and contact times for improved therapy success. For example, dips, wipes, sprays, crèmes, and mousse products are applied without rinsing, whereas shampoos are applied for 10 minutes prior to rinsing. Topical therapy should be continued for 1 week beyond clinical and cytological resolution of lesions.

Systemic antibiotic therapy is indicated when topical therapy proves unsuccessful, owner/patient compliance is a known issue, a large body surface area is affected, or the patient is significantly immunocompromised. Consideration of the drug availability, safety, cost, and geographic antimicrobial resistance patterns is needed when selecting an antibiotic. Empirical selection of a first-tier antibiotic (e.g., cephalexin, amoxicillin/clavulanate, cefpodoxime, cefovecin, trimethoprim/ormetoprim-potentiated sulfonamides, or clindamycin) is recommended when culture and susceptibility results are not available. However, culture and susceptibility testing is needed anytime antibiotics from the second tier are selected (e.g., doxycycline/minocycline, chloramphenicol, fluoroquinolones, rifampin, or amikacin). Any other antibiotics would fall into the third-tier category and are not recommended for treating superficial bacterial folliculitis. Antibiotic treatment should continue 1 week beyond clinical and cytological resolution of lesions. Whenever possible, topical therapy should be used in conjunction with systemic antibiotic therapy.

Determining the primary cause of folliculitis as discussed previously is mandatory for treating and preventing recurrence of the folliculitis.

IMPETIGO—PUPPY PYODERMA

Definition/Overview

Impetigo is a form of superficial bacterial dermatitis characterized by nonfollicular subcorneal pustules affecting skin with little hair including the ventral abdomen, groin, axillae, and head.

Etiology

The most commonly isolated causative agent is *S. pseudintermedius*.

Pathophysiology

Impetigo is a noncontagious condition affecting young, peripubescent dogs. Causes include ectoparasites, viral infections, inadequate nutrition, filthy living environment, or idiopathic. It is observed rarely in adult dogs secondary to other diseases (e.g., hypothyroidism, hyperadrenocorticism, etc.). A similar condition occurs in kittens and is postulated to occur from overzealous grooming by the queen. Subsequently, bacteria involved include *Pasteurella multocida* and β–hemolytic streptococci.

Clinical Presentation

Small, nonfollicular pustules found on the glabrous skin of the groin, axillae, and ventral abdomen (**Figure 18.19**). Lesions are nonpainful, variably pruritic, and rupture easily creating a yellow-colored crust or epidermal collarettes.



FIGURE 18.19 Few large pustules on the abdomen of a puppy typical of puppy pyoderma. (*Courtesy of Dr. Schaer.*)

Differential Diagnoses

Contact allergic, irritant contact dermatitis, demodicosis, dermatophytosis, and adverse food reaction are all valuable differentials. In very severe cases, puppy strangles may also be considered.

Diagnosis

The presence and ventral distribution of nonfollicular pustules in a puppy, along with the presence of intracellular cocci confirms the diagnosis.

Management

Impetigo is a self-limiting disease for most puppies, especially if a primary cause is identified and corrected (e.g., poor nutrition, dirty living environments). Topical chlorhexidine therapy is the preferred treatment approach; however, systemic antibiotics are used when topical therapy fails to improve the condition, the lesions are severe/widespread, or when the condition recurs. Continue topical therapy for 1 week beyond clinical and cytological resolution of lesions.

Consideration of any underlying conditions leading to the development of these lesions should be identified and corrected.

MUCOCUTANEOUS PYODERMA

Definition/Overview

This is a superficial bacterial infection and inflammation of the haired skin and mucosal membranes of the eyelids, lips, nares, prepuce, vulva, and anus.

Etiology

The etiology is unknown, although bacterial overgrowth and infections contribute to the developing skin lesions, especially considering lesions improve with the use of systemic and topical antibacterial therapies and recur once these are discontinued.

Pathophysiology

The mechanisms by which skin lesions develop is unknown; however, some dogs have other underlying diseases including allergic dermatitis and endocrinopathies, which may contribute to the development of lesions. Genetic predispositions are thought to occur as German Shepherd Dogs and their crosses have an increased risk, though dogs of any age, breed, or sex may be affected.

Clinical Presentation

The disease has a striking symmetrical distribution to the mucocutaneous areas primarily, including the commissures of the lips and perioral skin (Figure 18.20); however, lesions may extend to the eyelids, nares, prepuce, vulva, and anus. Lesions consist of swelling, erythema, exudate, erosion, ulceration, depigmentation, and crusting. Lesions are painful.

Differential Diagnoses

Differential diagnoses include lip fold dermatitis or intertrigo, cutaneous lupus erythematosus, pemphigus foliaceus, pemphigus erythematosus, zinc-responsive dermatosis, cutaneous adverse drug reaction, demodicosis, dermatophytosis, allergic dermatitis (e.g., atopic dermatitis, food allergy, and contact allergy), irritant contact dermatitis, chemical burns, and epitheliotropic lymphoma.

Diagnosis

Physical exam findings, cytological evaluation, and response to antibacterial therapies provide a diagnosis

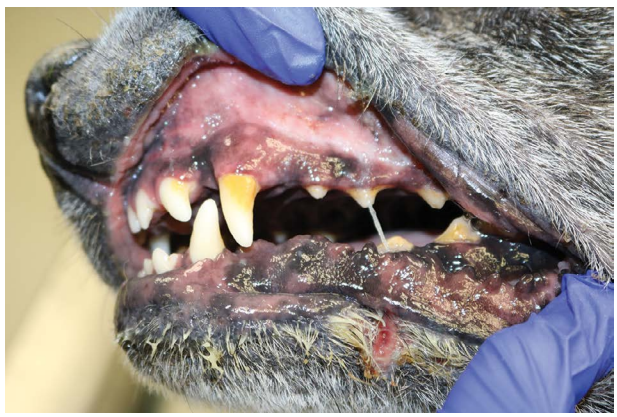


FIGURE 18.20 Alopecia, crusting, purulent exudate, and ulceration of the periorbital haired skin with depigmentation of oral mucosa and lips in a dog with mucocutaneous pyoderma.

in the majority of cases; however, histopathology and bacterial cultures may be beneficial in complicated cases.

Management

This disease is a lifelong condition and relapses occur commonly. Topical antibacterial therapy is the preferred treatment approach; however, systemic antibiotics are used when topical therapy fails to improve the condition, the lesions are severe/widespread, or when the condition recurs. Continue topical therapy for 1 week beyond clinical and cytological resolution of lesions. Clip the hair around the affected areas to improve penetration of the topical agents. One effective topical therapy approach is cleaning with an antiseptic solution (e.g., chlorhexidine, benzoyl peroxide). Consider implementation of a topical therapy routine in cases where relapses are ongoing.

DEEP PYODERMA AND FURUNCULOSIS

Definition/Overview

Deep pyoderma is a bacterial infection and inflammation extending into the dermis or subcutis. Furunculosis is a specific type of deep pyoderma developing as a consequence of follicular epithelium rupture into the dermis.

Etiology

Deep pyoderma may occur as a consequence of traumatic inoculation of bacteria, spread from another body site, or rupture of hair follicle epithelium (furunculosis). Furunculosis is a common cause of deep pyoderma and results in free hair shafts and keratin in the dermis. This stimulates a strong host pyogranulomatous "foreign body" reaction to the free keratin. Underlying causes of deep pyoderma include allergic dermatitis (e.g., atopic dermatitis, food allergy, flea bite hypersensitivity, and contact allergy), demodicosis, dermatophytosis, endocrinopathies, obesity, abnormal weight distribution or ambulation, short/stubby haircoat, calluses, trauma, solar dermatitis, or idiopathic.

Pathophysiology

Once a pyogranulomatous reaction occurs, lesions will progress from nodules to hemorrhagic bullae that fistulate and heal via scarring. With more severe lesions, cellulitis may develop. Fibrosis formation may trap bacteria and free keratin in the dermis, which contributes to recurrence of lesions at the same site.

Clinical Presentation

Lesions consist of painful to pruritic nodules, papules, fistulae, hemorrhagic bullae, and alopecia (Figure 18.21a–d). Fistulated lesions become covered in crusts as exudate dehydrates. Furunculosis lesions occur commonly in areas of friction, including the chin, paws, sternum, and over bony prominences. Lesions typically are multifocal but may be localized in cases of traumatic inoculation of an organism. Peripheral lymphadenopathy is common, and some dogs may experience fever, inappetence, and lameness in more severe cases.

A unique form of furunculosis occurs in dogs after grooming (also known as postgrooming folliculitis and furunculosis) with contaminated shampoos or grooming equipment. Numerous bacteria have been implicated in these infections, including *S. pseudintermedius, P. aeruginosa, Serratia* spp., and *Burkholderia* spp. Affected dogs usually are short to medium-coated, and lesions tend to be distributed along the dorsum. Lesions are painful.

Differential Diagnoses

Differential diagnoses to consider include demodicosis, dermatophytosis, foreign body, opportunistic environmental fungal or bacterial infections, sterile nodular panniculitis, nodular sebaceous adenitis, sterile granuloma pyogranuloma syndrome, and neoplasia.

Diagnosis

Clinical lesions and cytological evaluation are good starting places for achieving a diagnosis. Fine-needle aspirate from an intact furuncle or nodule reveals pyogranulomatous inflammation with intracellular bacteria, though very few bacteria may be observed. The most sensitive diagnostics include aerobic bacterial tissue culture and susceptibility testing and histopathology.

Management

Deep infections require more long-term antibacterial therapy to achieve complete resolution. Additionally, systemic antibiotics are required to adequately achieve drug penetration to the site of infection. Antibiotics ideally are selected based on culture and susceptibility testing, especially given the long-term therapy needed. For example, most deep bacterial infections and furunculosis require an average of 6–8 weeks of therapy, and therapy is continued 2 weeks beyond a clinical and cytological cure. If an inadequate antibiotic is empirically selected, this may significantly affect antimicrobial susceptibility patterns and future antibiotic options. Lesions tend to relapse if antibiotics are stopped too early. Topical therapy is helpful to assist with resolution of the superficial components of the infection, and topical glucocorticoids may serve as a safe alternative to systemic therapy for inflammation. Pain medications usually are required as most animals exhibit lameness and sensitivity on manipulation of the skin lesions. This disease is a lifelong problem. Consideration of any underlying conditions leading to the development of these lesions should be



FIGURE 18.21 **(a)** Severe lichenification, hyperpigmentation, alopecia, ulcers, erosions, and fistulation of the right lateral antebrachium in a German Shepherd Dog with deep pyoderma. **(b)** Numerous papules, pustules, erosions, ulcers, and fistula in a Labrador Retriever with postgrooming folliculitis and furunculosis. **(c)** Papule, crusts, and nodules with draining tracts and purulent exudate on the ventral mandible of a cat with chin acne. **(d)** Severe lichenification, erythema, and fistulae with hemorrhagic to purulent exudate of the interdigital skin of an English Bulldog with atopic dermatitis.

identified and corrected (e.g., obesity, allergic dermatitis, endocrinopathies, musculoskeletal disease, etc.). Long-term management with topical antimicrobial and anti-inflammatory agents helps to reduce flareups. When significant fibrosis occurs and serves as a nidus of lesion recurrence, the areas can be removed surgically (e.g., excisional biopsy, CO_2 laser ablation, or cryotherapy).

In some cases, lesions are sterile, and therapy aimed at reducing systemic inflammation may include glucocorticoids, modified cyclosporine (Atopica), oclacitinib (Apoquel), and tacrolimus (Protopic).

ABSCESSES AND CELLULITIS

Definition/Overview

An abscess is a well-organized, localized accumulation of purulent exudate in the dermis, subcutis, or deeper fascial layers. Cellulitis is an acute, unorganized, disseminated accumulation of purulent exudate extending from the dermis into the subcutis, fascial planes, musculature, and occasionally lymphatics.

Etiology

Most commonly, abscesses and cellulitis develop in response to bacterial infection, specifically *S. pseudintermedius*; however, any normal oral or cutaneous flora bacteria may cause infection, especially in the case of animal bites. The most common canine oral bacteria causing infection include *S.* pseudintermedius and *E. coli*, whereas feline oral bacteria typically include *P. multocida*, β-hemolytic streptococci, *Porphyromonas* spp., and *Fusobacterium* spp. Other causes include opportunistic bacteria such as *Mycobacteria* spp. or *Nocardia* spp. Occasionally, demodicosis and tooth root abscess may result in cellulitis.

Pathophysiology

Infection occurs when bacteria are traumatically inoculated in the skin as a result of the extension of a superficial infection into deeper layers of the skin, or



FIGURE 18.22 Large subcutaneous abscess with erythema and bruising on the ventral abdomen of a Yorkshire Terrier on glucocorticoids and mycophenolate for treatment of immune-mediated thrombocytopenia. Culture revealed *Clostridium* spp.

dissemination from another body location. Breaks in skin from animal bites or scratches, insect bites, chemical/thermal burns, surgical incisions, and intravenous catheters all serve as entry points into the deeper layers of skin. Dissemination is more likely to occur in immunosuppressed animals. Abscesses occur when bacteria are trapped deep in the skin, and the wound is sealed. This usually occurs 2–4 days after injury in the case of an animal bite or traumatic inoculation.

Clinical Presentation

A few days after inoculation, a firm, erythematous, painful, nodule to mass (abscess) develops in the deep layers of skin (Figure 18.22). In the case of cellulitis, tissue swelling is poorly demarcated and takes on a diffuse, erythematous, edematous, exudative dermatitis that is painful and hot to the touch. Fistulae may develop over time along with crusting. Fever, pain, lethargy, and decreased appetite may develop. Lesions are most common in areas prone to bites, including head, pinnae, neck, extremities, tail, and caudal dorsum. Sexually intact animals may be overrepresented.

Differential Diagnoses

Other causes of abscess and cellulitis include severe demodicosis, dermatophytic kerions and pseudomycetomas, opportunistic fungal and oomycotic infection, opportunistic bacterial infection, foreign body, surgical implants, sterile nodular panniculitis, sterile granuloma pyogranuloma syndrome, and neoplasia.

Diagnosis

History may provide evidence of a recent animal fight or other injury prior to the onset of clinical lesions. Clinical evaluation and cytology are useful initial diagnostic tools. Fine-needle aspirate of an abscess reveals purulent to pyogranulomatous inflammation with intracellular bacteria. Cellulitis may be more difficult to collect a sample for cytological examination. In both cases, tissue culture and susceptibility testing along with histopathology are important to confirm the diagnosis and implement appropriate antibiotic options. In the case of abscess and cellulitis, tissue cultures include aerobic, anaerobic, fungal, and mycobacterial cultures.

Management

Treatment is multifactorial. For abscesses, surgery to open the lesion to allow for draining as well as thorough cleaning using sterile saline lavage is helpful to reduce the bacterial load and improve penetration of systemic antibiotics at the site of infection. Remember to select antibiotics based on results of culture and susceptibility testing.

Treatment for cellulitis involves warm water Epsom salt soaks to reduce tissue swelling, deep tissue massage, and passive range-of-motion exercise to improve lymphatic flow, appropriate antibiotic selection, osmotic bandages to remove excessive fluid from tissue, and improved skin hygiene to prevent recurrence. If empirical antibiotic selection is chosen for initial therapy but the patient fails to improve, then tissue culture is paramount as the risk for an opportunistic bacterial (e.g., *Mycobacteria* spp., *Nocardia* spp.) or fungal (dimorphic fungi, pigmented and nonpigmented molds, oomycetes) organism(s) increases.

FUNGAL DERMATITIS

INTRODUCTION

There are over 100,000 types of fungi in the environment. Some of these are important pathogens in veterinary dermatology; however, most fungi do not cause disease in animals unless they are significantly immunocompromised (e.g., phaeohyphomycosis, hyalohyphomycosis, oomycosis, zygomycosis, etc.). This section will focus on the two most common types of fungal dermatoses in small animals (dermatophytosis and malasseziosis).

DERMATOPHYTOSIS

Definition/Overview

Dermatophytosis is an often overdiagnosed fungal infection of the skin, hair shaft, or claw by a keratin-loving (keratinophilic) fungal organism (termed dermatophyte). Dermatophytosis is a contagious and zoonotic disease.

Etiology

There are many species of dermatophytes that cause infection in dogs and cats. The three most common

are *Microsporum canis, Microsporum gypseum,* and *Trichophyton mentagrophytes*. The reservoir for *M. canis* is a cat, the reservoir for *M. gypseum* is soil, and the reservoir for *T. mentagrophytes* is a rodent.

Pathophysiology

Infection occurs most commonly by inoculation (e.g., clipper blades) or via entry through a compromised skin barrier (e.g., self-excoriation, abrasions, insect bites). Dermatophyte also produce fungal enzymes (proteases) that allow for further tissue penetration. The arthrospore is the infectious stage, and these are shed from infected animals into the environment where they are viable for greater than 12 months. Once the dermatophyte gains entry, hyphal invasion of skin, hair shafts, and claws leads to the development of clinical lesions. This is a self-limiting disease for most animals once the appropriate cell-mediated and humoral immune response is initiated. In cases of immunocompromised animals, the infection may persist. Rarely, some cats (e.g., Persian cats) may develop a unique form of disease (dermatophytic pseudomycetoma) characterized by nodular fungal dermatitis in the deep dermis and subcutis.

Clinical Presentation

Dermatophytosis has no age, breed, or sex predilection; however, young, debilitated, and chronically ill animals maybe be more likely to contract infection. Also, animals with an abnormal skin barrier (e.g., atopic dermatitis) may have an increased risk of infection. The most common clinical signs of infection include alopecia, crusting, scaling, broken hairs, and erythema (**Figure 18.23a, b**). Papules and pustules may be present. Occasionally, kerions (or localized, erythematous, raised nodules with ulceration) may develop when the immune response to the fungi is robust, and the fungi invade the dermis. Persian cats may develop a unique clinical presentation characterized by deep dermal/subcutaneous nodules (dermatophytic pseudomycetoma). Pain and pruritus are variable. This is a contagious disease, so other animals may be affected in the household. Keep in mind that many animals may serve as asymptomatic carriers, so in case of a positive animals, all in contact animals should be tested for dermatophytosis. This is a zoonotic disease, so people may become infected as well. Lesions present in an asymmetrical fashion. Lesions may be more common the face and thoracic limbs for *M. gypseum* and *T. mentagrophytes*

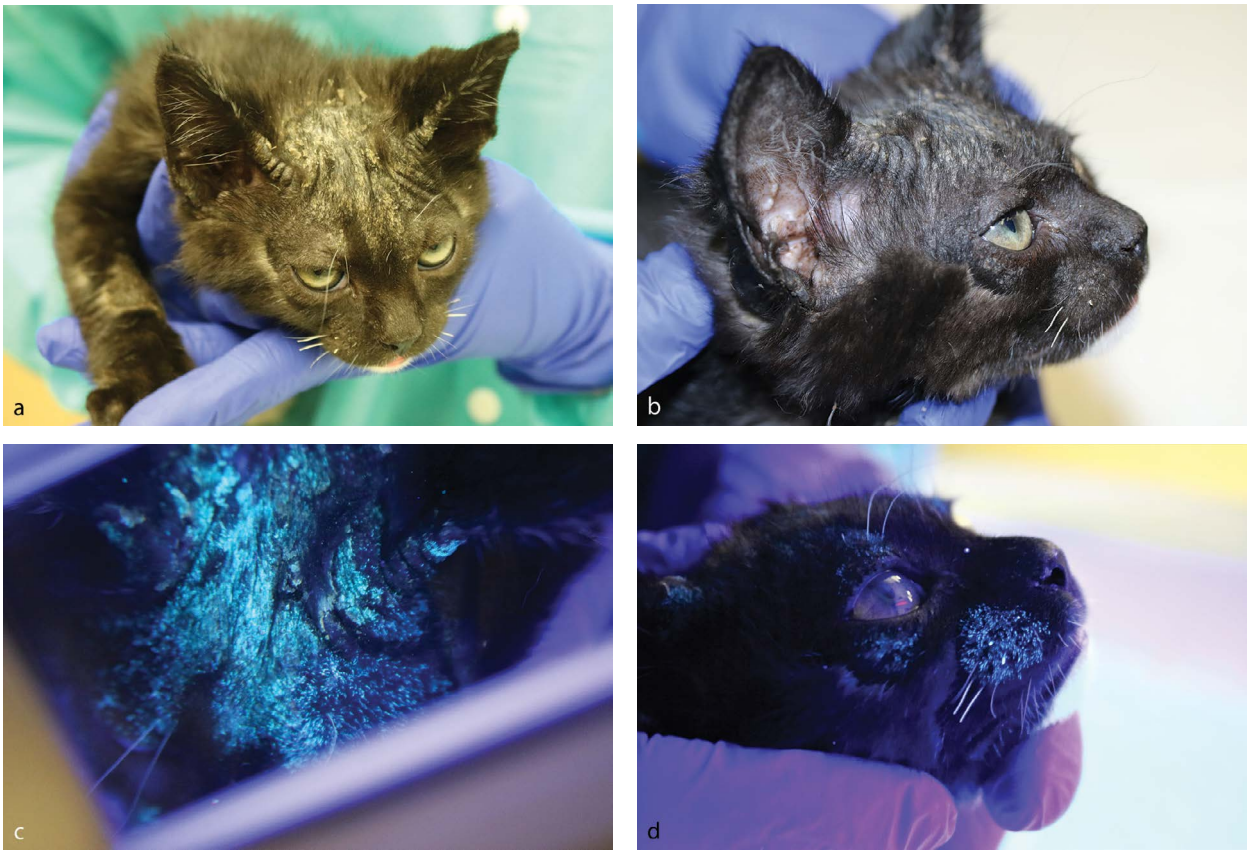


FIGURE 18.23 **(a)** Kitten with dermatophytosis characterized by alopecia, lichenification, scaling, and crusting of the dorsal head and pinnae. **(b)** Note the broken whiskers and hyperpigmentation of affected skin. **(c)** Scale and infected hairs demonstrating apple green fluorescence consistent with *Microsporum canis* infection. **(d)** Fluorescing hairs are the best to sample for dermatophyte culture and/or PCR testing.

due to the expected contact when digging in the soil or chasing rodents, respectively.

Differential Diagnoses

Other causes of folliculitis to consider include bacteria and *Demodex* spp. infections. For focal lesions, other differential diagnoses include abscess, injection site reaction, and ectoparasites. For widespread lesions, other differential diagnoses include allergic dermatitis (e.g., flea bite hypersensitivity, atopic dermatitis, adverse food reaction), telogen/anagen defluxion, psychogenic alopecia, autoimmune dermatoses (e.g., pemphigus foliaceus), or deep opportunistic bacterial/fungal dermatitis.

Diagnosis

There are several diagnostic tools that can be useful. Historical evidence of multiple in-contact animals with identical clinical lesions increases the suspicion of an infectious disease. Additionally, when owners develop similar crusting or erythematous lesions, the suspicion of dermatophytosis increases. Dermatophytosis is commonly overdiagnosed based on clinical lesions alone, so additional testing is required.

- *Wood's lamp:* Most *M. canis* isolates produce a metabolite that fluoresces bright green. Be sure the hair shaft, and not just the skin, is glowing (**Figure 18.23c, d**). Crusting, scaling, cloth fibers, medications, soaps, petroleum, and bacteria can glow (white to yellow) and cause a false-positive result.
- *Fungal culture:* Specialized fungal agars (e.g., DTM) for growing dermatophytes that contain phenol red are commonly used. This is a pH indicator that causes a red discoloration when dermatophytes grow and release alkaline metabolites. Other components of the culture are Sabouraud dextrose agar with added cycloheximide, gentamicin, and chlortetracycline to inhibit secondary growth of other fungi and bacteria. The interpretation of DTM cultures can be tricky if not constantly monitored. False-positive color change is possible, so perform cytological evaluation of all growing colonies to identify the dermatophyte species.
- Surface cytology from lesions usually reveals neutrophils and some macrophages. Occasionally, arthrospores are identified in heavily infected animals. Fine-needle aspirate of kerion or dermal nodules reveals pyogranulomatous inflammation and occasionally fungal hyphae and/or arthrospores.
- Trichography to evaluate for fungal hyphae within hair shaft and accumulation of arthrospores along or within hair shafts.
- Macerated tissue fungal culture is preferred for kerions or dermal nodular lesions.
- Dermatophyte PCR is a very sensitive and rapid technique for the identification of fungal DNA within or on hair shafts. This test does not prove fungi are living/viable, so be sure to pair this with a DTM culture for confirmation. Dermatophyte PCR is best used to make an initial, rapid diagnosis or to rule out dermatophytosis, while fungal cultures are more reliable for monitoring response to treatment and confirm the diagnosis.
- Histopathology is useful for kerions or dermal nodular forms of disease; however, they can aid in making the diagnosis of folliculocentric disease as well.

Management

While this is considered a self-limiting disease for most animals, treatment is pursued in most cases due to the zoonotic potential, with the main goal to reduce the amount of spores shed in the environment. Infected animals should be confined away from nonlesional, culture-negative housemates. A combination of topical and systemic therapy is useful to expedite time to improvement. Topical therapy helps limit transmission to people and other animals in the household by removing infectious arthrospores and hairs from the animal. Antifungal ingredients in topical therapies include lime sulfur, miconazole, ketoconazole, and enilconazole. Topical therapy can be applied as a dip or shampoo at least twice weekly and as a mousse, spray, or cream once to twice daily during active infection. Topical therapy is a safer alternative for young animals than systemic antifungal therapy. Systemic options include itraconazole, ketoconazole, fluconazole, terbinafine, and griseofulvin. Treatment is continued until two negative consecutive fungal cultures within 1 month from each other are achieved. Environmental decontamination to remove infected hairs is important to prevent transmission to other people or pets at home and prevent recurrence of infection. Daily vacuuming, steam cleaning, Swiffer dust wipes, accelerated hydrogen peroxide, bleach, and enilconazole are effective decontamination measures.

Dermatophytosis carries a good prognosis for cure; however, treatment can be frustrating in multianimal households. It is important to look for underlying causes of infection and initiate treatment if the disease is ongoing (e.g., allergies, stress, immunocompromise, etc.).

MALASSEZIA spp. DERMATITIS

Definition/Overview

This is a fungal skin infection due to an overgrowth of the yeast *Malassezia* spp. There are several species of *Malassezia* affecting dogs and cats, though the most common is *Malassezia pachydermatis*. Infections may cause intense pruritus due to hypersensitivity.

Etiology

Malassezia spp. yeast are normal commensals of the skin and ear canal. They prefer warm, dark, humid living conditions. As such, common locations include lip folds, interdigital skin, claw folds, ear canals, axillae, groin, perineal, and intertriginous skin. Diseases that alter normal skin conditions may make the skin more favorable for overgrowth of yeasts, including allergic

dermatitis (atopic dermatitis, food allergy, flea bite hypersensitivity), endocrinopathies (e.g., hypothyroidism, hyperadrenocorticism), and seborrheic dermatitis. Some dog breeds are overrepresented, including Basset Hound, Terriers, Poodles, American Cocker Spaniel, Shih Tzu, Dachshund, and English Setter.

Malassezia spp. overgrowth is less common in cats unless significant immunosuppression exists (e.g., FeLV/FIV positive cats, chronic glucocorticoid administration, and pemphigus foliaceus) or in case of allergic dermatoses.

Pathophysiology

The cause of *Malassezia* spp. overgrowth is unclear, though conditions that alter the normal skin environment causing increased lipid accumulation, temperature, or humidity may propagate overgrowth. Immunosuppression may contribute to loss of normal flora homeostasis.

Clinical Presentation

Malassezia spp. reside on the surface of the skin, and the most common clinical signs include pruritus, erythema, scaling, crusting, exudate, malodor, lichenification, and hyperpigmentation (Figure 18.24). Lesions occur more commonly in areas where *Malassezia* spp. reside (e.g., lip folds, ears, paws, claw beds, axillae, groin, tail folds, vulvar folds, etc.); however, lesions may be widespread in some cases.

Differential Diagnoses

Other causes of pruritus and erythematous dermatitis include allergic dermatitis (atopic dermatitis, flea bite hypersensitivity, food allergy), dermatophytosis, demodicosis, cutaneous adverse drug reaction, epitheliotropic lymphoma, sarcoptic and demodectic mange, ectoparasites, endocrinopathy (e.g., hypothyroidism), and idiopathic keratinization defects.



FIGURE 18.24 Epidermal dysplasia in a West Highland White Terrier characterized by severely lichenified and dysplastic skin with hyperpigmentation, erythema, alopecia, and crusting. Skin is greasy to the touch (seborrhea oleosa), and abundant *Malassezia* spp. organisms are present on skin cytology.

Diagnosis

Diagnosis is achieved easily through cytological evaluation of the affected skin for the peanut-shaped yeast. In some animals thought to be hypersensitive to *Malassezia* spp., very few yeast present on cytology could represent a significant clinical finding warranting treatment.

Management

The organisms live on the surface of the skin, so topical therapy is an important management tool. Antifungal ingredients in topical therapies include lime sulfur, miconazole, ketoconazole, terbinafine, and enilconazole. Topical therapy can be applied as a dip or shampoo at least twice weekly and as a mousse, spray, or cream once to twice daily during active infection. Systemic therapy may be needed in widespread, severe infections or in animals with suspected *Malassezia* spp. hypersensitivity. Systemic antifungal options include itraconazole, ketoconazole, fluconazole, and terbinafine.

Malassezia spp. dermatitis is a secondary dermatosis, so identification and management of the primary disease process is important to maintain treatment success.

PARASITIC DERMATOSES

Parasitic skin diseases are quite common in companion animals. Along with allergies and some infections, ectoparasites are the most common cause of pruritus in dogs and cats. Many parasitic dermatoses are seen in clinical practice; however, for brevity, the following will be discussed in this chapter: Canine and feline demodicosis, canine scabies, otoacariasis, cheyletiellosis and trombiculosis.

CANINE DEMODICOSIS

Definition/Overview

Canine demodicosis is one of the most common cutaneous parasitic diseases affecting young dogs. Canine demodicosis can be juvenile or adult onset, and it can be localized or generalized. The ability to differentiate the various forms is important when considering treatment options and prognosis. If untreated, the generalized form can become a very serious dermatological disease. For this reason, an early diagnosis is essential for successful treatment. A genetic predisposition for disease severity is suspect, so affected dogs should not be used for breeding purposes.

Etiology

Canine demodicosis is caused by species-specific demodectic mites living in the hair follicles or sebaceous glands of mammals. In dogs, demodicosis is due to two mites: *Demodex canis* and *D. injai*. *D. injai* is double

the length of *D. canis*. A hereditary "mite-specific" immune defect has been reported in affected dogs.

Pathophysiology

The exact pathogenesis of canine demodicosis is not clear. However, it is hypothesized, and in part demonstrated, that a defect in CD4+ T cells associated with an increase in oxidative stress contributes to the development of juvenile-onset demodicosis. Adult-onset demodicosis can be associated with systemic immunosuppression, either iatrogenic or associated to systemic diseases (e.g., neoplasia, Cushing's disease, etc.).

Clinical Presentation

The clinical presentation of canine demodicosis is extremely variable and is based on which mite is present: *D. canis* or *D. injai*. The typical presentation of demodicosis includes the presence of scales, erythema, well-demarcated alopecia, and folliculitis (Figure 18.25a, b). With time, it progresses to furunculosis with draining tracts, crusts, diffuse alopecia, and pruritus (Figure 18.25c, d). This latter sign is present mainly because of the presence of secondary bacterial infections. Lesions may appear anywhere on the body; however, face, ventrum, and extremities are the most common. Canine demodicosis caused by *D. injai* can include clinical differences like seborrhea oleosa on the dorsal midline and pruritus.

The differentiation in localized versus generalized forms is somehow arbitrary. In accordance to recently published guidelines, the localized form of demodicosis includes the presence of no more than five affected areas with a diameter less than 2.5 cm. If an entire body region (e.g., head, trunk, extremities) or more than one paw is affected, the demodicosis is classified as generalized. In juvenile onset, about 90% of the localized forms will disappear spontaneously, whereas 10% will progress to the generalized form. Canine demodicosis can also be classified as juvenile and adult onset. This distinction is based on the age of onset: Juvenile (18–24 months and adult >24 months.



FIGURE 18.25 **(a)** Shih Tzu with atopic dermatitis that received numerous long-acting steroid injections developed adult-onset generalized demodicosis localized to the ventral thorax and all four paws. Note the matting of the haircoat within purulent exudate, crusts, erythema, and hemorrhage. **(b)** The haircoat is shaved to reveal numerous erythematous to hemorrhagic papules and pustules with fistulation and ulceration of the skin. **(c)** Adult *Demodex canis* mite observed on skin scrapings from the ventral thorax. **(d)** Two weeks into treatment with topical antibacterial shampoo, systemic antibiotics, and oral isoxazoline treatment for the demodicosis.

Differential Diagnoses

Demodicosis is pleomorphic and can resemble many skin diseases. Bacterial (superficial pyoderma) and fungal (dermatophytosis) folliculitis are the most important differentials. Other differentials may include autoimmune diseases (e.g., pemphigus foliaceus, alopecia areata, sebaceous adenitis, rabies vaccine vasculopathy, cutaneous adverse drug reactions, sterile granuloma/pyogranuloma syndrome, etc.), and neoplasia (cutaneous T-cell lymphoma). When associated with secondary infections, allergies should also be considered, specifically when *D. injai* is isolated.

Diagnosis

The gold standard for a diagnosis of canine demodicosis is the presence of mites. This can be achieved in a variety of ways. The most effective test is deep skin scraping (**Figure 18.11a–e**), followed by trichography (hair plucking and evaluation) and histopathology. If correctly performed, deep skin scraping is able to rule out or rule in canine demodicosis. Trichography is less sensitive but equally effective if furunculosis and draining tracts are present. In addition, trichography is the recommended and safest test to sample sensitive areas (e.g., periocular, perilabial, interdigital). Histopathology should be reserved for granulomatous demodicosis and situations when skin scraping/trichography would not be as effective (e.g., severely lichenified skin, mucinotic skin of the Shar Pei).

Cytological evaluation of skin scrapings and hair plucks promotes identification of the different mite life stages. In addition, the differentiation among the life stages is essential to monitor treatment success (presence of immature forms [eggs and larvae] is indicative of an active disease; only adults may be indicative of a less active disease).

Management

Nowadays, many treatment options are available to treat canine demodicosis. However, very few of them are labeled for such disease. The oldest and only treatment labeled for canine demodicosis in the United States is amitraz. This is applied topically as a dip or sponged onto the skin weekly. In Europe, along with amitraz, weekly application of topical moxidectin (Advocate/Advantage Multi) is also labeled for demodicosis. Other equally effective, although not approved, treatments for demodicosis include daily oral ivermectin, daily oral moxidectin, and daily oral milbemycin. More practical treatment options include monthly administration of oral afoxolaner, sarolaner, and lotilaner as well as bimonthly or biquarterly administration of fluralaner.

Regardless of the therapy selected, the treatment for canine demodicosis should continue until obtaining two negative skin scrapings 1 month apart (or three negative skin scrapings 2 weeks apart). After that, the patients should be monitored for relapse via skin scrapings for 1 year (e.g., at 1, 3, 6, and 12 months post second negative scraping). Long-term treatment success is dependent on identification and correction of any immunosuppressive underlying cause. Secondary bacterial infections should also be properly treated when present.

Corticosteroids and oclacitinib are contraindicated in cases of canine demodicosis or in dogs with a history of demodicosis.

FELINE DEMODICOSIS

Definition/Overview

Feline demodicosis is an uncommon parasitic disease. Similar to canine demodicosis, it is caused by mites belonging to the genus *Demodex*. *Demodex gatoi* has a moderate geographic distribution, with most cases of feline demodicosis reported in Texas and the southeastern United States. *Demodex cati* is a very uncommon skin disease.

Etiology

Three morphologically different *Demodex* mites have been associated with feline demodicosis: *Demodex cati*, *D. gatoi*, and *Demodex* spp. (unnamed). The first one, *D. cati*, is a follicular mite very similar to *D. canis* in dogs, whereas *D. gatoi* is much shorter than *D. cati*. The third species, still unnamed but genetically different from the other two, is morphologically in between *D. cati* and *D. gatoi*.

Pathophysiology

Very little information is available on the pathogenesis of feline demodicosis. In particular, *D. cati* is quite uncommon, and it is generally associated with systemic immunosuppression. In particular, coinfections with FIV and FeLV are commonly reported. On the opposite, immunosuppression has not been associated with *D. gatoi*.

Clinical Presentation

Feline demodicosis can vary in clinical presentation based on the mite inducing the disease. For example, feline demodicosis caused by *D. cati* is very subtle and characterized by well-demarcated alopecia and erythema around the eyes, lips, nares, and ear tips (**Figure 18.26a, b**). Sometimes alopecia can be seen on the front limbs. On the contrary, *D. gatoi* is mainly associated with poorly demarcated alopecia and pruritus of the trunk and ventrum, and it is highly contagious between cats.

Differential Diagnoses

Differential diagnoses may include pruritic and nonpruritic skin diseases depending on which mite is present. For *D. gatoi*, allergies and other parasitic diseases (e.g., *Cheyletiella* spp., *Notoedres cati*, *Otodectes*



FIGURE 18.26 (a) Crusting and alopecia of the dorsal rostral muzzle in a cat receiving inhalant steroids for feline asthma. **(b)** Complete alopecia of the pinnae in the same cat. **(c)** *Demodex* spp. mites observed on skin scrapings and trichogram from the muzzle and pinnae.

cynotis) should be highly suspected. For *D. cati*, bacterial and fungal (dermatophytosis) folliculitis should be prioritized.

Diagnosis

Skin scraping is the gold standard for diagnosis feline demodicosis (Figure 18.26c). Skin scraping should be superficial for *D. gatoi* and deep for *D. cati*. In addition, hair plucking (trichography) can be used for diagnosing *D. cati*, whereas tape can be used instead of superficial skin scraping for *D. gatoi*. Fecal flotation can also be used to evaluate the parasite when cats are excessively licking. Because of the highly contagious nature of *D. gatoi*, other cats in the household should be tested, as they can serve as asymptomatic carriers.

Management

The management also differs based on which mite is found on skin scrapings. For *D. gatoi*, the gold standard treatment is weekly application of 2% lime sulfur for 6–8 consecutive weeks. However, recently the use of a topical application containing moxidectin/imidacloprid or fluralaner has been shown to be equally effective. All the cats in the household should be treated given the high percentage of transmission and the potential for asymptomatic carriers.

For *D. cati*, the treatment is very similar to canine demodicosis. Oral avermectins as well as topical moxidectin can be used. Amitraz can also been used, although it can be associated with severe side effects in cats and for this reason should be used as last option. Oral fluralaner was reported effective for treating generalized demodicosis caused by *D. cati* in a single case report.

CANINE SCABIES

Definition/Overview

Canine scabies (sarcoptic mange) is a very contagious species-specific parasitic disease. Sarcoptic mange is mainly reported in dogs; however, cats and wildlife canids can also be affected. This parasitic skin disease is one of the most pruritic skin diseases affecting dogs.

Etiology

The main parasite causing canine scabies is *Sarcoptes scabiei* var. *canis*.

Pathophysiology

The clinical presentation is due to a severe hypersensitivity reaction to the mites and mite feces. The pruritus is also associated with the actual presence of the mite burrowing in the epidermis. Because of the presence of a hypersensitivity reaction, most dogs are severely affected; however, some asymptomatic carriers with none or minimal pruritus can be observed. A cross-reactivity with other mites (e.g., house dust mites) has also been reported.

Clinical Presentation

Canine scabies is mainly characterized by an extreme pruritus distributed on the ventral aspect of the body. Other commonly affected areas include the ear margins, elbows, hocks, and paws (Figure 18.27a–c). Common clinical lesions observed include excoriations, scales, poorly demarcated alopecia, and yellow crusts. A pinnal-pedal reflex can be elucidated in 25%–90% of the affected dogs. It is important to remember that the pinnal-pedal reflex is not pathognomonic for scabies and can be elicited with other pruritic skin diseases.



FIGURE 18.27 **(a)** Stray puppy with severe pruritus demonstrating classic distribution pattern for canine scabies. Note the alopecia, lichenification, erythema, hyperpigmentation, scaling, crusting, and ulceration of the muzzle, pinnae, lateral elbows, lateral hocks, and distal extremities. **(b)** Magnified image of the hock of the same puppy. **(c)** *Sarcoptes* spp. mites observed on superficial skin scrapings.

Differential Diagnoses

Differentials should include other parasitic diseases (e.g., *Otodectes cynotis*, *Cheyletiella* spp., *Pelodera strongyloides*), allergies, and secondary pyoderma or *Malassezia* dermatitis.

Diagnosis

The gold standard for the diagnosis of sarcoptic mange is the evidence of the parasite, or part of it, on a superficial skin scraping. However, this is a poorly sensitive test considering a positive skin scraping is only present in up to 50% of the affected dogs. For this reason, the ultimate diagnosis occurs after treatment with appropriate miticidal medications followed by a resolution of the clinical signs. An ELISA serology test is also available, although more validation of this methodology is needed.

Management

A variety of topical and systemic treatment options are available for this parasitic disease. Topical 2% lime sulfur and systemic (or topical) avermectins are the most effective and commonly used products. More recently, the use of fluralaner, afoxolaner, sarolaner, and lotilaner demonstrate equally efficacy after a single dose. Despite the treatment implemented, an effective protocol dictates the use of a miticidal medication for at least 6 weeks. All in-contact animals should be treated because this is a contagious disease, and some animals may be asymptomatic carriers.

OTODECTES spp. ACARIASIS

Definition/Overview

Otodectes spp. acariasis (otoacariasis) is a fairly common parasitic skin disease affecting cats; however, dogs can also be affected. It is found mainly in young or shelter animals. The disease is very contagious and has zoonotic potential.

Etiology

Otodectes spp. acariasis is caused by a psoroptid mite, *Otodectes cynotis* (ear mites) (Figure 18.28a). These mites are mainly harbored in the external ear canal; however, extra-auricular localization has been reported.

Pathophysiology

Ear mites live in the external ear canal feeding on cellular debris and tissue fluid. The presence of the mites

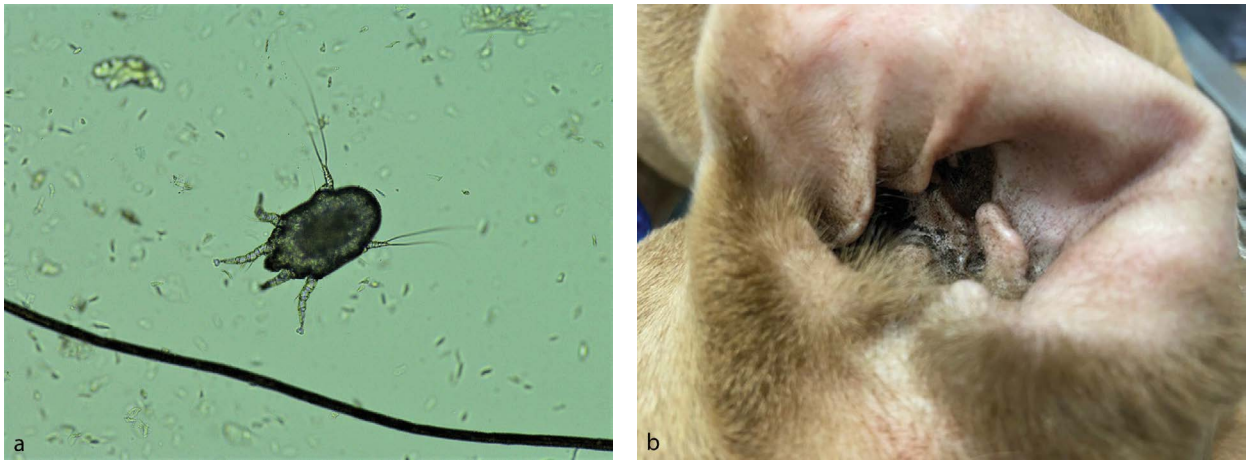


FIGURE 18.28 (a) *Otodectes* spp. mite identified from otic debris at 10× magnification. **(b)** Classic "coffee grounds" dry debris in the entrance of the external ear canal of a dog affected by *Otodectes* spp. (*Courtesy of Dr. Schaer*.)

feeding on the epidermis induces irritation and inflammation, leading to an overproduction of cerumen.

Clinical Presentation

The clinical presentation of *O. cynotis* is very characteristic. In fact, otoacariasis is associated with variable ear pruritus and head shaking. In addition, the presence of a black, dark brown, dry cerumen (coffee grounds) is very characteristic (Figure 18.28b). Because of the extra-auricular location of the mites, pruritus, papules, excoriations, and crusts can be observed in other locations as well (e.g., limbs, tail, and perianal).

Differential Diagnoses

Differentials should include any other cause of acute otitis externa, allergies, and secondary bacterial and yeast otitis/dermatitis. Dermatophytosis should also been considered in cases of extra-auricular localization.

Diagnosis

The diagnosis of otoacariasis is made by visualization of the mites on a skin scrapings or ear swabbing. This latter should be collected via a cotton-tipped applicator or a curette, and the material diluted in mineral oil. Ear mites are generally easily visualized; however, they may be difficult to see in the presence of an abundant inflammatory response.

Management

Systemic miticidal (e.g., avermectins) should be preferred to topical (aural) (e.g., thiabendazole) medications because of the potential extra-aural localization of the mites. Treatment should be performed for at least 6 weeks. Although not tested, fluralaner, afoxolaner, sarolaner, and lotilaner may potentially be useful treatment options as well. Because of the contagious nature of the disease, all in-contact animals should also be treated.

CHEYLETIELLOSIS

Definition/Overview

Cheyletiellosis ("walking dandruff") is a relatively common, pruritic skin disease mainly present in geographic areas where there is decreased use of flea prevention. Both dogs and cats are equally affected. A zoonotic potential is present for this mite.

Etiology

Cheyletiellosis is caused by multiple species of the genus *Cheyletiella* with minimal species specificity (Figure 18.29a). The most common species include *Cheyletiella yasguri* (dogs), *C. blakei* (cats), and *C. parasitovorax* (rabbits).

Pathophysiology

Cheyletiella mites live in the very superficial layers of the epidermis, feeding on epidermal debris and occasionally on tissue fluid or lymph. Eggs are laid and glued to the hairs.

Clinical Presentation

Symptoms are variable and can be associated with intermittent pruritus and alopecia. In addition, mild-to-severe scaling (Figure 18.29b), papules, and crusts can be present as well. Such lesions are mainly localized to the dorsal and ventral trunk, although other body regions can be affected.

Differential Diagnoses

Differentials should include other parasitic diseases (e.g., demodicosis, otoacariasis, and pediculosis), allergies, or infections (dermatophytes).

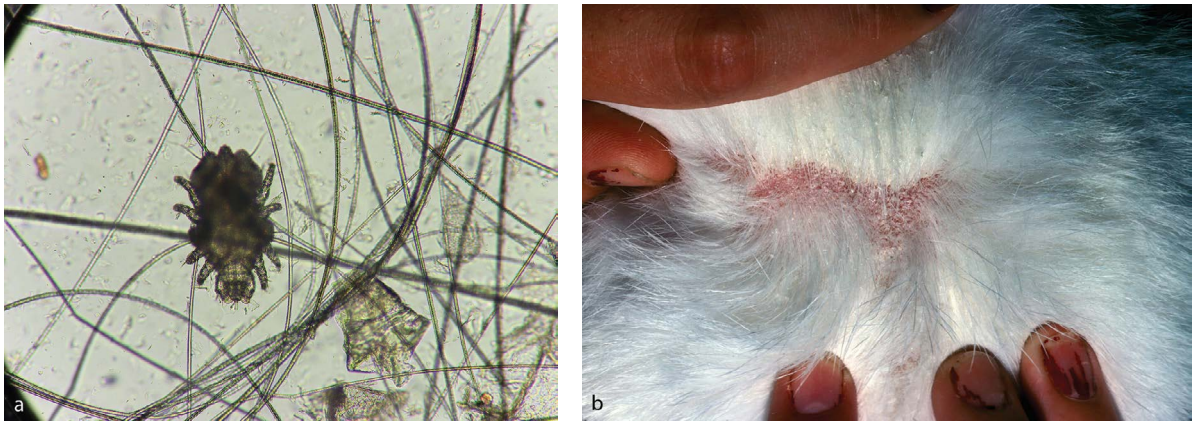


FIGURE 18.29 **(a)** *Cheyletiella* spp. mite identified on tape. **(b)** The separated fur on this rabbit illustrates the excess scaling typical of *Cheyletiella* spp. (b, *Courtesy of M. Schaer.*)

Diagnosis

The definitive diagnosis is based on direct observation of the mites or the eggs. This can be done with the naked eye by placing the "scales" on a dark paper and observing the mites moving ("walking dandruff"). An alternative is the visualization of the mites under the microscope by placing the scales in mineral oil. Importantly, a negative test does not rule out cheyletiellosis.

Management

Because of the ability for these mites to be transmitted via fomites, it is imperative to treat bedding and fomites with pyrethroid-based products. All affected and in-contact animals should also be treated. Most of the commercially available flea preventatives will be effective against *Cheyletiella* spp. However, topical 2% lime sulfur and systemic avermectins can also be used. The treatment should be implemented for 6–8 weeks.

TROMBICULOSIS

Definition/Overview

Trombiculosis is an uncommon pruritic skin disease affecting dogs and cats. It is caused by immature larvae of mites of the family Trombiculidae. Different species have been reported in Europe and in the United States. They are commonly knowns as "chiggers."

Etiology

Trombiculosis is caused by the six-legged larval stage of mites *Neotrombicula autumnalis* (European chigger), *Eutrombicula alfreddugesi* (North American chigger), *Walchia americana*, *Leptotrombidium subquadratum* (South Africa), and *Straelensia cynotis*.

Pathophysiology

The adult mites live in decaying plant material, whereas the larvae feed on animals.

Clinical Presentation

Chiggers can be extremely irritating and induce the rapid development of papules, crusts, and variable pruritus. Larvae are visible with the naked eye as red-orange dots adhering to the skin. The most commonly affected areas are the head (periaural), paws, and ventrum.

Differential Diagnoses

The presence of the red-orange larvae is quite characteristic. However, other causes of pruritus, including ectoparasites and allergies, should be considered. When papules and crusts occur, secondary infections should also be considered as viable differentials.

Diagnosis

The visualization of the red-orange larvae is diagnostic. However, they can be confirmed via microscopic examination to better identify the six-legged larvae.

Management

The use of most commercially available flea preventatives is effective to treat chiggers. In cases of extreme pruritus, a short course of corticosteroid may be indicated. For long-term management and prevention, the routine application of flea preventative is recommended.

ALLERGIES

Cutaneous hypersensitivity disorders (allergies) are very common in dogs and cats. Among others, flea-bite hypersensitivity, atopic diseases, and food allergy represent the majority of the hypersensitivity disorders seen in small animal practice. The pathogenesis of such disorders is not completely understood; however, the clinical signs are associated with a re-exposure to allergens to which the pet has been previously sensitized.

CANINE ATOPIC DERMATITIS

Definition/Overview

Canine atopic dermatitis (AD) is a genetically inherited inflammatory skin disease characterized by pruritus. AD generally is associated with an increase in allergen-specific IgE. However, cases with identical clinical signs but not associated with IgE also are present (canine atopic-like dermatitis). In temperate geographic regions, AD represents the second most common allergy in dogs, second only to fleabite hypersensitivity. Because of the strong genetic component, dogs with AD should not be used for breeding purposes.

Etiology

Canine AD is a multifaceted skin disease characterized by a defect of the skin barrier as well as an abnormal immune response to otherwise innocuous environmental allergens. Among others, the most common allergen for canine AD is house dust mite (*Dermatophagoides farinae* and *D. pteronyssinus*).

Pathophysiology

The pathophysiology of canine AD is not completely clear. However, in human AD, the most accredited theory hypothesizes the presence of a genetically predetermined defect in the skin barrier allowing the penetration of environmental allergens. Once in the skin, allergens stimulate the local immune response via the activation of dendritic cells (Langerhans cells and dermal dendritic cells), which trigger an immune response associated with T-helper type (Th) 2 lymphocytes. These produce specific cytokines, like interleukin (IL)-4 and IL-13, that inhibit the production of Th1 and regulatory cytokines such as IL-10 and transforming growth factor beta. This abnormal immune response leads to the activation and degranulation of cutaneous mast cells and other inflammatory cells with an increase in skin barrier damage initiating a vicious cycle of increased allergen penetration and pro-inflammatory immunological response. In chronic cases of AD, the local immune response switches from a predominantly Th2 to a Th1 milieu, which perpetuates the skin inflammation determining the clinical signs. Type 1 and 4 hypersensitivity reactions are associated with AD.

Clinical Presentation

Canine AD is a chronic skin disease that affects young to adult dogs with an average age of 1–3 years. However, cases as early as 6 months and as late as 6 years have been reported. A strong breed predisposition has been reported in Terriers and Retrievers. Canine AD is characterized by mild-to-severe pruritus mainly localized to head, ventrum, and extremities. Clinical signs of AD can be seasonal or nonseasonal depending upon the causing allergen(s); however, most seasonal presentations of disease gradually progress to nonseasonal. The most common clinical signs include pruritus, erythema, papules, and excoriations (Figure 18.30a–c). Chronic disease is

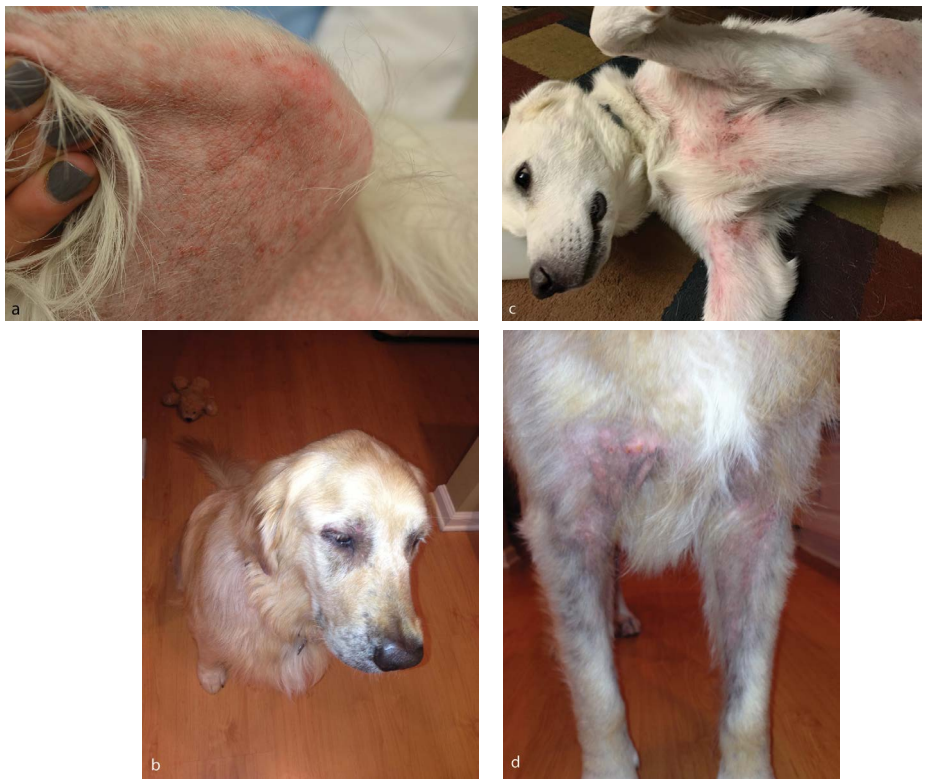


FIGURE 18.30 Classic lesions of atopic dermatitis in a dog. **(a)** Erythema, non-well-demarcated alopecia, papules, crusts, and hyperpigmentation on the flexor surface of the elbow both antebrachia, **(b)** periocular region, **(c)** medial aspect of the chest, **(d)** and thigh.

associated with lichenification and hyperpigmentation with alopecia (Figure 18.30d). The most common complications associated with AD include pyoderma, otitis externa, and *Malassezia* spp. dermatitis, with related clinical signs. Furthermore, association with other hypersensitivities (e.g., fleabite and food hypersensitivity) is common and expected.

Differential Diagnoses

Any other pruritic disease should be included in the differential list for canine AD. Among others, sarcoptic and demodectic mange, other parasitoses (e.g., cheyletiellosis, pediculosis), other allergies (food, contact, and fleabite), *Malassezia* spp. Dermatitis/otitis, bacterial pyoderma/otitis, and, occasionally, autoimmune dermatoses (e.g., pemphigus foliaceus, drug eruption) and epitheliotropic lymphoma.

Diagnosis

The diagnosis of canine AD is based on compatible history and clinical signs and after excluding any other pruritic skin disease. Secondary skin and ear infections are extremely common and should be considered as exacerbating factors for pruritus and inflammation.

Management

The best treatment for AD is allergen avoidance; however, this is impractical and extremely difficult to achieve. There are several potential treatment options to manage AD in dogs, although none of these can completely resolve (cure) the disease.

Allergen-specific immunotherapy (ASIT) is the most recommended long-term treatment by dermatologists for AD in dogs. ASIT consist of a mixture of allergens, relevant to the specific pet, that are administered either subcutaneously or sublingually. This is a lifelong treatment and can take up to 9–12 months before reaching full efficacy. In fact, when discontinued, AD relapses in most of the treated dogs. The formulation of ASIT is determined by allergy testing results via intradermal or serology testing. By themselves, positive results to either test are not considered diagnostic. An overall success rate, defined as the ability to decrease other symptomatic medications, of 65%–70% have been reported for ASIT.

A common alternative to ASIT is symptomatic therapy, which commonly is used concurrently with ASIT for more successful management of the disease. The main symptomatic therapy medications include corticosteroids, modified microemulsified cyclosporine, oclacitinib, and lokivetmab. Furthermore, less effective but commonly used as adjuvant medications are antihistamines (e.g., cetirizine, hydroxyzine, diphenhydramine, etc.), fatty acids, and pentoxifylline.

Fundamental for successful treatment is the use of topical anti-inflammatory/antipruritic, antimicrobial, and moisturizing agents. Frequent baths are essential not only to remove environmental allergens from the skin but also to rehydrate the skin, remove microorganisms, and restore the skin barrier.

FELINE ATOPIC SKIN SYNDROME

Definition/Overview

Feline atopic skin syndrome (FASS) is the feline counterpart of canine AD. Although extremely common, much less is known about FASS when compared to canine AD. Similar to canine AD, FASS is an inherited skin disease associated with an exaggerated immune response to otherwise innocuous environmental allergens.

Etiology

The etiology of FASS is very similar to canine AD.

Pathophysiology

Although much less is known about the pathophysiology of FASS, the most accredited theories hypothesize similar defects present in canine AD. Similar to canine AD, type 1 and 4 hypersensitivity reactions have been hypothesized for FASS.

Clinical Presentation

Likewise to canine AD, FASS is a chronic skin disease that affects young to adult cats with an average age of 1–3 years. A strong breed predisposition has not been determined, although domestic short-haired and long-haired cats, along with Abyssinians, are overrepresented. The clinical presentation of FASS is highly variable. Most of the affected cats express pruritus as main clinical sign (licking, pulling hair, chewing, rubbing); however, cats with mild to no pruritus are present. Clinical manifestations unique to cats with hypersensitivities (not only FASS) include eosinophilic plaques, indolent/rodent ulcer, linear and oral granulomas (Figure 18.31a, b). These presentations altogether form the eosinophilic granuloma complex. Other clinical manifestations include head and neck pruritus, self-inflicted alopecia, and military dermatitis. Furthermore, indicative of pruritus is the frequently observed presence of hairballs.

Clinical signs of FASS can be seasonal or nonseasonal depending upon the causing allergen(s); however, when starting as a seasonal disease, it gradually progresses to nonseasonal. The most common complications associated with FASS include pyoderma and *Malassezia* spp. dermatitis, with related clinical signs. Furthermore, association with other hypersensitivities (e.g., flea bite and food hypersensitivity) are common and expected.

Differential Diagnoses

Differentials for FASS vary based on the clinical signs. In general, other allergies should be included in the differential list. In addition, parasitic diseases, like feline



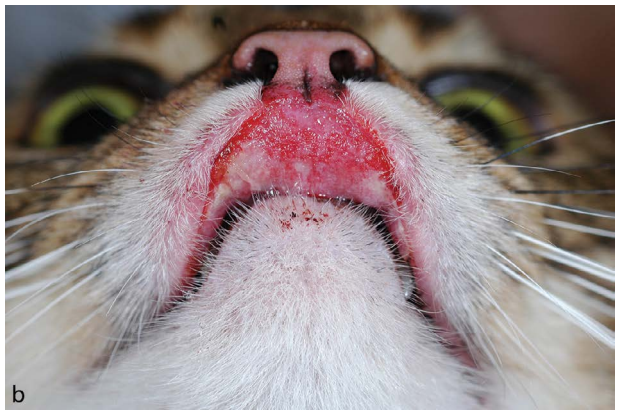


FIGURE 18.31 (a) Alopecic, eroded, erythematous plaques on the later thorax of a cat with eosinophilic granuloma complex (eosinophilic plaques). **(b)** Large ulcer on the dorsal aspect of the lip in a cat with eosinophilic granuloma complex (indolent ulcer).

sarcoptic (*Notoedres cati*) and demodectic (*Demodex gatoi*) mange, as well as otoacariasis (*Otodectes cynotis*) and cheyletiellosis should also been considered. Finally, dermatophytosis, skin infections (bacterial and *Malassezia*), viral dermatoses, and autoimmune diseases (e.g., pemphigus foliaceus) should also been included as potential differentials.

Diagnosis

As in canine AD, the diagnosis of FASS is based on compatible history and clinical signs after ruling out any other differential diagnosis listed previously.

Management

As in dogs, the best treatment for FASS is allergen avoidance. However, this is impractical and extremely difficult to achieve. Treatment options for FASS are available, although less in number.

ASIT is recommended as best potential long-term treatment for FASS. Similar to dogs, ASIT can be administered either subcutaneously or sublingually, although this latter option is much less utilized because of limitations due to the species (ability to administer it directly into the mouth). This is a lifelong treatment and can take up to 9–12 months before reaching full efficacy. As in dogs, the formulation of ASIT is based on allergy testing. These can be administered via intradermal or percutaneous test and via serology. By themselves, positive results to either test are not considered diagnostic.

Symptomatic therapy is the most used treatment option for FASS. The main symptomatic therapy medications include corticosteroids and cyclosporine. Although not labeled for cats, pharmacokinetic and safety studies for oclacitinib in cats have been published recently. Furthermore, less effective but commonly used medications include antihistamines (e.g., cetirizine, hydroxyzine, diphenhydramine, etc.), fatty acids, and pentoxifylline.

Fundamental for successful treatment is the use of topical anti-inflammatory/antipruritic, antimicrobials, and moisturizing agents. Because of the limitations intrinsic to the species, baths may not be feasible in some cats; thus, the use of leave-on mousse and sprays are used more commonly.

FLEABITE HYPERSENSITIVITY

Definition/Overview

Fleabite hypersensitivity is the most common allergy in dogs and cats living in temperate areas. However, it is quite uncommon in arid and high-altitude regions. Clinical signs are associated with an intermittent but constant exposure to flea bites. The re-exposure to minimal amounts of flea saliva (few bites) is enough to trigger severe clinical signs in dogs and cats.

Etiology

Fleabite hypersensitivity is associated with the exposure to flea saliva. Multiple allergens of different molecular weights have been identified in affected dogs and cats. The most common flea associated with this type of hypersensitivity is *Ctenocephalides felis felis*.

Pathophysiology

As in AD, the pathophysiology of flea bite hypersensitivity is complex and involves multiple cell types. A hypersensitivity reaction type 1 and 4 is associated with flea bite hypersensitivity. A large involvement of eosinophils and mast cells has been demonstrated in the first few days after exposure. An increase in total and allergen-specific IgE is also evident in affected dogs. A mixed inflammatory response, involving cytokines of both Th1 and Th2 response, have been detected in the blood of allergic dogs, although a clear predominance of Th2 cytokines was seen. Detailed pathophysiological information on flea bite hypersensitivity in cats is lacking; however, strong similarities are hypothesized between dogs and cats.

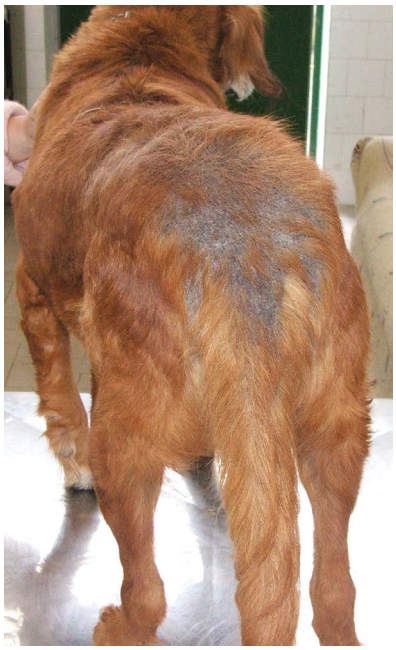


FIGURE 18.32 Alopecia, non-well-demarcated alopecia, erythema, and hyperpigmentation on the rump of a dog with flea allergy dermatitis.

Clinical Presentation

Fleabite hypersensitivity can occur in dogs and cats of any age and breed. Fleabite hypersensitivity is characterized generally by a lack of seasonality, although seasonal exacerbations, mainly in the warmer seasons, can occur. The classic clinical presentation of flea bite hypersensitivity in dogs is highly characteristic. This includes the presence of papules, erythema, alopecia, and pruritus mainly localized to the rump and base of the tail areas (Figure 18.32). With chronicity, lichenification and hyperpigmentation occur, and the lesions tend to extend to the whole back half of the body (Figure 18.32). In some cases, it is evident the presence of highly pruritic nodules in those areas as well. Generalized pruritus can occur in more chronic or severe cases.

In cats, this type of hypersensitivity is clinically almost indistinguishable from the others. The presence of military dermatitis is generally more evident in flea bite hypersensitivity than other allergies, but its presence cannot rule out other hypersensitivity reactions. Cats are generally presented for excessive grooming, pruritus, manifestations of the eosinophilic granuloma complex, excoriations, alopecia, and erythema. The most affected areas of the body include rump, abdomen, and neck. The frequent occurrence of hairballs suggests a highly pruritic cat.

As in other hypersensitivities, the insurgence of skin infections (bacterial and/or *Malassezia*) is present in affected dogs and cats.

Differential Diagnoses

Although in dogs the classic clinical presentation is highly suggestive of fleabite hypersensitivity, other allergies and parasites need to be ruled out in chronic and generalized cases. In cats, because of the high similarity of the clinical signs among allergies, FASS, food allergy, and parasites need to be excluded. Diseases like cheyletiellosis, pediculosis, sarcoptic and demodectic mange, trombiculosis, ear mites, and dermatophytosis have to be considered as likely differentials in dogs and cats affected by flea bite hypersensitivity.

Diagnosis

The diagnosis of fleabite hypersensitivity is mainly based on historical and clinical findings. However, the ultimate diagnosis occurs with resolution of the clinical signs after flea eradication. This can take up to 9–12 weeks before occurring. The presence of fleas or flea feces as well as the presence of *Dipylidium caninum* are highly supportive of a fleabite hypersensitivity. However, their absence is not enough to rule out this hypersensitivity. Allergy testing (intradermal or serology) can be used as valid aids to support the diagnosis but are not enough to make a definitive diagnosis by themselves.

Management

The management of fleabite hypersensitivity can be long and frustrating for pet owners. In the environment, fleas are extremely common. To achieve successful management, it is important to not only control the adult population of fleas but also the immature life stages in the environment. Nowadays, many insecticides are available on the market, and most of those are very effective and safe for dogs and cats. The use of adulticides along with insect growth regulators is mandatory to achieve full control of the disease. In some cases, an increased frequency of the applications (e.g., every 2 weeks) is also recommended in affected pets. If a repellent can be used, it should be implemented in affected pets. Furthermore, it is fundamental to ensure that all the pets in the household are on an effective flea preventative.

In the cases with the presence of secondary skin infections, this should be properly treated. In addition, the use of anti-inflammatory and/or antipruritic medications are highly recommended to manage the pruritus and inflammation.

FOOD ALLERGY

Definition/Overview

Food allergy is less common than flea bite hypersensitivity and AD/FASS. It is nonseasonal and associated with hypersensitivity to dietary substances. Food hypersensitivity is virtually identical to food intolerance, with the only difference being a lack of an immune response in the latter. A genetic component, although not confirmed, is highly suspected.

Etiology

Food allergy is associated with an abnormal immune response to ingested food ingredients. The most common allergens include proteins and glycoproteins. The natural protein conformation is essential in triggering the immune response. For this reason, reactions to raw ingredients may change once proteins are cooked. The most common allergens include protein from meat, milk, soy, and fish. Immune reaction to carbohydrates is much less common.

Pathophysiology

Compared with AD, much less is known about food allergy in dogs and cats. However, alterations of the gastrointestinal mucosal barrier, local immune system, oral tolerance, and structure of the allergens play a significant role in the sensitization process. In healthy pets, ingested allergenic substances are generally water soluble and degraded by the normal digestive process. In affected pets, allergenic proteins remain intact and are absorbed and recognized as foreign from the local immune system. A hypersensitivity reaction type 1, 3, and 4 is suspected to be associated with food allergy.

Clinical Presentation

Food allergy can affect any breed, although Terriers and Retrievers are overrepresented. Most commonly affected pets are less than 1 year of age or are elder pets. Clinical signs are indistinguishable from AD/FASS. In fact, a complete overlap of lesions and body distribution is present in the two diseases; it is not uncommon to even have AD/FASS (and/or fleabite hypersensitivity) and food allergy concurrently. One of the few differences with AD/FASS is the less common presence of gastrointestinal signs (e.g., flatulence, vomiting, diarrhea, soft stools, borborygmi, etc.) as with food allergy. Another difference is the possible absence of pruritus in food allergy as well as the high incidence of otitis and/or recurrent pyoderma as the only clinical signs. As in other types of allergy, the incidence of secondary skin and ear infections is very high.

Differential Diagnoses

As in AD/FASS, the most common differentials for food allergy include other allergies, parasitosis, and infections (bacterial and *Malassezia*). In particular, sarcoptic and demodectic mange, otoacariasis, and cheyletiellosis need to be included in the differential list. In cats, dermatophytosis, viral dermatoses, and autoimmune diseases (e.g., pemphigus foliaceus) should also been included as potential differentials.

Diagnosis

The diagnosis can only be achieved via a strict elimination diet trial. In fact, allergy tests (intradermal, epicutaneous, and serological) are not reliable in identifying the causative allergen(s). However, a high-negative predictive value (the likelihood that an ingredient is NOT associated with a reaction) has been associated with such tests. The elimination diet is performed using novel ingredients for the specific pet. Thus, it is fundamental to record a detailed feeding history to accurately select an elimination diet. The diet can be homemade or commercially available. The former can be more expensive and time consuming, although more targeted and selective. The most reliable commercially available diets are generally prescription diets, which guarantee the lack of or minimal food contamination between products. Diets useful for the trial include novel ingredients (e.g., kangaroo, rabbit, alligator, etc.) or hydrolyzed diets. Both options have pros and cons, and the choice of the diet should be based on the individual patient. Regardless of the diet chosen, the trial should be carried out for 8–10 weeks based on the resolution of the clinical signs. If anti-inflammatory, antipruritic, and antimicrobial medications are used, clinical signs may resolve faster, so the duration of the food trial can be decreased. It is important to avoid any flavored supplements or medications during the trial. Similarly, it is important to avoid contamination from food fed to other pets present in the household. Once there is a significant reduction in the severity of the clinical signs, a provocation test using the previous diet for up to 14 days should be performed to confirm the diagnosis. If medications were used to alleviate the clinical signs, it is important to discontinue those for at least 14 days before performing the provocation test. Once the diagnosis is confirmed, single ingredients, including treats/supplements, can be tested individually to identify the triggering ingredients.

Management

The best management is avoiding the triggering allergen. Most of the hypoallergenic prescription diets are fully balanced and represent a viable lifelong option for affected pets. However, if a relapse of the clinical signs occurs because of accidental ingestion of the incriminated allergens, the use of anti-inflammatory, antipruritic, and/or antimicrobial medications is highly recommended.

CONTACT ALLERGY

Definition/Overview

Contact allergy in an uncommon skin disease in dogs and cats. It is more common in tropical/subtropical climates where strongly allergenic plants (e.g., *Commelinaceae* spp.) proliferate. However, hypersensitivity reactions to different allergens have been described in dogs and cats. Recently contact allergy has been described as "an immune-mediated, antigen-specific inflammatory skin reaction following contact with a specific allergenic substance (sensitizer)" (e.g., poison ivy). As in food allergy/intolerance, the presence of a targeted immune reaction makes the distinction between contact allergy and irritant contact dermatitis.

Etiology

Contact allergy is generally due to an allergic reaction to plants or drugs. However, carpet deodorizers/cleaners, detergents, plastic dishes, synthetic carpet, etc., have been identified as potential culprits in dogs and cats.

Pathophysiology

The pathogenesis of contact allergy is still not completely understood. However, a delayed hypersensitivity reaction with the participation of CD8+ T cells is involved after percutaneous absorption of haptens. Contact allergy is characterized by a sensitization phase followed by a specific immune response to the allergen upon re-exposure. After sensitization, the immunological reaction can occur within 24 hours to several days after re-exposure. Once activated, cytotoxic T cells will be attracted to the skin and potentially induce apoptosis of the keratinocytes.

Clinical Presentation

The characteristic clinical signs of contact allergy include the presence of localized erythematous papules or macules with minimal to no erythroderma (diffuse erythema and scaling of skin; Figure 18.33). The lesions are commonly associated with variable pruritus and localized on the muzzle and glabrous areas (axillae, ventral aspect of the interdigital spaces, groin, perineum, pinnae). After the initial acute phase, secondary bacterial and/or *Malassezia* infections are expected.

Differential Diagnoses

The main differential diagnosis to consider is irritant contact dermatitis. However, other allergy (AD/FASS, food, flea bite, and insect) should be considered as well. Furthermore, parasitic skin diseases (sarcoptic and demodectic mange, hookworm dermatitis, *Pelodera* dermatitis) should also been included in the differential list.



FIGURE 18.33 Dog with contact allergy to *Commelina* spp. plants. Note the small erythematous papules on a normal-looking skin on the abdomen.

Diagnosis

The diagnosis is based on compatible history, clinical signs, and exclusion of other pruritic skin diseases. A patch test, open or closed, can be used as a valid and reliable aid to confirm the diagnosis and identify the offending allergen. The histopathological examination can also be highly suggestive of contact allergy and supplements the clinical diagnosis.

Management

The optimum treatment option is avoidance. When this is not completely possible, symptomatic treatments are available. Among others, pentoxifylline can be useful as preventative medication. Corticosteroids, cyclosporine, and oclacitinib have also been used as potential treatments. Topical and systemic antimicrobials should also be prescribed when necessary.

MOSQUITO BITE HYPERSENSITIVITY

Definition/Overview

Mosquito bite hypersensitivity is a relatively common cutaneous hypersensitivity affecting cats in temperate areas. The severity of the clinical signs varies from cat to cat and can be very mild to extremely severe.

Etiology

Mosquito bite hypersensitivity is directly associated with the exposure to mosquito bites.

Pathophysiology

The pathogenesis is not completely understood; however, similarities with flea bite hypersensitivity have been identified. A hypersensitivity reaction type 1 and 4 is associated with mosquito bite hypersensitivity. Once the allergen has been injected, it triggers a diffuse and severe eosinophilic and neutrophilic dermatitis of the affected areas.

Clinical Presentation

Mosquito bite hypersensitivity can occur in any breed at any age. The lesions tend to stay localized to areas directly affected by the bites. These include the tip of the ear, pinnae, and the bridge of the nose (Figure 18.34a, b). Lesions on the foot pads, lateral aspect of the elbows, and on the face (periorbital and perilabial areas) can also occur. The classic clinical presentation includes alopecia, erosions, ulcers, and variable pruritus. Eosinophilic granulomas and plaques have also been reported in affected cats. Outdoor cats living in temperate and tropical/subtropical regions are commonly affected. However, indoor cats can also be affected.

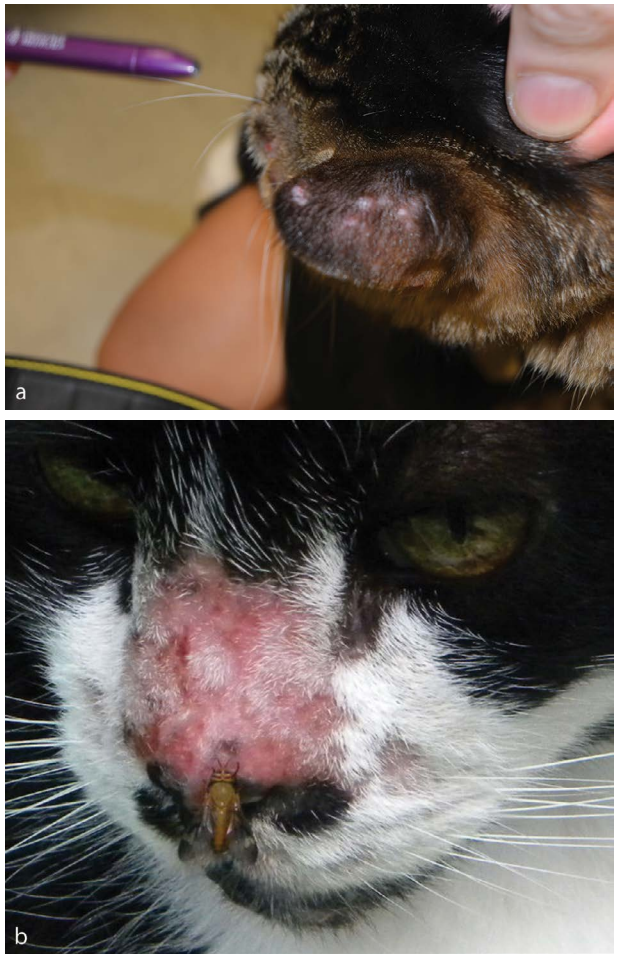


FIGURE 18.34 Alopecic and erythematous papules on the dorsal aspect of the convex surface of the ear pinna **(a)** and nose **(b)** in a cat with mosquito or other insect bite hypersensitivity.

Differential Diagnoses

In cats, because of the high similarity of the clinical signs among hypersensitivities, FASS, food and flea bite allergy should be excluded. Diseases like sarcoptic and demodectic mange, trombiculosis, ear mites, and dermatophytosis have to be considered as likely differentials in affected cats. Finally, viral dermatoses (e.g., herpesvirus and poxvirus), autoimmune diseases (e.g., pemphigus foliaceus), neoplastic diseases (e.g., squamous cell carcinoma and mast cell tumor), and infectious diseases (e.g., subcutaneous and systemic mycosis) should be included in the differential list.

Diagnosis

The diagnosis is based on compatible history (mosquito season), clinical findings, and confirmed by cytological and histopathological examination.

Management

The key in a successful management of mosquito bite hypersensitivity is avoiding the exposure to mosquitos. The use of repellants would be ideal. Unfortunately, few repellents are safe in cats. Neem oil as liquid spray or as spot-on solution is a popular repellant. Environmental control through the elimination of mosquito breeding habitats (e.g., standing water) and repellant sprays should be considered. The use of anti-inflammatory or antipruritic medications are also recommended. Topical and/or systemic antimicrobials should be prescribed when necessary.

AUTOIMMUNE SKIN DISEASES

Autoimmune skin diseases are rare in dogs and cats. They represent a subtype of the immune-mediated skin diseases. The major difference between autoimmune and immune-mediated is the identification of a self-antigen as the major target for the immune system in the former. Many autoimmune and immune-mediated skin diseases have been described in dogs and cats. However, in this chapter, only pemphigus foliaceus and sebaceous adenitis will be discussed. In addition, although the self-antigen has not been identified, diseases classically included in the group of autoimmune skin diseases like cutaneous lupus, vasculitis, lupoid onychitis, canine juvenile cellulitis/juvenile sterile granulomatous dermatitis, and lymphadenitis (puppy strangles) will also be discussed.

PEMPHIGUS FOLIACEUS

Definition/Overview

Although its prevalence is not known, pemphigus foliaceus is considered the most common autoimmune skin disease affecting dogs and cats. Pemphigus foliaceus is characterized by a pustular eruption due to loss of cohesion between keratinocytes. The major target for pemphigus foliaceus in dogs is desmocollin-1. A specific breed overrepresentation is seen in dogs (Akita, Newfoundland, Schipperke, Dobermann Pinscher, Finish Spitz, Dachshunds, English Cocker Spaniel, Chow Chow, Shar Pei, Collie, and Border Collie) and cats (Domestic Shorthaired, Siamese, Persians, and Ragdoll). The disease is exacerbated by exposure to UV light.

Etiology

Pemphigus foliaceus is associated with the production of autoantibodies directed toward the keratinocyte's adhesion molecule, desmocollin-1.

Pathophysiology

The pathogenesis of pemphigus foliaceus is not completely known; however, the disease seems to be multifactorial in origin. Genetic and environmental factors along with exposure to drugs seem to be highly involved in the development of the disease in dogs. Chronic antigenic stimulation (e.g., allergies) has also been hypothesized as potential trigger.

Pemphigus foliaceus is characterized by the presence of autoantibodies directed toward desmocollin-1 (in dogs) and desmoglein-1 (in people), weakening the desmosomal structures. Once these bonds between cells are weakened, neutrophils further disrupt the bonds creating loss of adhesion and formation of rafts of individual keratinocytes (acantholytic keratinocytes). This process leads to the formation of pustules characteristic of this disease.

Clinical Presentation

The clinical presentation of pemphigus foliaceus is quite diverse; however, lesions typically develop symmetrically on the body. Clinically, crusts, erythema, alopecia, erosions and ulcers characterize PF (Figures 18.35–18.37), although transient pustular eruption represents the primary lesion. The lesions generally progress caudally from the head, often starting from the nasal planum, which is the most commonly affected location. Pustules on the concave surface of the ear pinnae (dogs and cats) and nailbed (cats) are characteristic of pemphigus foliaceus. In same case, general malaise and fever can be observed.



FIGURE 18.35 Dorsal aspect of the bridge of the nose of a dog with pemphigus foliaceus. Note the large number of crusts, erosions, and alopecia symmetrically distributed.



FIGURE 18.36 Pustules on the abdomen of a dog with pemphigus foliaceus.



FIGURE 18.37 Cat with pemphigus foliaceus. Note the large amount of scales, alopecia, confluent papules forming erythematous plaques, yellow crust, and broken pustules.

Differential Diagnoses

The diagnosis of pemphigus foliaceus is not always straightforward. The list of top differential diagnoses should include superficial pyoderma, demodicosis, and dermatophytosis. Other autoimmune (e.g., lupus and dermatomyositis), neoplasia (cutaneous lymphoma), metabolic (necrolytic migratory erythema), and infectious (leishmaniasis) diseases should also be considered.

Diagnosis

History, clinical signs (distribution and type of lesions), skin cytology, and biopsies for histopathology are necessary to reach a definitive diagnosis. Fungal culture may also be required to rule out dermatophytosis. The characteristic cytological finding includes the presence of acantholytic keratinocytes. It is important to remember that acantholytic keratinocytes are not pathognomonic for pemphigus foliaceus, as superficial pyoderma and dermatophytosis can be associated with this finding. Because of the clinical similarities between pemphigus foliaceus and superficial pyoderma, a course of antibiotic is generally recommended before performing a skin biopsy for histopathology.

Management

The main goal of treatment is immunosuppressing the animal. To do so, drugs like corticosteroids (e.g., prednisone, prednisolone, triamcinolone, methylprednisolone, or dexamethasone), azathioprine, cyclosporine, chlorambucil, mycophenolate, and leflunomide are generally used at immunosuppressive dosages. Cats are much more responsive to treatment and carry a better prognosis than dogs. It is mandatory to monitor systemic organ function during treatment to avoid serious to life-threating side effects from the medications. In case of relapse, it is generally harder to control the disease without using highly immunosuppressive medications/

dosages. The treatment is generally lifelong except in cases of drug-induced pemphigus foliaceus.

CUTANEOUS (DISCOID) LUPUS ERYTHEMATOSUS

Definition/Overview

Cutaneous lupus erythematosus is a relatively common immune-mediated skin disease in dogs. It is considered a benign variant of systemic lupus with which it only shares the histopathological findings. A progression to systemic lupus has not been reported.

Etiology

The etiology of cutaneous lupus is unknown. A self-antigen is suspected but has not yet been identified. Similar to pemphigus foliaceus, cutaneous lupus is exacerbated by exposure to UV light.

Pathophysiology

The pathogenesis is not completely understood. However, the production of antibodies directed toward the keratinocytes and the basal membrane structures is hypothesized based on the histological findings. Once the antibodies have bounded to their target, the complement cascade and cytotoxic T cells are activated.

Clinical Presentation

Clinical signs are mainly localized to the nose (nasal planum and bridge of the nose) (Figure 18.38) extending to the periocular and perioral regions, ear pinnae, and eyelids. Uncommonly, lesions on the distal limbs, footpads, and perianal area have been reported. The severity of the lesions varies tremendously from mild discoloration (gray to bluish color change) of the nasal planum to erosions and severe ulceration with depigmentation and loss of cobblestone appearance of the nasal planum.

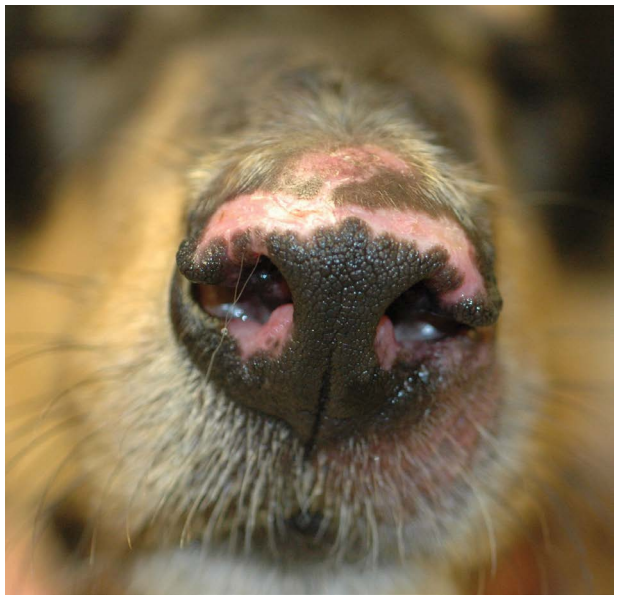


FIGURE 18.38 Nasal planum of a dog affected by cutaneous lupus erythematosus. Note the diffuse depigmentation of the nasal planum and loss of cobblestone appearance (atrophy) of the dorsal aspect of the nasal planum.

Differential Diagnoses

Differential diagnoses should include other immune-mediated/autoimmune diseases like pemphigus foliaceus, mucocutaneous pyoderma, pemphigus erythematosus, uveodermatologic syndrome, and systemic lupus. Cutaneous lymphoma, vitiligo, and contact dermatitis should also be considered.

Diagnosis

The diagnosis is mainly based on history, clinical signs, and confirmed by histopathological examination. The latter should be performed on nonulcerated areas. As in pemphigus foliaceus, sometimes a course of antibiotic prior to skin biopsy can help reduce the confounding alterations due to bacterial infections. Antinuclear antibody (ANA) test is generally negative (in contrast to systemic lupus).

Management

Due to the benign behavior of this disease, the most common treatments options include topical corticosteroids or calcineurin inhibitors (tacrolimus) and high sun protection factor (SPF) sunscreen creams. In more severe cases, the use of doxycycline and niacinamide combination, systemic corticosteroids (anti-inflammatory or immunosuppressive doses), or cyclosporine may be required. Administration of vitamin E and essential fatty acids have also been reported as an effective treatment in mild cases of cutaneous lupus.

LUPOID ONYCHITIS

Definition/Overview

Lupoid onychitis is a relatively common disease affecting the claws in dogs. A genetic predisposition has been identified in specific breeds like Bearded Collies. Lupoid onychitis can affect all breeds; however, Labrador Retrievers, Greyhounds, German Shepherd Dogs, Bearded Collies, and Rottweilers are overrepresented. Lupoid onychitis is unrelated to cutaneous or systemic lupus erythematous.

Etiology

The etiology is unknown.

Pathophysiology

Lupoid onychitis is associated with a severe inflammatory response at the level of the claw bed.



FIGURE 18.39 Onychodystrophy and onychomadesis in a dog with lupoid onychitis.

Clinical Presentation

Clinically, lupoid onychitis is associated with moderate to severe discomfort and pain. Claws show onychorrhexis, onychomadesis, subungual hemorrhage, and onychodystrophy (Figure 18.39). Paronychia can also be present with secondary bacterial infections.

Differential Diagnoses

Main differential diagnoses should include other causes of onychitis like bacterial or fungal onychitis, as well as trauma and neoplasia.

Diagnosis

The diagnosis is based on the characteristic clinical signs. Biopsy of the claw bed or phalanx three amputation may confirm the diagnosis, but it is not generally necessary. Bacterial and fungal culture may be required to definitely rule out bacterial and fungal onychitis. In some cases, a strict food trial has been suggested to rule out the potential involvement of food allergy.

Management

The main treatment options include the use of oral essential fatty acids (omega-3/omega-6) alone or in combination with doxycycline and niacinamide. Other treatment options may include systemic corticosteroids, vitamin E, and pentoxifylline. Pain control may be required in cases of severe pain and discomfort. In some cases, an elimination diet has been useful to control the clinical signs. Treatment should be continued until new claw growth is evident, although lifelong treatment is generally required to avoid relapses.

SEBACEOUS ADENITIS

Definition/Overview

Sebaceous adenitis is an uncommon inflammatory skin disease targeting the sebaceous glands. In chronic cases, the inflammatory response leads to complete destruction of the sebaceous glands.

Etiology

The etiology is unknown; however, an autosomal recessive mode of inheritance has been suggested in Poodles and Akitas. Affected dogs should not be used for breeding purposes.

Pathophysiology

Along with the genetic predisposition, immunological abnormalities have been suggested. In particular, a lymphocytic inflammatory pattern is observed in affected dogs. Lymphocytes mainly target sebaceous glands until complete destruction of the sebaceous glands is observed.

Clinical Presentation

The clinical presentation varies based on the hair coat length. In long-haired breeds, sebaceous adenitis is characterized by well-demarcated alopecia, scales, and follicular casts (Figure 18.40a–c). Lesions most commonly start on the head and progress caudally. On the contrary, short-haired breeds tend to present with well-demarcated alopecia, scales, nodules, and plaques. Secondary bacterial folliculitis is commonly observed in both forms. Pruritus can be present in cases with secondary infection.

Differential Diagnoses

Common causes of folliculitis (bacterial, fungal, and parasitic) should be considered. Other differentials may include hypothyroidism, primary seborrhea, ichthyosis, and follicular dysplasia.

Diagnosis

History, signalment, and clinical signs can be highly suggestive of sebaceous adenitis. Skin biopsy for histopathological examination is mandatory to confirm the diagnosis of sebaceous adenitis.

Management

Multiple treatment options are available to manage sebaceous adenitis. The most commonly used treatment is oral cyclosporine. This treatment can induce partial gland regeneration in cases in which complete glandular destruction has not occurred. Other treatments include the use of topical fatty acids, humectants, and propylene glycol. Oral or topical retinoids have also been used with success. In most cases, lifelong treatment is required, although systemic treatments may be reduced or discontinued overtime.

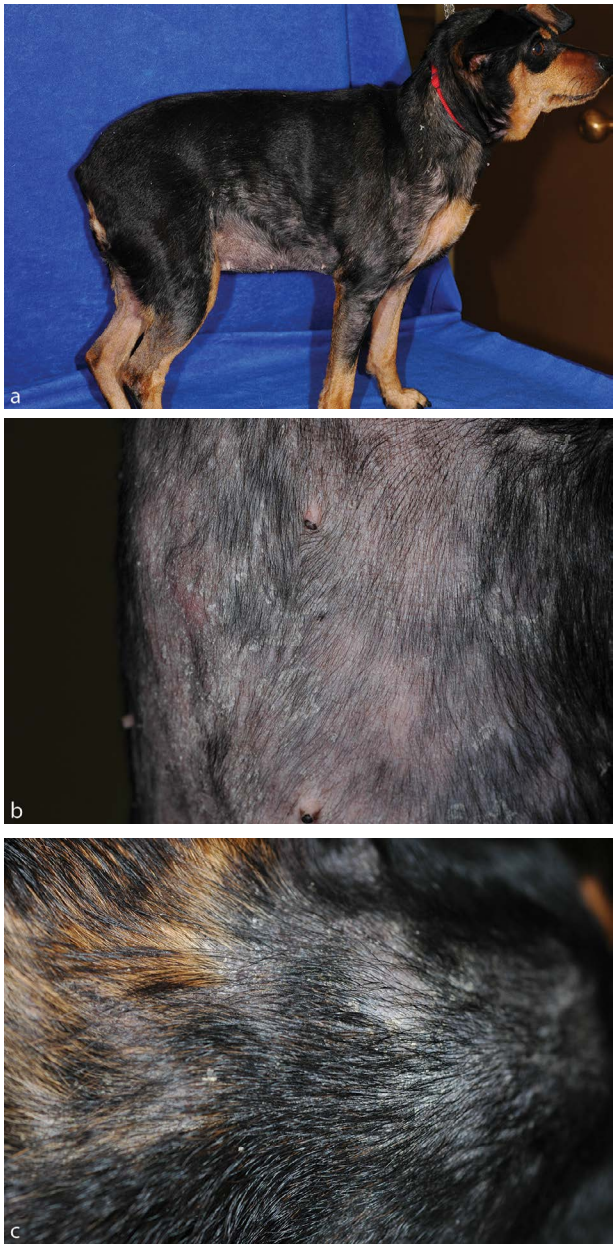


FIGURE 18.40 Dog with generalized sebaceous adenitis. Note the large scaling affecting the entire body but mainly focused on the cranial part of the body (a). A closeup image of the large scaling and alopecia affecting the abdomen (b). Alopecia and follicular casts affecting the head (c).

CANINE JUVENILE CELLULITIS/ JUVENILE STERILE GRANULOMATOUS DERMATITIS AND LYMPHADENITIS (PUPPY STRANGLES)

Definition/Overview

Canine juvenile cellulitis is an uncommon sterile granulomatous skin disease affecting the head. Lymphadenomegaly of lymph nodes in the head and neck, particularly the mandibular lymph nodes, and otitis are also commonly reported.

Etiology

The etiology of canine juvenile cellulitis is unknown. An abnormal immunological response to an unknown antigen is suggested. A potential hereditary component has also been hypothesized.

Pathophysiology

An underlying abnormal lymphocytic response has been suggested. A sterile suppurative response to an antigenic stimulation results in the observed clinical signs.

Clinical Presentation

Young dogs between 3 and 16 weeks of age are generally affected. The clinical presentation includes moderate-to-severe edema, pustules, crusts, and draining tracts mainly affecting the face (lips, muzzle, eyelids, and pinnae; Figure 18.41a); however, lesions on the abdomen (groin and prepuce) and perineal area have also been reported (Figure 18.41b). Lymphadenopathy, fever, polyarthropathy, and general malaise are also present.

Differential Diagnoses

Demodicosis, bacterial folliculitis/furunculosis, sterile granuloma/pyogranuloma syndrome, angioedema, insect bite, adverse drug/vaccine reaction, and dermatophytosis should be considered. Other differentials may include pemphigus foliaceus and otitis externa.

Diagnosis

The clinical picture is extremely suggestive of canine juvenile cellulitis. However, deep skin scraping and bacterial/fungal culture should be performed to rule out infectious organisms. Cytological and histopathological examination is essential to confirm the diagnosis.

Management

The use of immunosuppressive doses of corticosteroids is generally the first line of treatment. Once the clinical signs subside, the dose of corticosteroid is slowly tapered. In most cases, no relapse is observed; however, it is possible after discontinuation of the treatment. Cyclosporine is effective in refractory and/or relapsing cases. Secondary bacterial infections can also occur and need to be properly treated. Lesions may lead to permanent scarring.

NODULAR DERMATOSES

Nodules and masses are quite common in veterinary dermatology. When encountering such lesions, a

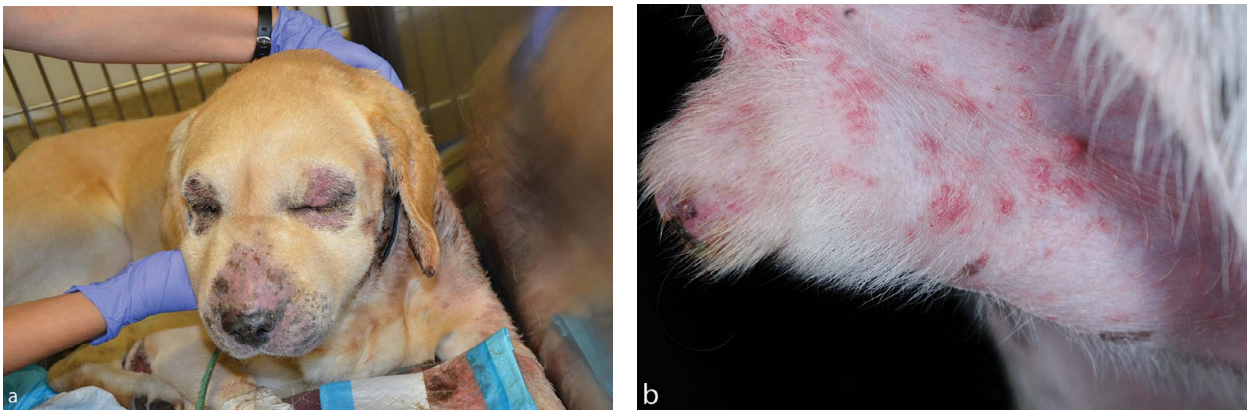


FIGURE 18.41 (a) Erythema, alopecia, crusting, and swelling of the face of a puppy typical of the canine juvenile cellulitis/juvenile sterile granulomatous dermatitis and lymphadenitis. **(b)** Pustules and papules in the groin of a dog affected by canine juvenile cellulitis/juvenile sterile granulomatous dermatitis and lymphadenitis. (a, *Courtesy of Dr. Schaer.*)

clinician needs to think about a variety of skin diseases. Based on the etiology, such lesions can be inflammatory (granulomas) or neoplastic in origin. Infectious (bacterial, fungal, oomycosis; Figure 18.42a), parasitic (Figure 18.42 b, c), or sterile diseases would be included in the first group. Inflammatory nodules are quite common in dogs and cats, and because of the variety of etiological agents involved, it is fundamental to proceed stepwise in order to reach an accurate diagnosis.

When a dog or a cat presents with cutaneous nodules/masses, it is imperative to collect an accurate history and perform a detailed physical and dermatological examination. This is followed by skin cytology (fine-needle aspirate of the lesions or impression from exudative/ulcerated lesions) to verify the nature of the process. This test is extremely informative to direct the clinician toward an inflammatory or a neoplastic process. Once neoplasia is excluded, the cytology should be followed by bacterial and fungal tissue cultures to rule out potential infectious organisms. Among others, mycobacteria and oomycetes need to be included in the differential diagnoses and properly ruled out using specialized test media. Along with the cultures, molecular diagnostics (PCR) can be extremely useful to rule out fastidious microorganisms (e.g., actinomycetes and mycobacteria), oomycetes, or protozoa (e.g., *Leishmania* spp.). Finally, skin histopathology collected using deep biopsy technique should always be performed to obtain the final diagnosis and definitely rule out (or confirm) a neoplastic process. Additionally, visualization of organisms within the skin confirms that growth in culture is true infection instead of contamination of the skin surface. In certain cases, the use of special staining (e.g., mycobacteria, fungi, oomycetes) or immunohistochemistry (e.g., leishmaniosis) is also essential to confirm the suspicion of infectious organisms.

Because of the diversity of treatments available for the various diseases (e.g., chemotherapy versus antimicrobials), it is of extreme importance to be able to reach a diagnosis before starting a systemic treatment. In fact, the use of an inappropriate treatment (e.g., immunosuppression) for an infectious disease may lead to catastrophic consequences for the animal's health.

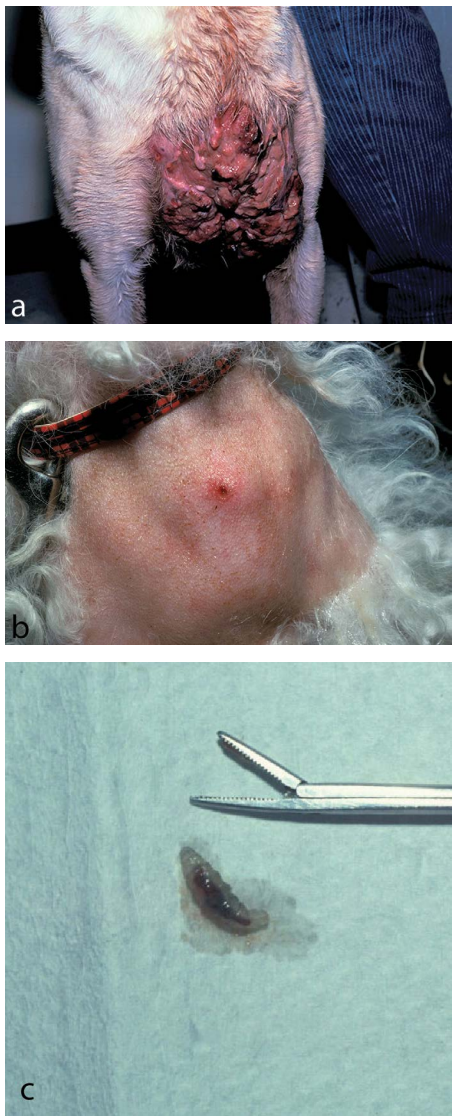


FIGURE 18.42 (a) Severe nodular dermatitis with draining tracts and serosanguineous discharge in a dog affected with cutaneous pythiosis. **(b)** A "blow-hole" caused by *Cuterebra* in a Maltese dog, and **(c)** the extracted worm larva. (*Courtesy of Dr. Schaer.*)

RAPID-GROWING MYCOBACTERIOSIS

Definition/Overview

The incidence of mycobacteriosis in dogs and cats is highly variable. It depends on the type of mycobacteria and the geographic locations. Based on the etiological agents, mycobacteriosis can be classified as rapid-growing and slow-growing mycobacteriosis. The former is more common than the latter. For slow-growing mycobacteria, a molecular diagnostic is necessary to isolate the organism (most do not grow in culture).

Etiology

Many different mycobacteria belong to this group of organisms. Among others, *M. fortuitum* group, *M. chelonae* group, and *M. smegmatis* group are the most commonly isolated rapid-growing microorganisms.

Pathophysiology

In order for the mycobacteria to initiate a disease process, a breach in the skin integrity is essential. Mycobacteria can be injected via bites or fomites (e.g., thorn or piece of wood). Once in the skin, the microorganisms stimulate a Th1 or Th2-type immune response leading to resolution or exacerbation of the process, respectively.

Clinical Presentation

The clinical presentation of mycobacteriosis varies based on the host and the organism. Most dogs and cats present with a single or multiple nodule(s), generally localized on the abdomen (adipose tissue) (Figure 18.43) or in other areas of the body (e.g., dorsum; Figure 18.44). The nodules can be individual or coalescing in larger masses or plaques. They can be ulcerated and create draining tracts oozing clear yellow exudate. Pruritus is generally not present to mild.



FIGURE 18.43 Cat with mycobacterial panniculitis. Note the extensive inflammation beside a previous attempt for surgical excision. This continuing spread of involvement is typical. (*Courtesy of Dr. Schaer.*)



FIGURE 18.44 Dog with mycobacteriosis. Note the large ulcerated and draining subcutaneous mass affecting the dorsum of this dog. (*Courtesy of Dr. Schaer.*)

Differential Diagnoses

The main noninfectious differential diagnoses include foreign body reaction, follicular/sebaceous cysts, sterile nodular panniculitis, sterile granuloma/pyogranuloma syndrome, histiocytosis, juvenile sterile granulomatous dermatitis and lymphadenitis, cutaneous xanthoma, and canine sarcoidosis. Among the infectious diseases, protozoa (e.g., *Leishmania* spp. and *Neospora* spp.), fungi (dermatophytosis, dimorphic, and opportunistic), algae, and oomycetes should be considered. Neoplastic skin diseases should also be included in the differential list.

Diagnosis

The diagnosis of mycobacteriosis can be frustrating. The definitive diagnosis is achieved via mycobacterial culture, although skin cytology may be indicative and, in some cases, diagnostic for mycobacteriosis. To increase the chances of success, a tissue biopsy is preferred to a swab. In addition, mycobacterial PCR can be a rapid and effective way to diagnose and speciate mycobacteria. When possible, an antimicrobial sensitivity panel should be requested.

Management

The treatment of mycobacteriosis varies based on the species of mycobacteria isolated. In cases of isolated nodules/masses, surgical removal maybe curative. In cases of large masses, medical treatment can be combined with surgical debulking to decrease the duration of the treatment. Generally, a combination of fluoroquinolones and macrolides is necessary, although the use of doxycycline may suffice. The appropriate antibiotic should be chosen based on sensitivity (preferred) or based on literature review. The treatment is generally implemented for several months after the clinical resolution.

CANINE LEISHMANIOSIS

Definition/Overview

Canine leishmaniosis (CL) is a protozoal systemic disease endemic in the Mediterranean basin, Middle East, and South America. However, the cases of canine leishmaniosis have increased in the past decades in North America. Most of those cases have a history of traveling to endemic areas. The clinical features are quite variable; however, they are frequently characterized by the presence of skin lesions and systemic clinical signs. This is a zoonotic disease.

Etiology

Canine leishmaniosis is caused by the protozoa of the genus *Leishmania*. Many species have been associated with CL; however, the most common organism is *L. infantum chagasi*. The parasite is transmitted by sand flies of the genus *Phlebotomus* and *Lutzomyia*.

Pathophysiology

CL is characterized by a Th2-predominant immunological response, which makes the host unable to eliminate infection. Once the parasite is injected (promastigote stage) into the skin by the sandfly, it is phagocytized by macrophages in which it changes to the amastigote stage. This latter stage is not killed by the macrophage, and the organism replicates until it induces rupture of the macrophage and diffusion of the parasite to other macrophages. Amastigotes multiply in the skin as well as in the reticuloendothelial system (liver, spleen, lymph nodes, and bone marrow), which induces organ enlargement and dysfunction.

Clinical Presentation

Canine leishmaniosis is a polymorphic disease. The most common clinical signs include lymphadenomegaly, anemia, weight loss, splenomegaly, and skin lesions (Figure 18.45a, b). The latter may include a diffuse exfoliative dermatitis, depigmentation of the nasal planum, vasculitis, nasal hyperkeratosis, alopecia, papular eruption, nodules, and ulcers. In addition, ocular lesions (from keratitis to panophthalmitis), muscle atrophy, lethargy, epistaxis, arthropathies, pyrexia, and renal failure also occur commonly.

Differential Diagnoses

The main noninfectious differential diagnoses include foreign body reaction, follicular/sebaceous cysts, sterile nodular panniculitis, sterile granuloma/pyogranuloma syndrome, histiocytosis, juvenile sterile granulomatous dermatitis and lymphadenitis, cutaneous xanthoma, and canine sarcoidosis. Among the infectious diseases, mycobacteria, fungi (dermatophytosis, dimorphic, and opportunistic), algae, and oomycetes should be considered. Neoplastic skin diseases, demodicosis, tick-borne diseases (e.g., ehrlichiosis, Rocky Mountain spotted fever, Lyme disease), and autoimmune diseases should also be included.

Diagnosis

The diagnosis of CL includes the presence of a suggestive history (e.g., traveling to endemic areas), compatible clinical signs, and diagnostics (blood work, circulating protein electrophoresis). The definite diagnosis is based on the visualization of the parasite on cytological samples



FIGURE 18.45 Dogs with leishmaniasis. Note the severe cachexia **(a)**, onychogryphosis, erosions, alopecia, hyperpigmentation, and crusts on both front limbs **(b)**, *Leishmania* spp. organisms within a macrophage of an infected dog; neutrophils and red blood cells are also present on this microscopic view **(c)**.

(Figure 18.45c) (lymph nodes, bone marrow, spleen, skin) or histopathology. However, serology and PCR are highly sensitive methods for the diagnosis of CL.

Management

Canine leishmaniosis is most commonly incurable but can be managed. The most common and effective treatment includes the combination of meglumine antimoniate and allopurinol. The former is administered in cycles of 30 days, whereas the allopurinol is administered daily for at least 6–12 months (sometimes for life). In the past decade, this combination has been partially substituted by the combination of miltefosine and allopurinol because of the better tolerability of the miltefosine. Other possible treatment options include aminosidine, amphotericin B, metronidazole/spiramycin, ketoconazole, and metronidazole/enrofloxacin. Because most dogs cannot be cured of this disease, the prevention of the transmission of the parasite is extremely important. Thus, the use of repellents containing permethrin or deltamethrin are essential. Recently, the use of vaccines has also been investigated as prevention or treatment of CL.

STERILE PYOGRANULOMATOUS DERMATITIS AND PANNICULITIS

Definition/Overview

Sterile pyogranulomatous dermatitis and panniculitis (sterile nodular panniculitis, SNP) is an uncommon skin disease mainly affecting young adult dogs. Many breeds seem to be predisposed to this syndrome. These include Dachshunds, Collies, Dobermann Pinscher, Golden Retriever, Boxer, and Poodles.

Etiology

The etiology is currently unknown.

Pathophysiology

The pathophysiology of sterile nodular panniculitis is not completely clear.

Clinical Presentation

Most dogs and cats affected by sterile pyogranulomatous dermatitis and panniculitis present with a single or multiple nodule(s), generally localized on the trunk (Figure 18.46a, b). The nodules can be individual or coalescing in larger masses or plaques. They can become ulcerated and create draining tracts oozing clear yellow viscous exudate. Pruritus is generally not present unless a secondary infection is present. In some cases, lethargy, fever, cutaneous pain, polyarthritis, hyporexia, and general malaise are significant clinical signs. Rarely, some dogs have a history of recent or active pancreatitis, but the association of this disease and SNP is unclear.

Differential Diagnoses

The main noninfectious differential diagnoses include foreign body reaction, follicular/sebaceous cysts, sterile granuloma/pyogranuloma syndrome, histiocytosis, juvenile sterile granulomatous dermatitis and lymphadenitis, cutaneous xanthoma, and canine sarcoidosis. Among the infectious diseases, protozoa (e.g., *Leishmania* spp. and *Neospora* spp.), fungi (dermatophytosis, dimorphic, and opportunistic), mycobacteria, algae, and oomycetes should be considered. Neoplastic skin diseases should also be included in the differential list.

Diagnosis

The diagnosis of sterile pyogranulomatous dermatitis and panniculitis can be very laborious at times, mainly when a secondary infection is present. The definitive diagnosis is achieved by ruling out any infectious disease able to mimic the same clinical presentation. Among others, mycobacterial, fungal, and oomycete infections have to be ruled out. To do so, specific tissue cultures and/or PCR should be performed along with histopathology of the skin.



FIGURE 18.46 Dog with sterile nodular panniculitis. Note the ulceration oozing sanguineous material associated with multiple nodules, crusts, scales, and alopecia on the dorsum (a) as well as on the muzzle (b).

Management

The main treatment of sterile pyogranulomatous dermatitis and panniculitis includes the use of immunomodulatory drugs with systemic corticosteroids as the first line of treatment. Noncorticosteroid immunomodulatory options include cyclosporine and doxycycline/niacinamide combination therapy. Mycophenolate mofetil and azathioprine are generally reserved for unresponsive cases.

CASE EXAMPLE

Case 18.1: Canine Demodicosis

Case Information

Signalment: A 3-year-old intact female Labrador Retriever

Presenting complaint: Multifocal, nonpruritic crusting and alopecia

History: One week prior to presentation, owners initially noticed a focal area of erythema and crusting with alopecia develop dorsal to the right eye. The area is not pruritic, and this dog has never had dermatological problems in the past. The lesion has continued to enlarge and become raised above the skin surface, and similar lesions are developing around the left eye. Owners noticed recently that the dog was holding her left eye more closed. This dog is a competition field trial dog that competes often and was artificially inseminated 3 weeks ago.

Physical examination: There was an approximately 3 cm × 2 cm erythematous, alopecic, crusted nodule dorsal to the right eye (**Figure 18.47**). Beneath the hemorrhagic crust was purulent exudate with ulceration (**Figure 18.48**). The lesion was mildly painful on palpation. There were numerous erythematous, alopecic, and exudative nodules present around the left eye, most notably on the dorsolateral aspect OS with mild blepharospasm (**Figure 18.49a, b**).



FIGURE 18.47 Approximately 3 cm × 2 cm erythematous, alopecic, crusted nodule dorsal to the right eye.



FIGURE 18.48 Approximately 3 cm × 2 cm erythematous, alopecic, crusted nodule dorsal to the right eye. The hemorrhagic crusts is lifted and reveals purulent, hemorrhagic exudate.

Assessment: The *problem list* included: (1) Multifocal nodular dermatitis, (2) blepharospasm, and (3) unknown pregnancy status. *Differential diagnoses* for problem #1 included deep bacterial infection, deep fungal infection, foreign body, demodicosis, insect bite hypersensitivity (eosinophilic folliculitis and furunculosis), cyst, or neoplasia. The lifestyle of the dog made infectious dermatitis or foreign body the most likely differentials, followed by demodicosis and, less likely, neoplasia. The most likely differential diagnosis for problem #2 was corneal erosion/ulceration secondary to trichiasis from periocular swelling or self-trauma from scratching. Confirmation of pregnancy was needed to resolve problem #3.

Diagnostic Plan

Cytology: Numerous neutrophils and cocci bacteria (**Figure 18.50**)

Deep skin scrapings: Numerous live *Demodex canis* mites—adults, nymphs, larvae, and eggs (**Figures 18.51–18.54**)

- DTM: Negative for growth
- Abdominal ultrasound: Normal uterus with no fetuses observed; Conclusion: Not pregnant
- Fluorescein staining OU: No uptake
- Schirmer's tear test OU: 22 OS, 19 OD

Diagnosis: Adult-onset demodicosis with secondary bacterial dermatitis. The stress of estrus and artificial insemination were presumed to be the cause of demodicosis in this case.

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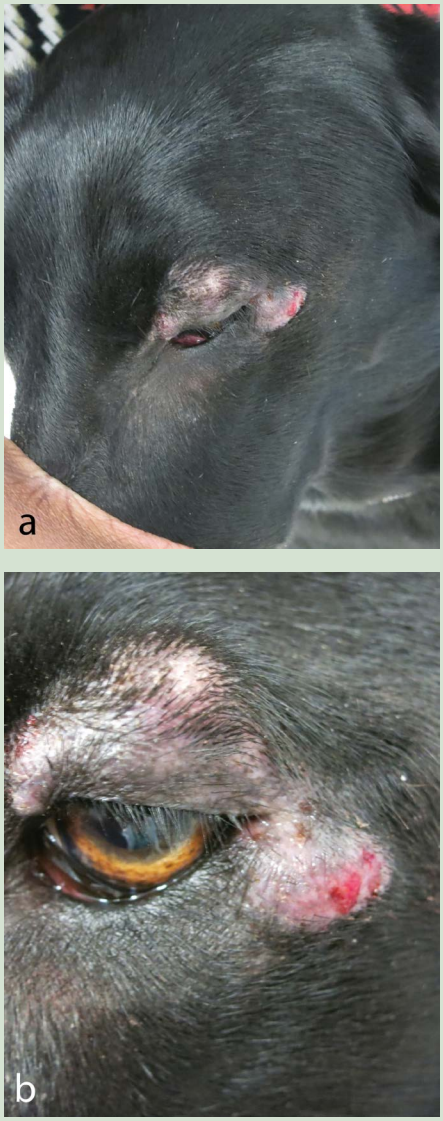


FIGURE 18.49 (a) Multinodular, erythematous, alopecic, and exudative periocular dermatitis OS. **(b)** Closeup: Multinodular, erythematous, alopecic, and exudative periocular dermatitis OS.

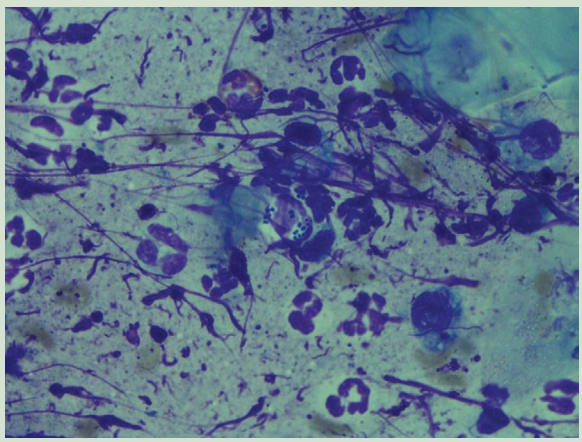


FIGURE 18.50 Neutrophils with intracellular cocci.



FIGURE 18.51 *D. canis* adult.



FIGURE 18.52 *D. canis* nymph.

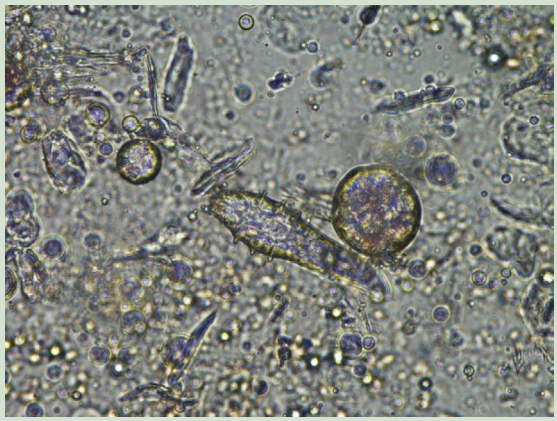


FIGURE 18.53 *D. canis* larva.

Treatment: Oral sarolaner once every 30 days to treat demodicosis; topical chlorhexidine 3% followed by topical mupirocin 2% ointment every 12 hours.

Rationale: Isoxazoline parasiticide therapies have proven highly efficacious in the treatment of canine demodicosis. Additionally, they have a wide safety profile because the therapeutic dose for the treatment of demodicosis is equivalent to the labeled dose for flea and tick prevention. Given the localized nature of the

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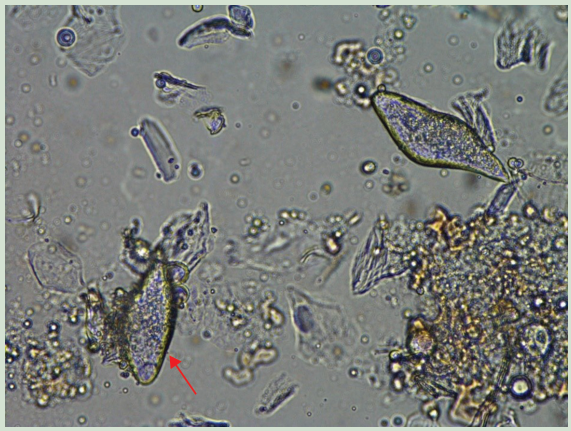


FIGURE 18.54 *D. canis* egg.

bacterial dermatitis, topical therapy was preferred. Topical chlorhexidine is effective against bacteria and yeast; however, care should be taken to avoid contact with the eyes. A wipe formulation was selected for this reason. Mupirocin ointment is effective against Gram-positive organisms such as *Staphylococcus pseudintermedius*.

Follow-up (3 weeks): Complete resolution of bacterial dermatitis with signification reduction of nodular appearance of lesions. Only alopecia remained. Skin cytology revealed no bacteria. Skin scrapings and trichography from affected areas revealed very few, dead *Demodex canis* mites. Mupirocin and topical chlorhexidine were discontinued after 1 additional week, and sarolaner was continued once monthly.

Follow-up (8 weeks): Complete resolution of nodular skin lesions with near-complete hair regrowth. No mites observed on skin scrapings or trichography from the previously affected area. Sarolaner was continued once monthly.

Follow-up (12 weeks): Complete resolution of dermatitis with complete hair regrowth. No mites observed on skin scrapings or trichography from the previously affected areas. Sarolaner was continued once monthly indefinitely.

Follow-up (6, 9, and 12 months): No recurrence of infection.

Discussion: The inciting cause of demodicosis in this dog was presumed to be stress-induced immunocompromise. The two postulated sources of profound stress included either estrus with artificial insemination and/or frequent participation in field competitions. Owners were counseled that relapse of demodicosis may occur at the time of estrus, pregnancy, and/or parturition in the future. Because the dog was performing in field competitions with the same frequency for the past 18 months, stress induced by these events was considered less likely. However, the combined stress of estrus and high physical performance could have been the cause. Because it was confirmed the dog was not pregnant at the time of diagnosis of demodicosis, this eliminated the concern for using isoxazolines for treatment. If demodicosis did relapse during a viable pregnancy, treatment options would be limited. Owners were advised to monitor closely for signs of recurrence, though risk of occurrence would be less likely if the dog continued on once monthly isoxazoline for flea and tick prevention.

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CHAPTER 19

Ocular Manifestations of Systemic Diseases

Ralph Hamor

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INTRODUCTION

Ophthalmic manifestations of systemic disease (OMSD) can be seen in almost every periocular and ocular tissue, depending on the species and the disease process. As the globe, periocular, and orbital tissues have a limited response to disease processes, the clinical signs of an OMSD are often similar for many diseases. A complete ophthalmic examination of dogs and cats with confirmed or suspected OMSD remains, however, a critical diagnostic tool that can assist the clinician in the diagnosis, prognosis, and response to treatment of systemic disease processes. Infectious, neoplastic, autoimmune, immune-mediated, nutritional, toxic, and metabolic diseases may have ocular manifestations that can occur acutely and/or chronically. Current visual status and/or visual prognosis may also be an important deciding factor as owners determine how aggressively they may wish to pursue potential diagnostic and therapeutic options. The most common cause of uveitis in dogs and cats is idiopathic. Depending on the source read, the most common causes of uveitis in dogs are idiopathic (60%–70%), followed by infectious (18%–25%) and neoplastic (5%–25%). For cats, the most common causes of uveitis are idiopathic (40%) followed by infectious (30%) and neoplastic (5%). Determination of the exact cause of an OMSD can be challenging to the clinician and a source of frustration for the owner. With that said, the globe, periocular tissues and orbital tissues can provide important clues to assist in the diagnosis and treatment of numerous OMSDs.

BACTERIAL INFECTIONS

See also Chapter 21.

BACTEREMIA

Definition/Overview

Bacteremia from any source may result in seeding of the iris, ciliary body, or choroid with bacteria. This seeding of bacteria can cause anterior or posterior uveitis, endophthalmitis, chorioretinitis, and optic neuritis. Bacterial embolization may occur in pyometra, prostatitis, pancreatitis, bacterial endocarditis, periodontal disease, and salmonellosis or as an immune-mediated phenomenon associated with circulating antigen–antibody complexes (chronic inflammatory disease processes). Bacterial meningitis can be associated with signs of direct ocular involvement or with ocular signs that are related to the area of the brain affected.

LEPTOSPIROSIS

Definition/Overview

Leptospirosis is caused by a spirochete, which is a filamentous bacterium within the genus *Leptospira*. Organisms can be transmitted through contact with infected urine or contaminated water, bites, or

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ingestion of infected material. After infection, bacteremia can result in vasculitis and endotheliitis. Dogs with leptospirosis may demonstrate conjunctivitis, anterior uveitis, and scleritis. Leptospirosis does not commonly cause ophthalmic signs in cats. It is considered a zoonotic disease, and appropriate precautions should be taken when handling affected animals or contaminated materials. The penicillin class of drugs (specifically ampicillin and amoxicillin) and doxycycline effectively treat this condition.

BRUCELLOSIS

Definition/Overview

Brucella canis is an aerobic, Gram-negative coccobacillus that can penetrate the mucous membranes of the conjunctiva, oropharynx, and genital tract. Ocular signs occur in about 14% of dogs, including recurrent corneal edema, anterior uveitis, hyphema, chorioretinitis, optic neuritis, endophthalmitis, and secondary glaucoma. Brucellosis should be considered in any dog that has chronic or recurrent uveitis, particularly in animals that are intact. The organism can be cultured from aqueous and vitreous, and titers detected in serum and aqueous humor. It is a zoonotic disease diagnosed by bacteriologic culturing. Systemic therapy with oral tetracycline and intramuscular streptomycin has been reported to be effective in over 90% of treated cases. A combination therapy of systemic streptomycin, rifampin, ciprofloxacin, and doxycycline has been shown to effectively treat ocular brucellosis. With any treatment regimen, relapses can occur.

LYME DISEASE

Definition/Overview

Borreliosis (Lyme disease), caused by the spirochete *Borrelia burgdorferi*, is a tick-borne disease transmitted by ticks of the *Ixodes* species, but transmission has also been associated with *Amblyomma americanum*. The primary reservoirs borreliosis are small rodents and birds. Transmission of the disease is related directly to contact time of the infected onto the host. The organism then spreads by moving through connective tissue but can, rarely, spread hematogenously. Prevention of borreliosis is most commonly achieved by vaccination and tick control. Ocular lesions in dogs include conjunctivitis, corneal edema, anterior uveitis, retinal petechiae, chorioretinitis, retinal detachment (RD), and orbital disease. Diagnosis by antibody testing remains challenging as vaccination may result in false-positive results, and high antibody titers for IgM may persist for months in naturally infected dogs. Systemic doxycycline remains the antibiotic of choice for borreliosis and generally requires chronic treatment of at least one month.

CLOSTRIDIAL DISEASE

Definition/Overview

Tetanus is caused by the bacterium *Clostridium tetani*. This organism is a motile, nonencapsulated, anaerobic, Gram-positive, rod-shaped, spore-forming bacterium. Spores of *Clostridium tetani* infect skin wounds or enter through a surgical procure. These spores then become vegetative and produce a potent neurotoxin, tetanospasmin, that migrates along axons to the central nervous system. This toxin causes the typical clinical signs by preventing inhibitory neurotransmission to motor neurons. Clinical signs can be localized or generalized. Ocular signs in dogs and cats are associated with third eyelid elevation and enophthalmos secondary to retraction of the globe due to contraction of the extraocular muscles. Contraction of the facial muscles also occurs. Dogs and cats are not as easily infected as other species such as horses and humans. Diagnosis is generally made by clinical signs, but the organism can be cultured, and antibodies to tetanospasmin can be measured to assist or confirm the diagnosis. Treatment is through administration of tetanus antitoxin. Penicillin-G and metronidazole may also be utilized to eliminate any remaining bacteria and prevent the binding of unbound tetanospasmin.

BARTONELLOSIS

Definition/Overview

Bartonella henselae is the causative agent for human "cat scratch disease" and is a zoonotic disease. *Bartonella* species are fastidious, hemotropic, Gram-negative, pleomorphic bacteria. *Bartonella vinsonii (berkhoffii)*, *B. clarridgeiae*, and *B. elizabethae* cause naturally occurring disease in dogs. *Bartonella henselae*, *B. clarridgeiae*, *B. koehlerae*, *B. elizabethae*, *B. weissii*, *B. quintana*, and *B. bovis* have all been associated with infection in cats, but infection with species other than *B. henselae* and *B. clarridgeiae* is rare. Tick transmission is likely the most common mode of transmission in dogs. While flea transmission is likely, the most common mode of transmission in cats, ticks can act as vectors for cat-to-cat or cat-to-human transmission. Because cats are a reservoir for *B. henselae* and most carrier cats do not have clinical disease, it is difficult to associate clinical disease with this organism in cats. Seropositivity in cats ranges from 5% to 90%, so serum antibody testing may be most useful in identifying seronegative cats in an attempt to rule out bartonellosis as a potential cause for uveitis. For sick cats, serum antibody titers with blood culture or polymerase chain reaction (PCR) testing may assist in confirming a diagnosis. Aqueous humor can also be harvested and submitted for PCR and antibody testing to calculate a Goldmann-Witmer coefficient (C value). A C value greater than 3 is suggestive of local antibody within the globe. Numerous studies have evaluated the efficacy of diagnostic testing in cats utilizing serology, PCR, aqueous humor

and/or blood culture in cats. Unfortunately, more recent studies demonstrated that it is not possible to associate ocular or systemic signs of disease with positive diagnostic testing due to the facts that this infectious agent is widespread within the general cat population, and so few cats are affected with clinical signs. In dogs, ocular signs include anterior uveitis, hyphema, chorioretinitis, and RD (due to systemic hypertension). In cats, 5%–10% of infected cats have ocular signs, including blepharitis, conjunctivitis, keratitis, uveitis (Figures 19.1 and 19.2), and chorioretinitis. Treatment of systemic bartonellosis in dogs and cats involves the use of systemic antibiotics such as azithromycin, enrofloxacin, or doxycycline for several weeks.

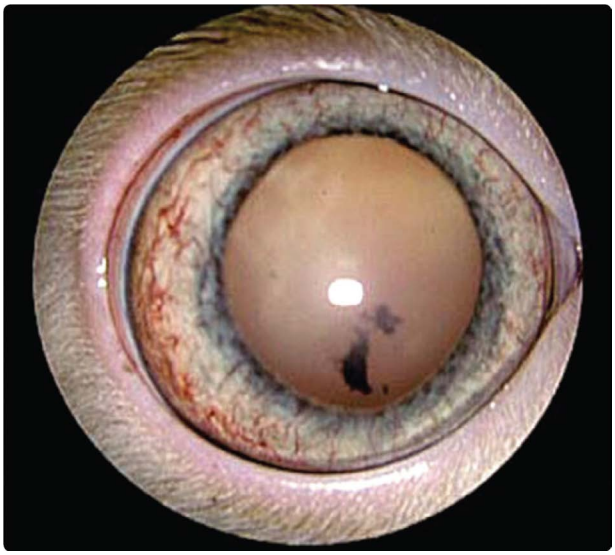


FIGURE 19.1 Rubeosis iridis, corneal haze, lens opacity, and pigment on the lens capsule in the eye of a cat with bartonellosis. The pupil is dilated from topically administered atropine.



FIGURE 19.2 Fibrin in the anterior chamber obscures the pupil in this cat with bartonellosis.

MYCOPLASMA

Definition/Overview

Mycoplasma spp. are the smallest free-living organisms and are classified as prokaryotes. The organism has been isolated from cats affected with conjunctivitis as well as from healthy cats.

Etiology

Mycoplasma felis, *M. gatae*, *M. arginine*, *M. canadense*, *M. cynos*, *M. lipophilum*, and *M. hypopharyngis* have all been isolated for the conjunctiva of both sick and healthy cats. Experimentally, *M. felis* has caused conjunctivitis in some kittens but not in other kittens or in adult cats. As such, the role of *Mycoplasma* spp. in conjunctivitis in cats is unknown, and it is considered a rare cause of conjunctivitis. The disease is not self-limiting in all cases.

Pathophysiology

It is likely that *Mycoplasma* spp. are most able to establish infection in the conjunctiva of a cat already infected by another pathogen such as feline herpesvirus or *Chlamydophila felis*. An altered or immature immune system may also allow the establishment of infection.

Clinical Presentation

Initially, conjunctivitis may be unilateral, with the opposite eye usually becoming affected in 7–14 days. Early in the disease, the ocular discharge is serous with chemosis, hyperemia, and blepharospasm also present. Over time, the exudate increases, becoming mucopurulent and the chemosis more severe. The thick exudate may adhere to the conjunctiva and appear as a pseudomembrane. The nictitans may become hyperemic, swollen, and protrude. Papillary hypertrophy of the conjunctiva may occur. Conjunctival cytology reveals a predominantly neutrophilic response. *Mycoplasma* organisms are coccoid or coccobacillary, basophilic clusters found within the cytoplasm of infected conjunctival epithelial cells. Once the ocular discharge becomes more mucopurulent, the identification of organisms is much more challenging.

Differential Diagnosis

Conjunctivitis and/or conjunctival hyperemia is an extremely common clinical finding in numerous ocular diseases. It may be infectious (herpesvirus, calicivirus, *Mycoplasma*, and *Chlamydophila* in cats) or noninfectious with noninfectious being much more common. It may be primary or be secondary to ulcerative keratitis, eyelid disease (entropion, ectropion, blepharitis), orbital cellulitis, nasolacrimal duct obstruction, keratoconjunctivitis sicca (KCS), atopy, environmental irritation, and neoplasia (lymphoma). Episcleral injection also causes the white part of the globe to be red and is associated

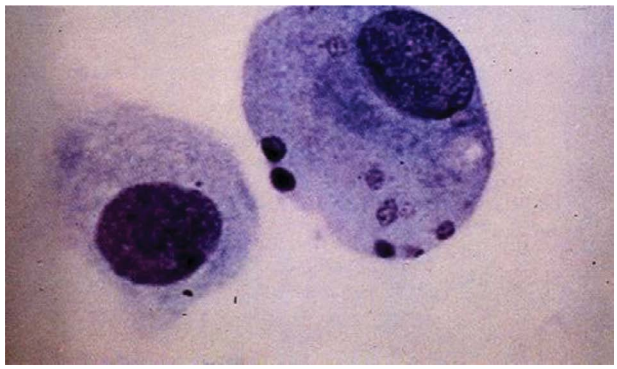


FIGURE 19.3 Conjunctival epithelial cell containing multiple, small basophilic inclusion bodies suggesting mycoplasma infection. Mycoplasma was identified in cultures from this eye. Giemsa stain.

with scleral or intraocular diseases such as episcleritis, anterior uveitis, glaucoma, and intraocular neoplasia.

Diagnosis

The diagnosis of mycoplasmosis can be confirmed by the culture of the organism on special media or by the cytologic identification of the characteristic coccoid or coccobacillary, basophilic clusters found within the cytoplasm of infected conjunctival epithelial cells (Figure 19.3).

Management

Treatment of conjunctivitis due to *M. felis* consists of application of topical antibiotics for 3 weeks. Effective topical antibiotics include tetracycline or erythromycin. Oral doxycycline has also been used to treat affected patients, but most cases should respond to topical therapy.

VIRAL INFECTIONS

See also Chapter 21.

FELINE CALICIVIRUS

Definition/Overview

Feline calicivirus (FCV) is a nonenveloped, single-stranded RNA picornavirus. It is primarily a respiratory pathogen but has also been associated with oral ulceration and polyarthritis. Compared with feline herpesvirus, FCV has low pathogenicity to infect the conjunctiva of cats. Calicivirus conjunctivitis is suspected when conjunctivitis accompanies oral ulceration in cats. Most cats spontaneously recover from FCV infection, but cats may remain chronically infected and asymptomatically shed the virus. The diagnosis of FCV can be made through virus isolation (VI), immunofluorescence assay (IFA), and polymerase chain reaction (PCR) assay. Specific topical antiviral preparations are not effective against a ribonucleic acid (RNA) virus.

RABIES

Definition/Overview

Rabies remains an important zoonotic disease across the world. Transmission occurs through the bite of an infected animal to any warm-blooded animal. Along with the known systemic effects, dogs and cats may show pupillary dilation, uveitis, slowed palpebral and corneal reflexes, and photophobia due to neurologic dysfunction.

CANINE HERPESVIRUS

Definition/Overview

Canine herpesvirus (CHV) is an enveloped, double-stranded deoxyribonucleic acid (DNA) virus and can be infective in all canids. The presence of ocular lesions is dependent on the age and immune status of the dog. Ocular lesions can occur in primary or recurrent infections. Ocular lesions in adult dogs are generally limited to blepharitis, conjunctivitis, ulcerative keratitis, and nonulcerative keratitis. The presence of conjunctival petechia and/or dendritic corneal ulceration are suggestive of CHV infection. In adult dogs with normal immune systems, CHV infection is generally mild and self-limiting. Puppies infected with CHV generally have much more dramatic ocular signs, including keratitis, panuveitis, synechia, cataracts, retinal necrosis, retinal dysplasia, retinal atrophy, optic neuritis, and optic nerve atrophy. Infection is generally fatal in puppies. Diagnosis is generally through the documentation of clinical signs but can be confirmed with VI, PCR, or identification of virus by transmission electron microscopy. Therapy is generally supportive, but topical antiviral medications such as cidofovir 0.5%, idoxuridine, and trifluridine 1% have been utilized along with topical antibiotics as well as topical and systemic pain control for dogs with corneal ulcers.

CANINE DISTEMPER VIRUS

Definition/Overview

Ocular signs have been observed in animals with acute and chronic infection with canine distemper virus (CDV).

Etiology

Canine distemper is caused by an enveloped, single-stranded RNA morbillivirus. The virus is spread mainly by inhalation of aerosolized respiratory viral particles

or other infected secretions such as urine. Widespread vaccination of dogs has markedly decreased the incidence of canine distemper.

Clinical Presentation

Clinical signs of CDV infection can vary with patient age, immune status of the dog, and the strain of the virus. CDV infection has systemic features ranging from mild-to-severe coughing, dyspnea, lethargy, anorexia, vomiting, diarrhea, and central nervous system (CNS) signs. Ocular signs include serous to mucopurulent bilateral ocular discharge, chorioretinitis, retinal detachment (RD), KCS (Figures 19.4–19.7) (which may last 4–8 weeks or be permanent), corneal ulcers, optic neuritis (sudden blindness), and cortical blindness. Chronic retinochoroidopathies can be seen as areas of increased tapetal reflectivity ("gold medallion lesions") and altered pigmentation in tapetal and nontapetal fundic areas but

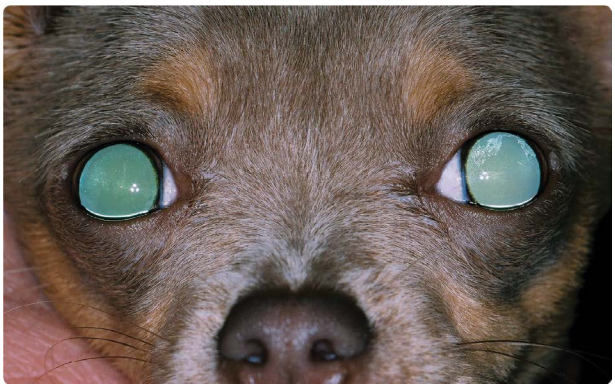


FIGURE 19.4 Dog with bilateral optic neuritis from canine distemper. Note the dilated pupils.

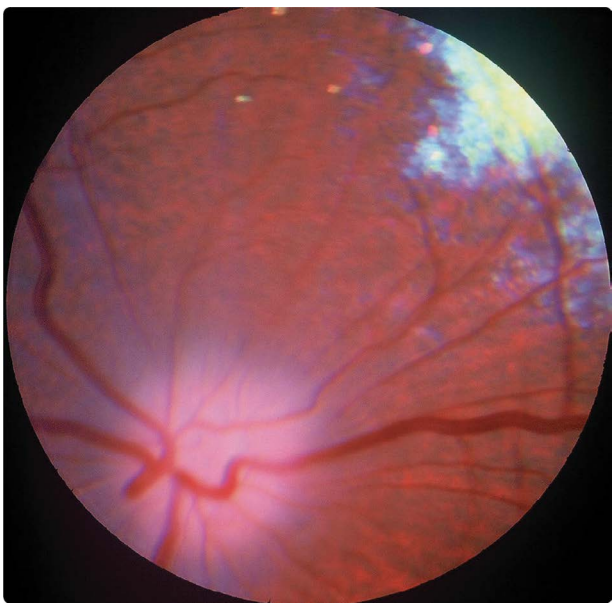


FIGURE 19.5 The optic nerve swelling, blurred edges (peripapillary edema and retinal detachment), and hyperemia of the optic disc indicate active optic neuritis.

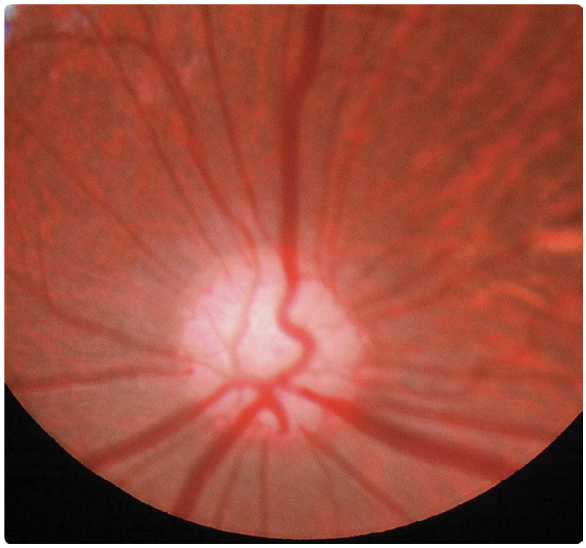


FIGURE 19.6 Mild optic nerve atrophy is present 2 months later.

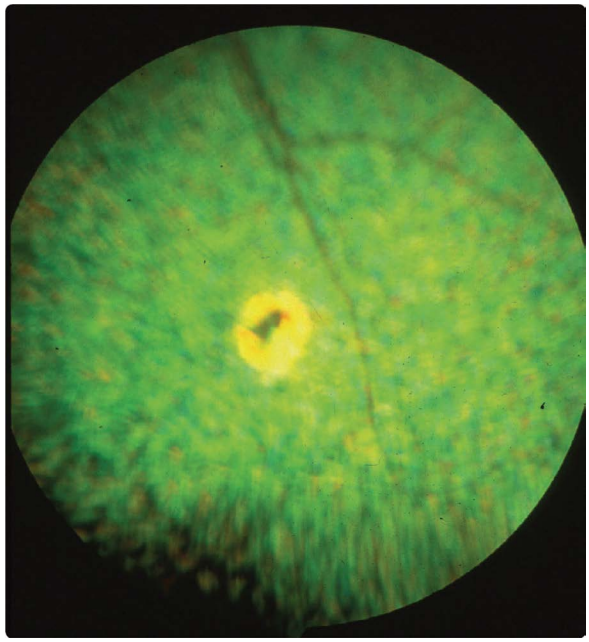


FIGURE 19.7 A focal area of healed chorioretinitis from distemper is found in this dog. The remaining chorioretinal scar is hyperreflective with a hyperpigmented center. In the past, these have been referred to as "gold medallion" lesions and were considered associated with CDV; however, any inflammatory and/or infectious lesion can result in a similar scar.

similar lesion may occur with any chorioretinal scar. The most profound and vision-threatening ocular lesion is optic neuritis resulting in mydriasis and vision loss. If the lesion affects the optic disc, then optic nerve swelling, hyperemia, hemorrhage, and peripapillary retinal edema may be present. If the inflammation is behind the globe, then additional diagnostic testing such as electroretinography and advanced imaging may be required to diagnose retrobulbar optic neuritis.

Differential Diagnosis

See Table 19.1.

Diagnosis

Conjunctival scrapings reveal mononuclear leukocytes and giant cells initially, then neutrophils. Intracellular inclusion bodies in conjunctival epithelial cells may be noted but are challenging to find if the patient does not have active conjunctival inflammation. Immunofluorescence of conjunctival smears may be positive 5–10 days post infection, although the virus disappears 21–28 days post infection. Reverse-transcriptase polymerase chain reaction (PCR) assays have been shown to be both sensitive and specific for detection of CDV.

Management

Treatment is aimed at controlling secondary infections, although ribavirin inhibits CDV replication in vitro. Acute optic neuritis is generally treated with systemic anti-inflammatory and/or immunomodulatory agents. Supportive treatment improves the chance for recovery and quality of life. Vaccination is the key to preventing CDV infection, as the prognosis for dogs with neurologic disease is considered guarded to poor.

INFECTIOUS CANINE HEPATITIS

Definition/Overview

Canine adenovirus 1 (CAV-1) may cause ocular signs, including anterior uveitis and corneal edema in naturally infected dogs and in dogs vaccinated with the modified live canine adenovirus type 1 vaccine. Keratouveitis occurs as after vaccination in about 0.4% of dogs. Due to the potential reaction to CAV-1, newer vaccines contain CAV type 2 to minimize the incidence of this condition.

Etiology

CAV-1 is a nonenveloped, double-stranded DNA adenovirus.

Pathophysiology

The corneal edema is a result of an Arthus-type hypersensitivity reaction in the corneal endothelium rather than direct viral replication. Classically, clinical signs develop 14–21 days post vaccination or 10–21 days following natural infection.

Clinical Presentation

Dogs generally present with severe, generally unilateral anterior uveitis with aqueous flare, hypotony, and corneal edema ("blue eye") appears in affected eyes (Figure 19.8). The clinical signs are bilateral in about 30% of cases. The anterior uveitis generally resolves

TABLE 19.1 Etiologies of uveitis secondary to ophthalmic manifestations of systemic disease most commonly affecting dogs and cats

- **Idiopathic**
  - Most common cause of uveitis: D&C
- **Immune-mediated**
  - Immune-mediated thrombocytopenia: D&C
  - Immune-mediated vasculitis: D&C
  - Meningoencephalitis of unknown etiology: D
  - Uveodermatologic syndrome: D
- **Infectious**
  - ***Algae***
    - *Geotrichum* spp.: D
    - *Prototheca* spp.: D
  - ***Bacteria***
    - Septicemia or endotoxemia: D&C
    - *Anaplasma platys*: D
    - *Bartonella* spp.: D&C
    - *Borrelia burgdorferi*: D
    - *Brucella* spp.: D
    - *Ehrlichia canis* or *platys*: *D*
    - *Leptospira* spp.: D
    - *Mycobacterium* spp.: C
    - *Rickettsia rickettsii*: D
  - ***Fungi and Yeasts***
    - *Aspergillus* spp.: D&C
    - *Blastomyces* spp.: D&C
    - *Candida albicans*: C
    - *Coccidioides immitis*: D
    - *Cryptococcus* spp.: D&C
    - *Histoplasma capsulatum*: D&C
    - *Pseudallescheria boydii*: D
  - ***Parasitic***
    - *Angiostrongylus vasorum*: D
    - *Baylisascaris* spp.: D&C
    - *Dirofilaria immitis*: D
    - *Encephalitozoon cuniculi*: C
    - *Onchocerca lupi*: D&C
    - *Metastrongylus* spp.: D&C
    - *Taenia multiceps*: D
    - *Toxocara* spp.: D&C
    - *Trypanosoma* spp.: C
  - ***Protozoa***
    - *Leishmania* spp.: D&C
    - *Neospora caninum*: D&C
    - *Toxoplasma gondii*: D&C
  - ***Viruses***
    - Canine adenovirus 1 and 2: D
    - Canine distemper: D
    - Coronavirus (FIP): C
    - FeLV: C
    - FeSV: C
    - FIV: C
    - Herpesvirus 1: D&C
    - Rabies: D&C
  - ***Metabolic***
    - Coagulopathies: D&C
    - Diabetes mellitus (lens-induced uveitis): D
    - Hyperlipidemia: D
    - Systemic hypertension: D&C
  - ***Neoplastic***
    - Granulomatous meningoencephalitis: D
    - Histiocytic disease: D
    - Hyperviscosity syndrome: D&C
    - Lymphosarcoma (most common secondary neoplasia): D&C
    - Melanoma (metastatic): D&C

C, cat; D, dog; D&C, both dog and cat.
Etiologies are listed in alphabetical order, not in order of importance.



FIGURE 19.8 Infectious canine hepatitis causes immune-mediated damage to the corneal endothelium which results in diffuse corneal edema ("blue eye").

over a 2- to 3-week period, although persistent corneal edema can occur. Ocular complications include bullous keratopathy, keratoconus/keratoglobus, phthisis bulbi, and secondary glaucoma.

Differential Diagnosis

See Table 19.1.

Diagnosis

Diagnosis is generally based on the clinical history and signs and can be confirmed with immunohistochemistry for CAV-1 and detection of viral DNA using PCR in infected ocular tissue.

Management

Therapy is symptomatic and includes topically administered corticosteroids, hyperosmotics, atropine, and nonsteroidal anti-inflammatory drugs.

FELINE HERPESVIRUS (RHINOTRACHEITIS)

Definition/Overview

FHV-1 is a double-stranded DNA virus that is highly species specific. FHV-1 has marked tropism for the conjunctival epithelium and less so for the corneal epithelium. The virus is spread from cat to cat through fomites, aerosolization, or direct contact.

Etiology

Herpesvirus is the major cause of respiratory disease and associated conjunctivitis in cats. It is estimated that >90% of cats are seropositive to the virus, with as many as 80% of infected cats remaining latently infected on a life-long basis. Approximately 45% of these latently infected cats shed virus throughout their life. Cats with chronic herpetic conjunctivitis may also be feline immunodeficiency virus (FIV) positive.

Pathophysiology

FHV-1 infects the epithelial surfaces of the respiratory tract, conjunctiva, and, with less frequency, the cornea. The virus then ascends by axons of sensory neurons to the trigeminal ganglion to establish life-long latency with a potential for recrudescence. Cytolytic pathology and immune-mediated disease are associated with FHV-1 infection. FHV-1 was isolated from the conjunctiva, cornea, uveal tract, retina, optic nerve, ciliary ganglion, pterygopalatine ganglion, trigeminal ganglion, brainstem, visual cortex, cerebellum, and olfactory bulb of infected cats during the acute phase. Trigeminal and cranial cervical ganglia harbor latent virus in the latent phase.

Clinical Presentation

Early signs of herpesvirus conjunctivitis include a bilateral serous ocular discharge that becomes mucopurulent (neutrophilic) with time. Secondary bacterial infections enhance the mucopurulent exudate. Unilateral or bilateral conjunctivitis is likely the most common ocular clinical sign in cats with or without concurrent upper respiratory signs (Figures 19.9 and 19.10). Dendritic corneal and/or conjunctival ulcers from viral-induced cytolysis and larger geographic, immune-mediated stromal ulcers can be associated with FHV (Figures 19.11 and 19.12). Dendritic corneal ulcerations are the hallmark sign of FHV infection, but simple, geographic corneal ulceration remains a far more common clinical sign. Corneal ulcers may heal rapidly or become chronic. Stromal keratitis may occur as a secondary, immune-mediated reaction to the virus. Stromal keratitis results in inflammatory cell infiltrates and deep

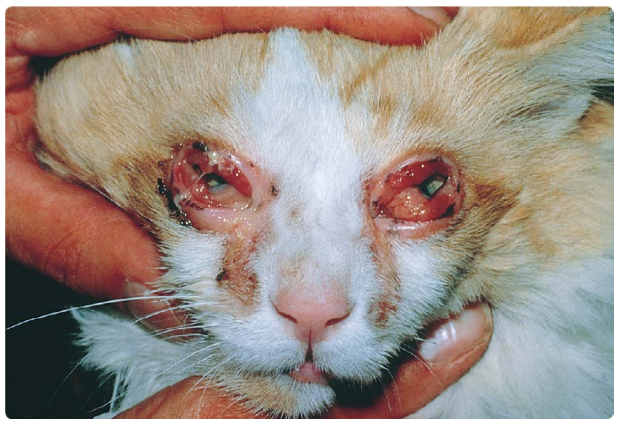


FIGURE 19.9 Bilateral blepharitis, conjunctival chemosis, hyperemia, and a mucoid discharge are found in this cat with herpesvirus.

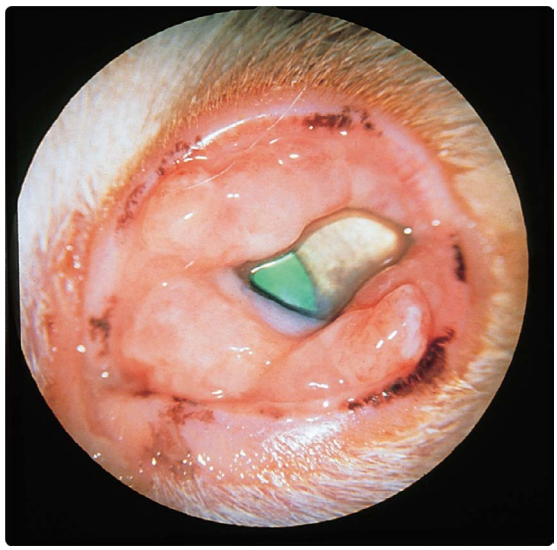


FIGURE 19.10 Chemosis is so severe in this cat with herpesvirus that the cornea can be barely seen. The cat also has diffuse, mild conjunctivitis.

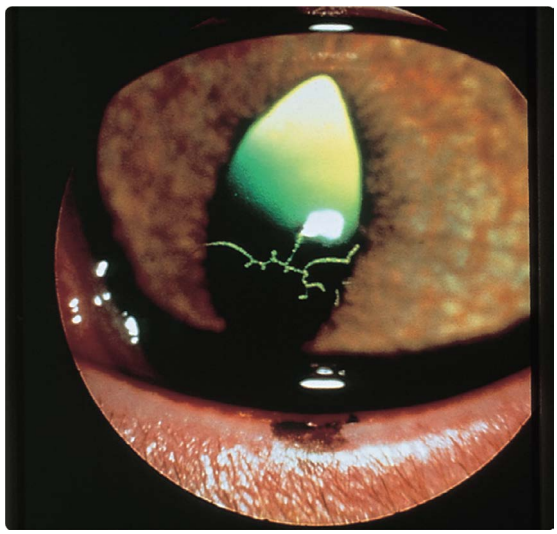


FIGURE 19.11 Linear, dendritic corneal ulcers are unique to herpesvirus.



FIGURE 19.12 Dendritic rose Bengal-positive lesions of the third eyelid conjunctiva are present in this cat with herpesvirus.

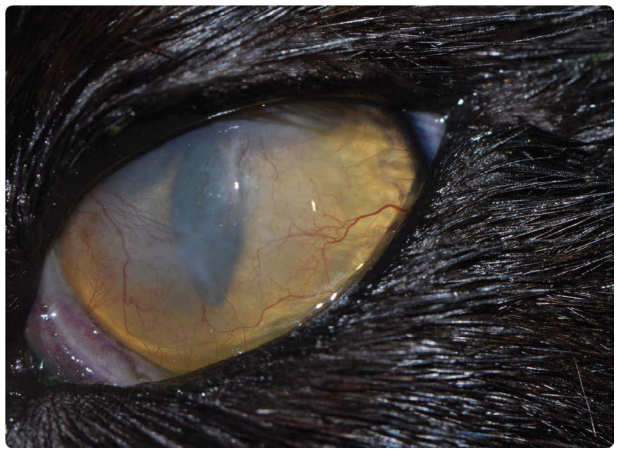


FIGURE 19.13 Generalized stromal keratitis is caused by FHV-1 in this cat.



FIGURE 19.14 Symblepharon (adhesions of conjunctiva to cornea or another conjunctival surface) from herpesvirus is present in this cat.

stromal vascularization (Figure 19.13). Symblepharon, secondary to conjunctival and corneal ulceration, is more common during a more acute primary infection (Figure 19.14). Neonatal ophthalmia can result from FHV infection during birth or within the perinatal period. Anterior uveitis may also be noted in some infected cats. KCS, while uncommon, may develop over time. Corneal sequestration and eosinophilic keratitis are also associated with FHV infection in cats (Figures 19.15 and 19.16).

Differential Diagnosis

Conjunctivitis is found in many types of eye diseases. It may be infectious (herpesvirus, calicivirus, *Mycoplasma*, and *Chlamydia* in cats) or noninfectious. Conjunctivitis may be primary or be secondary to ulcerative keratitis, eyelid disease, orbital cellulitis, nasolacrimal duct obstruction, KCS, atopy, environmental irritation, and neoplasia (lymphoma). Episcleral injection also causes the white part of the globe to be red and is associated with scleral or intraocular diseases such as episcleritis, anterior uveitis, glaucoma, and intraocular neoplasia.

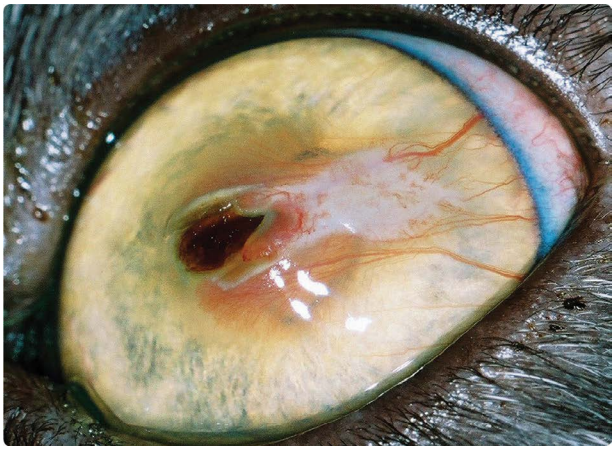


FIGURE 19.15 The dark corneal lesion with corneal fibrosis and vascularization is a corneal sequestrum and are clinically associated with chronic feline herpesvirus.

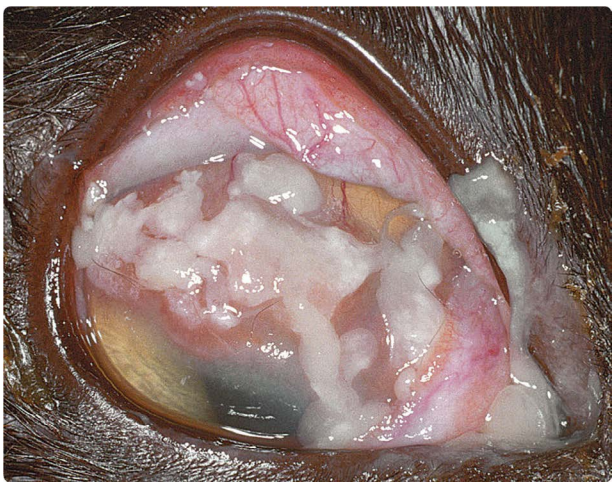


FIGURE 19.16 Eosinophilic keratitis is associated with feline herpesvirus in this cat. Note the white, proliferative, plaque lesions on the corneal surface.

Diagnosis

Due to the widespread presence of virus in normal and potentially infected cats, diagnostic confirmation of FHV infection remains challenging. While immunofluorescent antibody (IFA) and VI testing of conjunctival or corneal scrapings for herpesvirus is widely available, both are relatively insensitive in chronically infected cats. Serum antibody testing is only useful in nonvaccinated cats. Because it is an IFA test, prior fluorescein staining may yield false positives, so scrapings should be taken before staining. PCR and reverse-transcriptase PCR testing are more sensitive than the IFA tests. Although the extreme sensitivity (and specificity) of PCR has improved detection of virus, it has also confirmed that virus can be demonstrated in up to 31% of apparently normal cats. Conjunctival and/or corneal cytology is indicated in any cat with clinical signs of FHV infection. Lymphocytes generally predominate early, and large mononuclear cells are not uncommon. Neutrophils and giant epithelial cells are seen with chronic or secondary infection. Intranuclear inclusion bodies are seen very rarely, if ever, in clinical cases. Cytology can also be useful to assess for other cause of conjunctivitis such a *C. felis* or to rule out associated diseases like eosinophilic conjunctivitis or keratitis. Clinically, keratoconjunctivitis with dendritic branching corneal ulcers is generally assumed to be diagnostic of herpesvirus infection (**Figures 19.11** and **19.12**). Herpetic keratitis in the cat may or may not be associated with upper respiratory disease, particularly in more chronic cases.

Management

Therapy for herpesvirus remains challenging as a wide variety of both topical and systemic treatments have been utilized, each with varying degrees of success. In general, conjunctivitis and ulcerative keratitis are treated with topical antiviral preparations and broad-spectrum antibiotics to control any secondary bacterial infection. The efficacy of the antiviral medication in controlling the herpesvirus conjunctivitis (without corneal involvement) is variable. Herpesvirus vaccines are available for cats; however, herpesvirus conjunctivitis can occur in vaccinated cats. Recurrent herpesvirus may be associated with the immunosuppression by FIV/FeLV.

Antiviral agents should be prescribed when ocular signs are severe, persistent, or recurrent or when there is corneal ulceration. Of all the many topical antiviral agents that have been utilized and/or tested for the treatment of FHV, topical cidofovir (0.5%–1%) appears to be the most effective and has the added benefit of only needing to be given twice daily. Oral famciclovir (40 mg/kg p.o. q.8 h.) for 3 weeks can improve ocular, periocular, and systemic FHV disease. Oral treatment with L-lysine remains safe but controversial. While it has been documented to reduce clinical signs and viral shedding, it has not been confirmed to shorten clinical disease or reduce recurrence. Some owners feel, however, that chronic treatment with oral lysine is effective. The recommended dose of oral lysine is 500 mg q.12 h. in adult cats and 250 mg q.12 h. in kittens. Systemic interferon may be beneficial in cats that are refractory to other therapies. Treatment with topical steroids is more likely to result in corneal ulceration and also more likely to result in the development of stromal keratitis. If conjunctivitis or keratitis remains after antiviral treatment, then the addition of topical diclofenac (0.1%) or topical cyclosporine (0.2%) while maintaining antiviral therapy may be beneficial. Client education to establish clear goals of treatment is important. Regardless of any therapy or combination of therapies, many cats will continue to have clinical signs and recurrence of disease. It may also be beneficial to try different treatments for different cats, even those that have similar clinical signs, as different cats appear to respond to different therapy. Reduction and/or avoidance of stress can be beneficial to reduce recurrences. Recurrent and chronic herpes infections may suggest systemic immunosuppression, so cats should be evaluated for FeLV and FIV.

FELINE INFECTIOUS PERITONITIS

Definition/Overview

Effusive (wet) and noneffusive (dry) forms of feline infectious peritonitis (FIP) are known. The dry (noneffusive or parenchymatous) form of FIP is associated with the most ocular changes. There is increased risk of development of disease in young cats, sexually intact cats, and in certain breeds (Abyssinians, Bengals, Birmans, Himalayans, Ragdolls, and Rexes).

Etiology

FIP is caused by a coronavirus. Infection with feline coronavirus may result in no clinical disease, enteric disease, or FIP.

Pathophysiology

FIP replicates within macrophages and results in deposition of virus-laden macrophages within the endothelium of small blood vessels, which leads to pyogranulomatous lesions in a variety of tissues. Granulomatous lesions in the dry form are often found outside the abdomen and thorax, especially in the eye and the CNS. A fatal Arthus-type immune reaction of cats is associated with infection with the FIP virus.

Clinical Presentation

Ocular signs may occur without concurrent systemic signs or may be prodromal to systemic signs. The ocular signs are often bilateral but can be unilateral, even in patients with concurrent systemic disease. The most common ocular manifestation is bilateral, granulomatous anterior uveitis (Figures 19.17 and 19.18). Clinical signs include pyogranulomatous anterior and posterior uveitis, aqueous flare, "mutton-fat" keratic precipitates (Figure 19.19), hypopyon, synechiae, secondary glaucoma, exudative RD, choroiditis (Figure 19.20), retinal hemorrhages, vasculitis with pyogranulomatous sheathing or cuffing of retinal vessels (Figure 19.21), and optic neuritis. There have been several cases of remission in cats with ocular signs only and high FIP antibody titers.

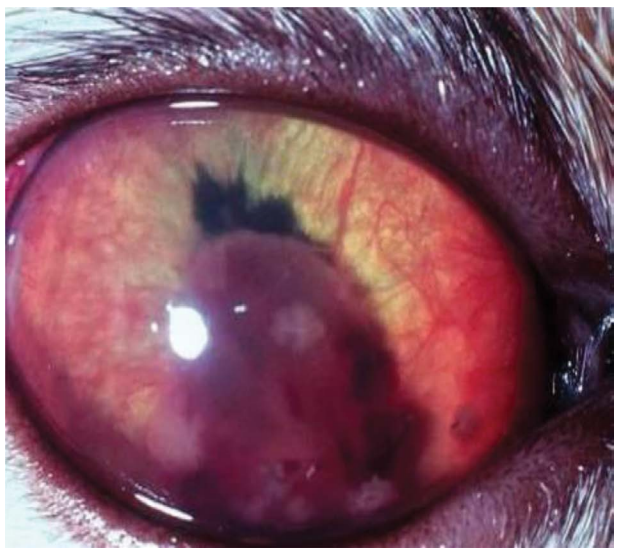


FIGURE 19.17 Fibrin clot, hypopyon, hyphema, iritis, iris neovascularization, miosis, and posterior synechia are found in this cat with FIP.



FIGURE 19.18 This is the same cat as in **Figure 19.17** 2 weeks after initial diagnosis. The cat has now developed iris bombe and secondary glaucoma.

Differential Diagnosis

See Table 19.1.

Diagnosis

Antemortem diagnostic confirmation of FIP remains particularly challenging, if not impossible. Serology can only be used as a guide to indicate current or previous infection. In general, a cat's history, clinical signs, and suggestive laboratory findings lead to a presumptive diagnosis. A presumptive diagnosis may be aided by clinical pathologic alterations, with the total plasma protein frequently very elevated, a polyclonal gammopathy, and elevated serum fibrinogen present. Anterior chamber

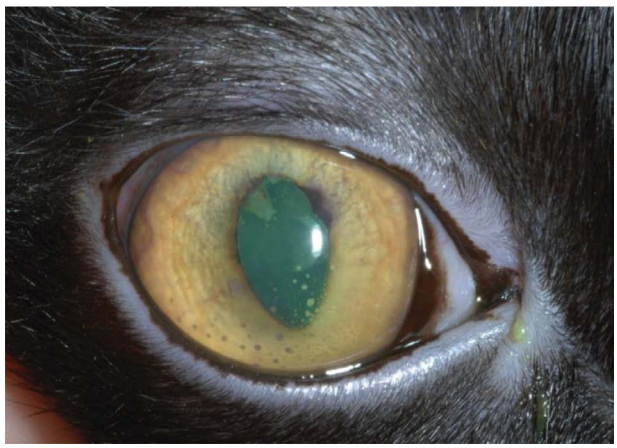


FIGURE 19.19 This cat with FIP has keratic precipitates.

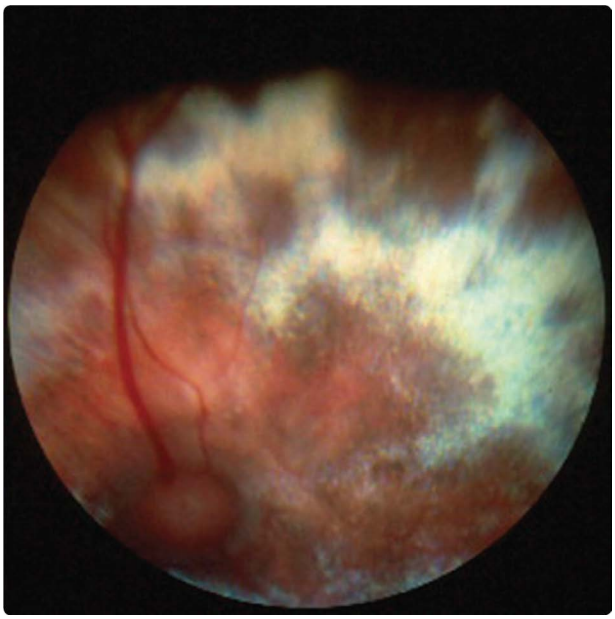


FIGURE 19.20 Focal regions of granulomatous and pigmented chorioretinitis are noticed in this cat with FIP.

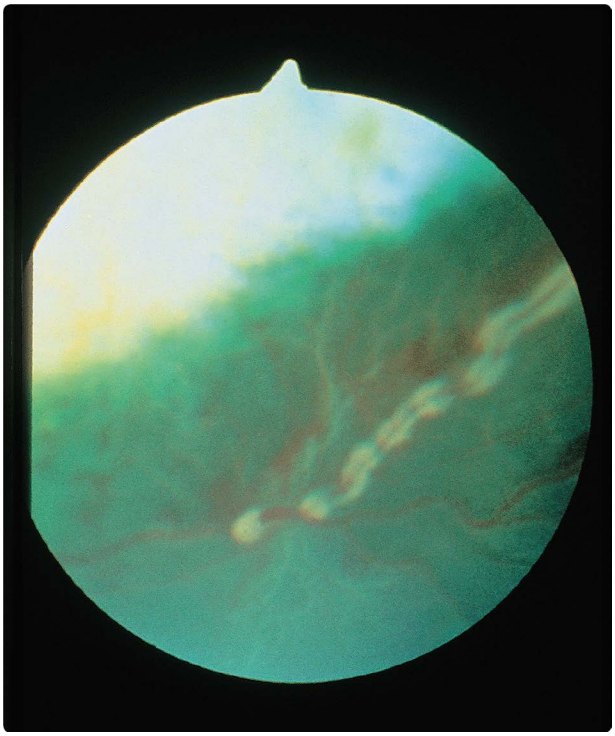


FIGURE 19.21 Perivascular cuffing, retinal edema, and retinal hemorrhage are noticed in the retina of a cat with FIP. (*Courtesy of B. Spiess.*)

paracentesis reveals protein, fibrin, neutrophils, erythrocytes, and mononuclear cells, but this is not specific to FIP cases. Recently, the sensitivity and specificity of an immunocytochemical assay in aqueous humor of cats suspected of having FIP was evaluated and not found to be clinically useful. No antemortem test, including histopathology, has proven to be diagnostic.

Management

There is no known effective treatment for FIP. Therapy for ocular manifestations of FIP is symptomatic for the anterior uveitis and generally includes topical steroids, topical atropine (if secondary glaucoma is not present), and systemic steroids. Response to therapy is generally temporary as the disease progresses.

FELINE LEUKEMIA VIRUS

Definition/Overview

FeLV can cause anterior uveitis (one or both eyes), retinitis, irregular or asymmetrical pupils, and secondary glaucoma.

Etiology

FeLV is a retrovirus whose genetic material is transmitted from host to host as RNA.

Pathophysiology

Infection with FeLV itself causes minimal ocular disease with the exception of its role in lymphosarcoma. The uveal tract is a common site for metastasis of leukemic lymphocytes. Cats with ocular lymphosarcoma may present initially with signs of mild uveitis, including miosis, aqueous flare and keratic precipitates, or subtle iridal masses. As the disease progresses, the iris becomes greatly thickened and distorted with the infiltration of tumor cells. Glaucoma is a common sequela as lymphoma cells infiltrate the iridocorneal angle.

Clinical Presentation

Ocular and periocular clinical signs include orbital masses, eyelid masses, conjunctival and third eyelid masses, anterior uveal masses, anterior uveitis, hypopyon, secondary glaucoma, chorioretinitis, choroidal masses, retinal hemorrhage, retinal detachments, and optic neuritis. Retinal changes include hemorrhages (Figure 19.22), pale retinal vessels (anemia), leukemic infiltrates appearing as multifocal gray opacities, and RDs. Corneal changes are uncommon but include keratitis, edema, and a keratopathy appearing as a wide opaque band of neoplastic stromal lymphoid cells. Conjunctivitis with proliferation of lymph follicles may be noted. Horner syndrome associated with mediastinal lymphosarcoma in FeLV-positive cats has been reported. Isolated iridal tumor formation may occur. Anisocoria, dyscoria, and abnormal pupillary light reflexes ("feline spastic pupil syndrome") have also been associated with FeLV infection of the ciliary ganglia and short ciliary nerves. The prognosis for cats affected with feline spastic pupil syndrome is poor.

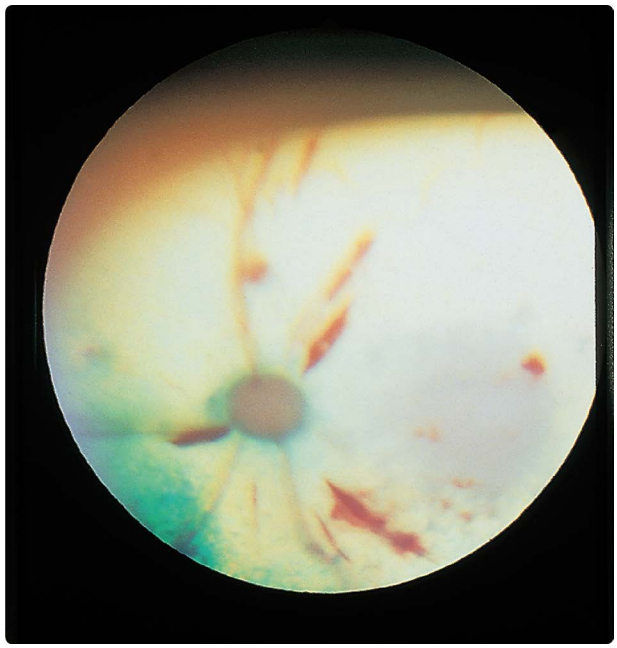


FIGURE 19.22 Linear flame hemorrhages of the nerve fiber layer and a focal exudative retinal detachment are noticed in this FeLV-positive cat.

Differential Diagnosis

See Table 19.1.

Diagnosis

Anterior chamber or vitreal paracentesis may reveal neoplastic cells in cases of lymphosarcoma but is usually nonspecific as to the etiology. A serum enzyme-linked immunosorbent assay (ELISA) antigen test is a good initial test for screening. If positive, indirect IFA testing can be performed on a peripheral blood smear of ELISA-positive cats. Indirect FA, ELISA, or PCR on bone marrow aspirates, lymph node biopsies, or biopsies of intraocular masses may also be useful. FeLV antigens and proviral DNA have been found in normal corneal tissue, and all potential donors should be screened prior to corneal transplantation.

Management

Therapy for FeLV includes management of opportunistic infections and supportive therapy that is directed toward the ocular and systemic clinical signs of each patient. Cats with an increased risk of exposure to FeLV should be vaccinated regularly.

FELINE PANLEUKOPENIA VIRUS

Definition/Overview

Feline panleukopenia virus is a parvovirus known to cause cerebellar hypoplasia and retinal dysplasia, with retinal rosette formation, loss of normal retinal layered architecture, and reduced thickness of the neural retina in kittens. Focal retinal dysplasia appears as sharply defined hyperreflective areas in the tapetal fundus and depigmented areas in the nontapetal fundus. Optic nerve hypoplasia may also occur with the feline panleukopenia virus.

FELINE IMMUNODEFICIENCY VIRUS

Definition/Overview

Feline immunodeficiency virus (FIV) is a lentivirus. FIV infection results in progressive loss of $CD4^+$ T-helper cells early in the infection, followed by depletion of $CD8^+$ T cells in the advanced stages of the disease. Anterior uveitis, lens luxation, pars planitis, and conjunctivitis are reported with FIV. Anterior uveitis and chorioretinitis are the most common ocular findings in cats coinfected with both FIV and *Toxoplasma gondii*. Currently marketed PCR assays for the detection of FIV lack sensitivity and vary significantly in accuracy, as false-positive results are higher in FIV-vaccinated cats than in unvaccinated cats. Positive serum antibody titers for toxoplasmosis are more common in FIV-positive cats. When testing for toxoplasmosis in these cases, it is important to test for both IgM and IgG, as up to 43% of coinfected cats can be positive for IgM but not for IgG.

FELINE SARCOMA VIRUS

Definition/Overview

Feline sarcoma virus is a naturally occurring, replication-defective, acute, transforming FeLV that has incorporated one of several cellular oncogenes. Under experimental conditions, it has been associated with uveal melanoma and anterior uveitis in cats. It is unknown if it plays any role in naturally occurring uveitis in cats.

PROTOZOAL INFECTION

LEISHMANIASIS

Definition/Overview

Leishmaniasis is of major public health significance in Central and South America, the Mediterranean region, Africa, and Asia. The visceral and cutaneous forms are associated with blepharitis, conjunctivitis, keratitis, KCS, anterior uveitis, rubeosis iridis, and severe panuveitis. Dogs are more commonly affected than cats.

Etiology

Leishmania spp. are diphasic protozoan parasites. Dogs are considered important primary reservoirs of *Leishmania* spp., and sandflies (*Phlebotomus* or

Lutzomyia spp.) are the vectors. *Leishmania donovani* has been reported as the cause of leishmaniasis of dogs within the United States and Canada. Naturally occurring leishmaniasis has been increasingly reported in cats in the last few years. Feline leishmaniasis is generally caused by *L. mexicana* in Texas, *L. major* in Egypt, and *L. (Viannia) panamensis* in Brazil. *L. infantum*, a causative agent of feline leishmaniasis in southern France and Italy, also causes leishmaniasis in dogs.

Pathophysiology

Transmission to vertebrates is via bites from infected sandflies, and sandflies are infected by reservoir hosts. The incubation period may be a few months to between 3 and 4 years. Over 90% of infected dogs develop clinical disease, and 81% of infected dogs will develop ocular lesions that are typically bilateral. The inflammation is mononuclear with the organism found in histiocytes.

Clinical Presentation

Cutaneous lesions begin on the head and can result in alopecia, scaliness, and vesicular lesions that may appear similar to pemphigus complex. Focal granulomatous blepharitis and conjunctivitis may occur. Scleritis, superficial or deep keratitis, KCS, anterior uveitis, and secondary glaucoma are also reported with *Leishmania* infections (**Figure 19.23**) in dogs, but the choroid and retina are usually spared. Documented lesions also occur in intraocular, extraocular, and adnexal muscles as well as the optic nerve of dogs. In cats, ocular lesions include ulcerative keratitis, panuveitis, and secondary glaucoma.

Differential Diagnosis

See Table 19.1.

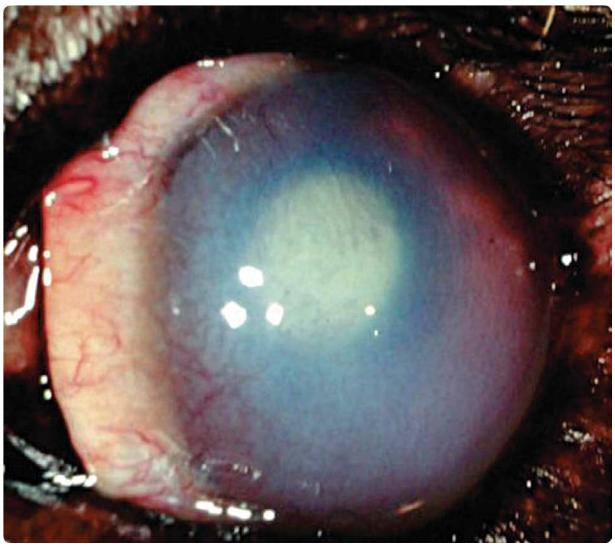


FIGURE 19.23 Leishmaniasis is causing keratouveitis in this dog from Italy. (*Courtesy of A. Guandalini.*)

Diagnosis

The *Leishmania* organism can be diagnosed with histopathologic or immunoperoxidase evaluation of cutaneous or ocular biopsy specimens, PCR of anticoagulated blood, or isolation of the organism from the subcutaneous tissue, bone marrow, lymph node aspirates, or skin impression smears. Serologic tests are available that use ELISA and indirect IFA testing.

Management

Elimination of the organism is difficult, and recurrence is common, so the prognosis is guarded. Allopurinol combined with meglumine antimoniate has been recommended for treatment. Allopurinol combined with sodium stibogluconate has been shown to be successful in the treatment of canine leishmaniasis without recurrence for over 24 months. Symptomatic therapy is used for the ocular lesions such as topical anti-inflammatory agents.

TOXOPLASMOSIS

See also Chapter 21.

Definition/Overview

Ocular signs of toxoplasmosis are more common in cats than dogs. Cats are both the definitive and the intermediate hosts of toxoplasmosis.

Etiology

Toxoplasmosis is an infection caused by the obligate intracellular coccidian parasite *Toxoplasma gondii*.

Pathophysiology

As cats are the definitive hosts, only they can shed oocysts that can be infective to other species. Cats can shed oocysts for about 7 days, beginning 3–5 days after infection. Oral ingestion of tissue cysts or oocysts results in spread of *Toxoplasma* tachyzoites to extraintestinal organs via the blood or lymph. Focal necrosis of the heart, eye, and brain results due to proliferation of *T. gondii*. Uveitis secondary to toxoplasmosis may result from rapid replication of tachyzoites within ocular tissue or from deposition of immune complexes within uveal tissue. Intraocular production of antibodies specific for *T. gondii* has been reported, and the organism has been identified within the uveal tract by histopathology and in the aqueous humor by PCR.

Clinical Presentation

Toxoplasmosis in cats occurs with ocular signs alone, or it can occur with generalized systemic involvement of the liver, heart, lungs, and meninges. The uveitis in cats is most frequently documented as multiple foci of retinitis or retinochoroiditis (**Figure 19.24**) with varying

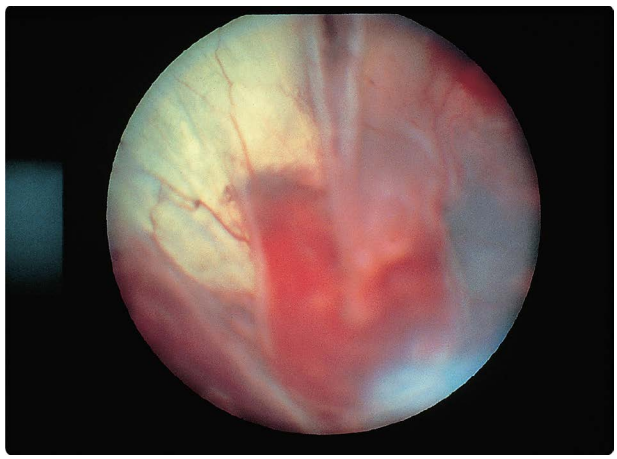


FIGURE 19.24 Extensive retinal hemorrhage and detachment are associated with intraocular toxoplasmosis in this cat.

degrees of anterior uveitis. Clinical signs in dogs (in decreasing order of frequency) are anterior uveitis, retinitis, choroiditis, extraocular myositis, scleritis, optic neuritis, and keratoconjunctivitis.

Differential Diagnosis

See Table 19.1.

Diagnosis

The definitive diagnosis of toxoplasmosis remains challenging. The presumptive diagnosis of toxoplasmosis can be made in cats with signs of uveitis and a positive serum titer IgM and/or IgG titer. Cats coinfected with FIV may never seroconvert from an IgM titer to an IgG titer. ELISA tests for detection of IgM antibodies and toxoplasma antigen have been developed for diagnosis of toxoplasmosis. Levels of the IgM class of antibody rise and fall over approximately 3–4 months after infection, whereas those of the IgG class of antibody may rise more slowly and remain elevated in cats for years after exposure to *T. gondii*. Detection of antibodies in the serum and aqueous humor can be compared through the calculation of a Goldmann-Witmer coefficient (C value). A C value of 3 or greater is consistent with local production of antibody within the globe. Histologic demonstration of the parasite is the sole definitive means of confirmation. Fecal examination for *Toxoplasma* oocysts can be useful to determine if the cat is shedding and potentially infectious for other animals or humans.

Management

Toxoplasmosis is a zoonotic disease. Owners should be instructed in basic hygiene rules to prevent toxoplasmosis, including daily cleaning of the litterbox, restriction of hunting (keep cats indoors), and do not feed cats raw or undercooked meat. Treatment for toxoplasmosis is most commonly done with oral clindamycin for 3–4 weeks along with topical and systemic corticosteroids and topical atropine. In cats with confirmed titers, uveitis may be chronic and require chronic therapy to control the uveitis.

FUNGAL DISEASES

See also Chapter 21.

Ocular manifestations of disseminated mycotic infections are relatively common in endemic areas. Systemic mycotic infections that commonly involve the eyes include cryptococcosis, histoplasmosis, blastomycosis, and coccidioidomycosis. Medium- to large-breed dogs are most commonly affected as their exposure to the organism is greater than small dogs. Inhalation is believed to be the primary route of infection, with hematogenous spread to the eye. Diagnosis is based on clinical and ocular signs, organism identification from ocular or other tissues, fungal culture, histopathology, serological testing (urine or serum), and imaging (thoracic and abdominal). The typical histopathologic lesion for systemic mycoses is granulomatous or pyogranulomatous inflammation with identification of organisms enhanced by special stains. Less common fungi/yeasts that may cause ocular signs (including conjunctivitis, endophthalmitis, keratitis, and/or chorioretinitis) are *Candida* spp., *Geotrichum* spp., *Aspergillus* spp., *Sporotrichum* spp., and *Paecilomyces* spp. *Candida* has caused corneal ulcers in cats.

CRYPTOCOCCOSIS

Definition/Overview

Cryptococcosis is an opportunistic systemic fungal infection. It is not a contagious disease. It is considered to be the most common feline systemic fungal infection. Birds such as pigeons are considered to be significant vectors of *Cryptococcus* spp.

Etiology

Cryptococcosis is caused by the saprophytic yeast-like organism *Cryptococcus neoformans* or *Cryptococcus gatii*. *C. neoformans* is associated with soil enriched with avian feces containing high levels of nitrogen. *C. neoformans* is yeast-like organism (3.5–7 microns) with a thick capsule.

Pathophysiology

The organism is most commonly inhaled from the environment. Cryptococcosis may infect the eye by hematogenous means or by extension from the nose or CNS. The organisms may be found in the ocular tissues, including the vitreous.

Clinical Presentation

Clinical signs in dogs are mainly associated with the CNS but ocular, upper respiratory, or cutaneous lesions

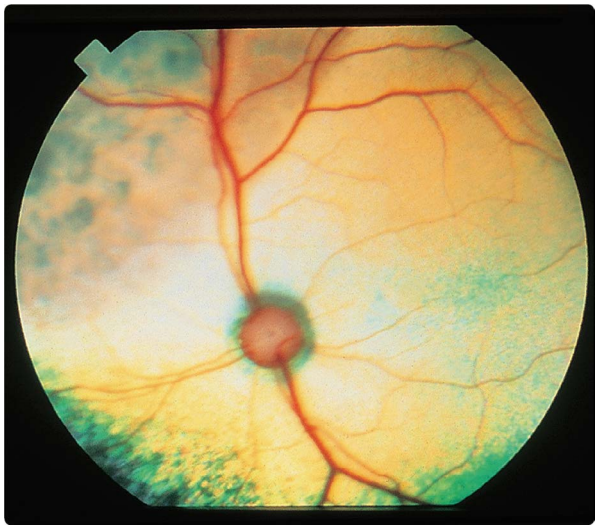


FIGURE 19.25 A large, focal, granulomatous lesion with hyperpigmented regions caused by cryptococcosis in a cat.

are also regularly found. Ocular or periorbital lesions are found in 20%–40% of dogs. In cats, clinical signs are primarily associated with the nasal passages, cutaneous lesions, or the CNS. Common ocular lesions in cats include chorioretinitis, RDs, anterior uveitis, exophthalmos, and optic neuritis (Figures 19.25 and 19.26).

Differential Diagnosis

See Table 19.1.

Diagnosis

Diagnosis is based on identification or culture of the organism by cytology of tissue aspirates, histology, or serologic testing. Organisms may be identified in subretinal or vitreal aspirates or cerebrospinal fluid (CSF) tap. A latex agglutination test against capsular antigens is available, and the titers appear to correlate with disease severity and response to treatment.

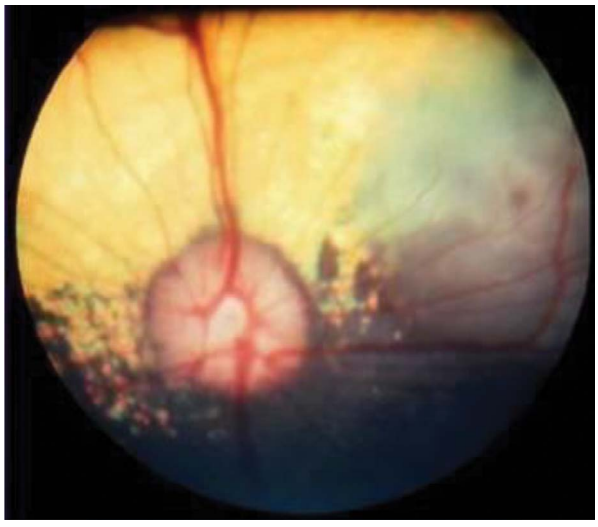


FIGURE 19.26 A large, focal, granulomatous lesion with hyperpigmented regions caused by cryptococcosis in a dog.

Management

Cryptococcosis has been successfully treated in cats with itraconazole and fluconazole, which may have fewer side effects than ketoconazole and amphotericin B. Numerous systemic antifungal agents, used either alone or in combination, have shown efficacy in dogs, including itraconazole, amphotericin B, flucytosine, ketoconazole, and fluconazole. Therapy is symptomatic for the anterior uveitis and generally includes topical steroids and topical atropine (if secondary glaucoma is not present).

COCCIDIOIDOMYCOSIS

Definition/Overview

Coccidioidomycosis is a systemic fungal infection found in dogs and rarely in cats. It is not a contagious disease. It appears to be a posterior segment disease, which can extend to the anterior segment.

Etiology

Coccidioidomycosis is caused by a dimorphic fungus *Coccidioides immitis*, found in the alkaline soil of the dry climate of the Southwestern United States, Western Mexico, and Central America.

Pathophysiology

Infection is through inhalation of arthrospores from the environment. Hematogenous and lymphatic dissemination of endospores causes disseminated disease. The eye is one of several organs that are most commonly affected.

Clinical Presentation

Systems commonly affected in dogs and cats include the bones, joints, respiratory tract, CNS, heart, lymph nodes, and eyes. Ocular signs may appear first and consist of granulomatous panuveitis, anterior uveitis, secondary glaucoma, orbital cellulitis, keratitis, retinitis, and RDs (Figure 19.27). Cats may also have subpalpebral, subconjunctival, and periocular swelling. Between 30% and 50% of cases in dogs have ocular signs.

Differential Diagnosis

See Table 19.1.

Diagnosis

Diagnosis is based on identification of the organism by cytology of tissue aspirates, histology, or serologic testing. Vitreous or subretinal aspiration may reveal endospores. Serologic tests (precipitin and complement



FIGURE 19.27 A large chorioretinal granuloma caused by *C. immitis* is present in the nontapetum of this dog.

fixation) are available. Histopathologically, a granulomatous uveitis, either unilateral or bilateral, is most common. The cornea, iridocorneal angle, ciliary body, retina, and choroid are affected. Hyphema and vitreal hemorrhage may be present.

Management

Oral ketoconazole, fluconazole, itraconazole, and amphotericin B have been used in dogs. Long-term use of ketoconazole in dogs has been found to be associated with the development of cataracts. Cats have been successfully treated with fluconazole. Therapy is symptomatic for the anterior uveitis and generally includes topical steroids and topical atropine (if secondary glaucoma is not present).

HISTOPLASMOSIS

Definition/Overview

Histoplasmosis is a systemic fungal infection of dogs and cats. It is a primary respiratory disease with dissemination to liver, spleen, intestine, lymph nodes, CNS, and bone. Histoplasmosis is widespread in alkaline soils of North and South America but particularly in the Ohio, Mississippi, and Missouri River valleys. Young hunting breeds of dogs may have an increased risk.

Etiology

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*. *H. capsulatum* organisms are 2–4 microns, round to oval, and typically found within macrophages.

Pathophysiology

Infective conidia are either inhaled or ingested. Dissemination is hematogenous or via the lymphatics to the lungs, GI tract, liver, bone marrow, and eyes, resulting in a granulomatous inflammatory response. The choroid appears to be a preferred target region in the eye.

Clinical Presentation

Experimentally, ocular signs were identified in about 60% of eyes in dogs. Ocular signs in dogs and cats include granulomatous chorioretinitis (Figure 19.28), optic neuritis, RD, anterior uveitis, blepharitis, and conjunctivitis. Cats can also be affected with mass lesions of the conjunctiva and third eyelid (Figure 19.29).

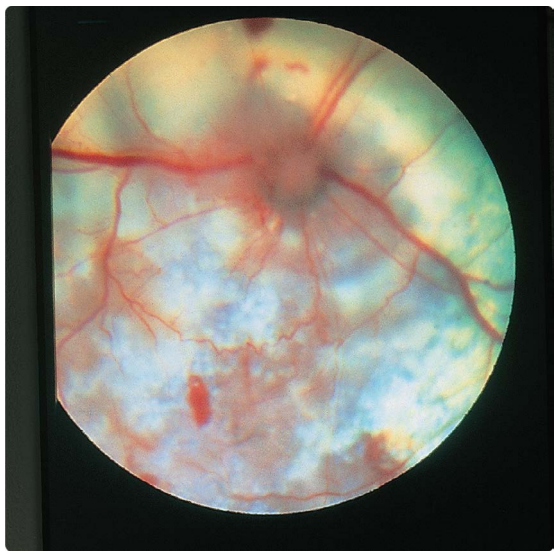


FIGURE 19.28 Retinal hemorrhage, peripapillary retinal edema, and flat retinal detachment due to histoplasmosis-induced chorioretinitis in a cat.

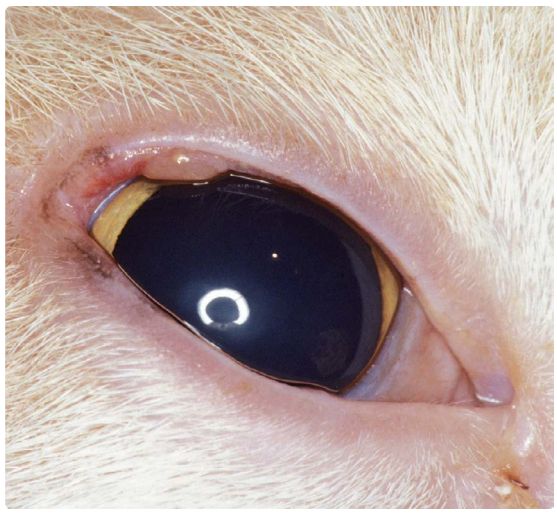


FIGURE 19.29 Histoplasmosis is present as a lump in the upper eyelid of this cat.

Differential Diagnosis

See Table 19.1.

Diagnosis

Diagnosis is based on identification or culture of the organism by cytology of tissue aspirates, histology, or serologic testing. Normocytic, normochromic, nonregenerative anemia is the most common hematologic abnormality. The organism may occasionally be seen in circulating mononuclear cells and eosinophils. Cats and dogs with disseminated histoplasmosis may have negative serologic tests. In dogs, serologic diagnosis with an agar gel immunodiffusion (AGID) test is 80% sensitive and 100% specific.

Management

Cases may respond to itraconazole or fluconazole alone. Combined treatment with amphotericin B and itraconazole may be more efficacious in patients with severe or fulminating disease. Cats have been successfully treated with itraconazole and fluconazole. In both dogs and cats, long-term therapy is generally required, and recurrence is common. Therapy is symptomatic for the anterior uveitis and generally includes topical steroids and topical atropine (if secondary glaucoma is not present).

BLASTOMYCOSIS

Definition/Overview

Blastomycosis is a systemic fungal infection that usually originates in the lungs and then disseminates to other organ systems. All systems of the body may be infected. The disease affects dogs more than cats. Bluetick Coonhounds, Treeing-walker Coonhounds, Pointers, and Weimaraners have been reported to have the highest risk of *Blastomyces dermatitidis* infection.

Etiology

Blastomycosis is caused by the dimorphic fungus *B. dermatitidis*. Water and soil contamination play an important role in the spread of blastomycosis. The budding yeast found in tissue is 5–20 microns with a thick, double-contoured wall.

Pathophysiology

Infection usually occurs by inhalation of infective conidiophores from the environment. Alveolar macrophages phagocytize the conidia. These cells may be transported into the pulmonary interstitium from where they gain access to the vascular system and lymphatics. Hematogenous and lymphatic dissemination leads to pyogranulomatous disease. The eyes are commonly affected in both dogs and cats.

Clinical Presentation

Ocular signs include conjunctivitis, corneal edema, corneal vascularization, anisocoria, anterior uveitis (Figure 19.30), secondary glaucoma, exophthalmos (retrobulbar inflammation), granulomatous chorioretinitis (Figures 19.31 and 19.32), RD, and optic neuritis (Figure 19.33).

Differential Diagnosis

See Table 19.1.

Diagnosis

Diagnosis is based on identification or culture of the organism by cytology of tissue aspirates, histology, or serologic testing. Detection of antigen in the urine is the

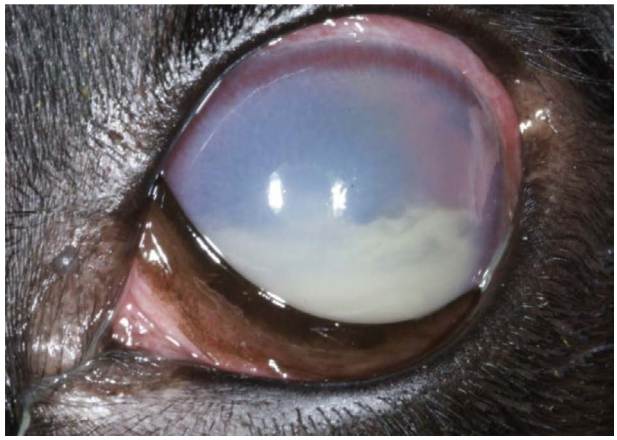


FIGURE 19.30 Scleral injection, deep perilimbal neovascularization, diffuse corneal edema, and hypopyon secondary to severe anterior uveitis in a dog with blastomycosis.

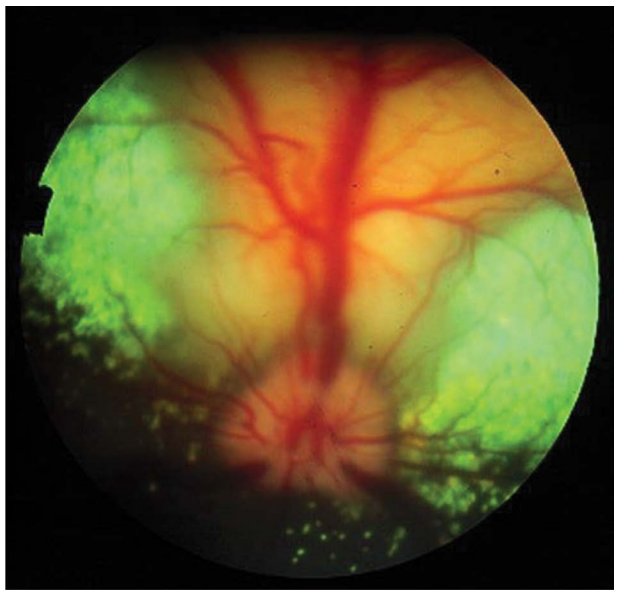


FIGURE 19.31 Large, subretinal granuloma in the central tapetum of a dog with blastomycosis.

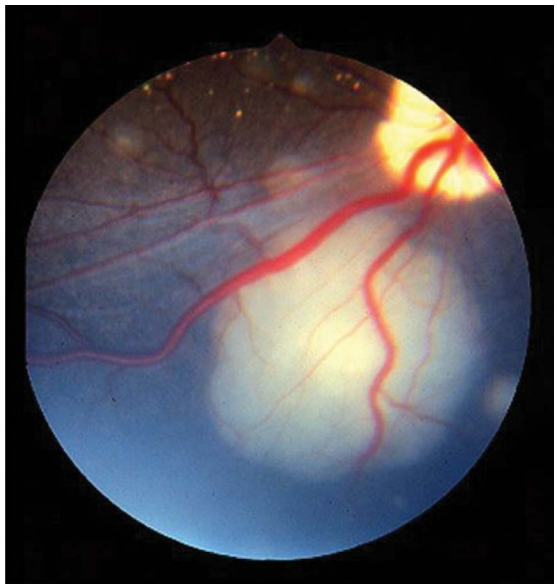


FIGURE 19.32 A subretinal granuloma in the nontapetum is present in this dog due to blastomycosis.

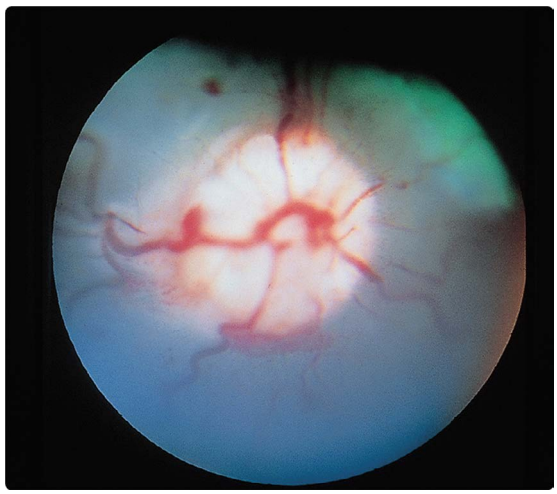


FIGURE 19.33 Optic neuritis, peripapillary retinal edema, and retinal hemorrhages in a dog with blastomycosis.

preferred method of diagnosis if the organism cannot be found of cytology or culture. The sensitivity of the urine antigen test is 93%.

Management

Itraconazole, ketoconazole, fluconazole, and amphotericin B are effective in treating some cases of canine blastomycosis, with itraconazole being the most commonly utilized. Itraconazole and itraconazole/amphotericin B can be used to treat blastomycosis in the cat. Therapy is symptomatic for the anterior uveitis and generally includes topical steroids and topical atropine (if secondary glaucoma is not present). The use of systemic anti-inflammatory agents will improve the prognosis for chorioretinal lesions, particularly the use of anti-inflammatory dose of steroids, but not all clinicians are



FIGURE 19.34 Severe granulomatous chorioretinitis with subretinal granuloma and retinal detachment caused by aspergillosis in a dog.

comfortable with this treatment regimen and will recommend systemic nonsteroidal agents instead.

ASPERGILLOSIS

Definition/Overview

Aspergillosis is caused by the filamentous fungus *Aspergillus* spp. Animals are infected opportunistically after inhaling *Aspergillus* spores. Disseminated aspergillosis has been reported to cause panuveitis, chorioretinitis, exudative RDs, and endophthalmitis (Figure 19.34). Recently, histopathologic evaluation of the eye of two different dogs demonstrated lens capsular rupture and intralenticular invasion of organism. German Shepherd Dogs are at increased risk. Diagnosis is made based on identification and culture of urine sediment, serum, synovial fluid, vitreous, lymph node, or intervertebral disc fine-needle aspirate biopsy specimens. Treatment is directed at eliminating the organism by administering amphotericin B, itraconazole, or fluconazole. Long-term therapy is required. Regardless, the prognosis for recovery from disseminated aspergillosis is poor.

ALGAE

PROTOTHECOSIS

Definition/Overview

Protothecosis is a rare and often fatal algal disease in the dog. The disseminated disease is most common in large-breed dogs and may be more common in females and Boxer dogs.

Etiology

Protothecosis is caused by two species of green algae, *Prototheca zopfii* (causes disseminated disease) and *P. wickerhamii* (associated with skin disease). These organisms are found in animal wastes and sewage. They are transmitted by ingestion of contaminated food, soil, or water.

Clinical Presentation

Systemic features in dogs include intermittent or protracted bloody diarrhea, CNS signs, skin lesions, lymphadenopathy, respiratory signs, and renal signs. Cats are reported to have skin lesions only. Ophthalmic signs are severe in >50% of the reported cases in dogs and include focal, diffuse, granulomatous chorioretinitis (Figures 19.35 and 19.36), vitreal exudate, RDs and degeneration, retinal hemorrhage, and panuveitis. The ocular signs may be the initial clinical abnormality and are usually bilateral.

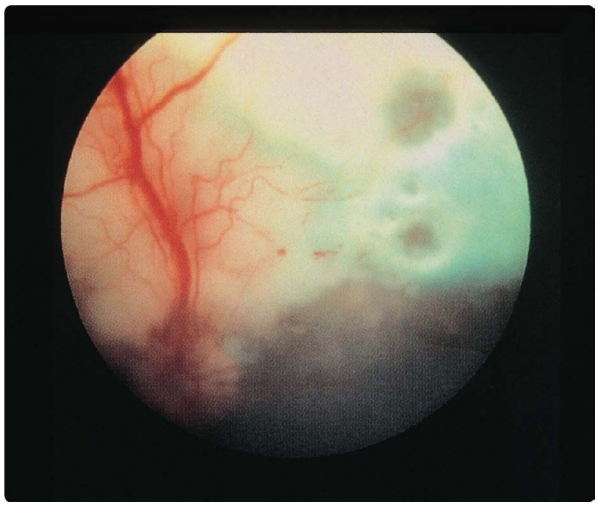


FIGURE 19.35 A subretinal granuloma elevates the retinal vessels dorsal to the optic disc. Focal hyperpigmented areas of chorioretinitis are also found in this dog with protothecosis.



FIGURE 19.36 Note the posterior synechia and vitreal opacification from protothecosis in the dog in Figure 19.35.

Differential Diagnosis

See Table 19.1.

Diagnosis

Diagnosis is by clinical signs, tissue aspiration, cytologic and histologic examination, and culture. Because colitis is one of the more common systemic signs associated with protothecosis, any dog with a history of hemorrhagic diarrhea and ocular lesions should be considered to be a candidate for this diagnosis.

Management

Amphotericin B and itraconazole have been shown to be initially effective, but most systemic infections are difficult to control, and the prognosis is grave. Therapy is symptomatic for the anterior uveitis and generally includes topical steroids and topical atropine (if secondary glaucoma is not present).

RICKETTSIA

EHRLICHIA CANIS

See also Chapter 21.

Definition/Overview

Ehrlichiosis is a tick-borne systemic disease known to be caused by a variety of rickettsial species. Several species of *Ehrlichia* are known to infect the dog, although *E. canis* is the most common. *E. canis* infection is associated with acute, subclinical, and chronic phases.

Etiology

E. canis is a small pleomorphic rickettsial organism that infects circulating mononuclear cells. The brown dog tick, *Rhipicephalus sanguineus*, is the arthropod vector of *E. canis*.

Pathophysiology

The prevalence of ocular lesions in canine ehrlichiosis has been reported as 10%–37%, and they are typically bilateral. Ocular lesions result from vasculitis, a platelet deficiency, and/or hyperviscosity. Chronic disease occurs in those dogs unable to mount an effective immune response to the organism. Neurologic signs consistent with meningoencephalitis are typical of dogs with disease manifestations that develop during chronic infection.

Clinical Presentation

Systemic features include lymphadenopathy, fever, nasal discharge, thrombocytopenia, and pancytopenia with an underlying vasculitis. Ocular signs are most commonly bilateral and may occur in both the acute and

chronic forms. Anterior uveitis and exudative retinal detachments are the most common ocular signs (Figures 19.37 and 19.38). Other ophthalmic signs include conjunctival and iridal petechia, panuveitis, retinitis, vasculitis, and tortuous retinal vessels with gray perivascular circular retinal foci in the early stages. Chorioretinitis and retinal vasculitis appearing as dark gray spots with surrounding hyperreflectivity in the tapetal fundus, subretinal hemorrhages, RD, optic neuritis, and papilledema are found in the later stages. Iridal petechiae, hyphema, and keratic precipitates may also be prominent (Figure 19.39).

Differential Diagnosis

See Tables 19.1 and 19.2.



FIGURE 19.37 Mild, diffuse corneal edema, fibrin clot, hyphema, and iritis in a dog with ehrlichiosis.

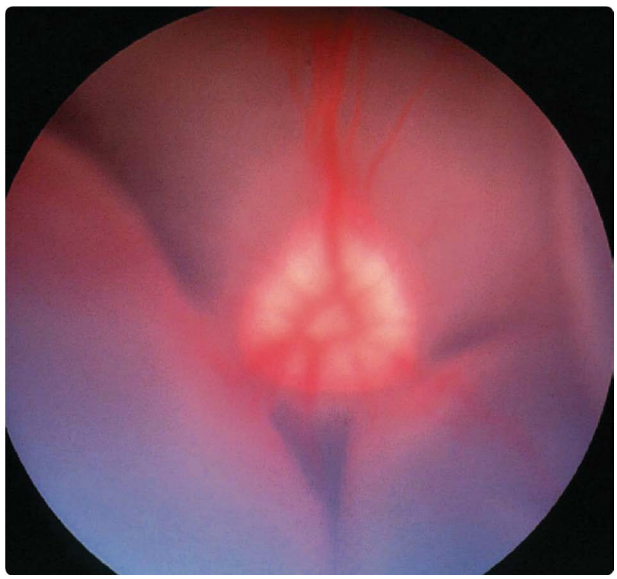


FIGURE 19.38 Retinal detachment with vasculitis and mild subretinal exudate involves nearly the entire retina in this dog with ehrlichiosis.



FIGURE 19.39 A blood clot is attached to the anterior lens capsule in this dog with ehrlichiosis. This dog has mild episcleral injection, perilimbal edema, and a blood clot in the anterior chamber secondary to anterior uveitis due to ehrlichiosis.

TABLE 19.2 Etiologies of hyphema and retinal hemorrhage associated with ophthalmic manifestations of systemic disease in dogs and cats

- Blood parasites
- Coagulopathies
- Hypertension (common cause of retinal hemorrhage)
- Hyperviscosity syndromes
- Intraocular neoplasia
- Retinal detachment
- Trauma (penetrating wounds of globe and, possibly, blunt trauma to head or globe)
- Uveitis associated with bacterial/fungal/viral/parasitic/immune-mediated diseases

Etiologies are listed in alphabetical order, not in order of importance.

Diagnosis

A diagnosis of ehrlichiosis is usually made on the basis of clinical signs, hematologic abnormalities, and serology. Nonregenerative anemia and thrombocytopenia are the predominant hematologic findings. Diagnosis of ehrlichiosis also involves direct visualization of morulae in peripheral blood smears, detection of *E. canis* antibodies, or PCR amplification of *Ehrlichia* spp. DNA.

Management

Tetracycline and doxycycline are used for systemic therapy. Anti-inflammatory doses of oral steroids may also improve res olution of ocular signs. Therapy is symptomatic for the anterior uveitis and generally includes topical steroids and topical atropine (if secondary glaucoma is not present).

ROCKY MOUNTAIN SPOTTED FEVER

Definition/Overview

Rocky Mountain spotted fever (RMSF) is a rickettsial disease of several vertebrate species that is transmitted by numerous ticks of the genus *Dermacentor*, *Amblyomma*, and *Rhicephalus*. Rodents and other small mammals serve a reservoirs for *Rickettsia rickettsii*.

Etiology

RMSF is caused by *Rickettsia rickettsii*, which is a small coccobacillary, Gram-negative obligate intracellular bacterium.

Pathophysiology

After entering the circulatory system, the rickettsiae replicate in the endothelial cells of capillaries and small blood vessels. Direct damage to the endothelial cells leads to vasculitis, necrosis, and increased vascular permeability. This process results in extravasation of fluid and blood cells into the extravascular fluid space. Varying degrees of damage are shown by the extent of ocular abnormalities.

Clinical Presentation

RMSF has ocular signs, including petechia of the conjunctiva and iris, scleral injection/edema, anterior uveitis, hyphema, retinal edema, and focal retinal petechiae associated with a mucopurulent oculonasal discharge, cough, lymphadenopathy, muscle and joint pain, vasculitis, splenomegaly, and thrombocytopenia (Figures 19.40 and 19.41).

Differential Diagnosis

See Tables 19.1 and 19.2.

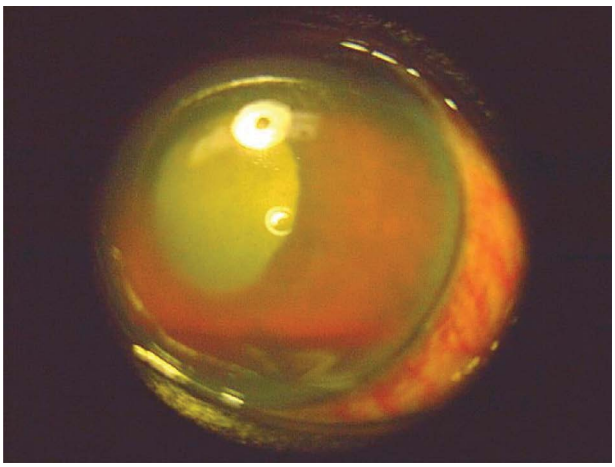


FIGURE 19.40 Episcleral injection, perilimbal corneal edema, hyphema, and iritis secondary to Rocky Mountain spotted fever in a dog.



FIGURE 19.41 Multiple, focal, deep retinal hemorrhages are present in this dog with Rocky Mountain spotted fever.

Diagnosis

Diagnosis is based consistent history, bloodwork, and on direct immunofluorescent testing for the organism, serologic testing, PCR, or rickettsial culture.

Management

Doxycycline is used for systemic therapy. Therapy is symptomatic for the anterior uveitis and generally includes topical steroids and topical atropine (if secondary glaucoma is not present).

CHLAMYDIA

Definition/Overview

Chlamydia felis produces a mild conjunctivitis in cats and is considered a zoonotic disease. C. *felis* is endemic in cats worldwide and may also infect the respiratory tract causing rhinitis and respiratory disease.

Etiology

C. *felis* is an obligate intracellular bacterium that contains both DNA and RNA.

Pathophysiology

Chlamydophilosis in transmitted by direct contact with other cats, aerosols, or fomites. Ocular disease results from host cell lysis that occurs during the release of elementary bodies. If untreated, infection with C. *felis* can produce chronic conjunctivitis. Asymptomatic carrier states can exist and are likely significant in spreading the organism within a population. Chlamydophilosis

may be complicated by coinfection with other microorganisms including *Mycoplasma* spp., *Bordetella bronchiseptica*, feline calicivirus, FHV-1, and FIV.

Clinical Presentation

Initially, the disease is unilateral, becoming bilateral in 7–14 days. Early in the disease, the conjunctiva is chemotic, hyperemic, and the ocular discharge is serous. Mild nasal discharge and sneezing may occur. As the disease progresses, the discharge becomes mucoid and then mucopurulent, the chemosis decreases, and the conjunctiva becomes hyperemic and thickened. Follicular conjunctivitis occurs in chronic untreated cases.

Differential Diagnosis

Conjunctivitis is found in many types of eye diseases. It may be infectious (herpesvirus, calicivirus, *Mycoplasma* and *Chlamydia* in cats) or noninfectious.

Diagnosis

Diagnosis of chlamydophilosis has been established by using a variety of ELISAs or using cell culture. Demonstration of the characteristic inclusion body within the conjunctival epithelial cell cytoplasm on cytologic examination of Giemsa-stained conjunctival smears may be helpful in lending support for a diagnosis of chlamydophilosis (Figure 19.42). However, inclusions are typically only detectable during early infection and in some cases not at all. PCR assays have become available for the diagnosis of *C. felis*.

Management

Treatment of chlamydial conjunctivitis consists of topical tetracycline, erythromycin, rifampin, fluoroquinolones, or azithromycin for several weeks. Generally, topical tetracycline q.8 h. for 3 weeks is effective. Systemic therapy with oral doxycycline may also be necessary. Oral azithromycin appears to be ineffective in clearing infection. Therapy should be continued for several weeks after clinical signs subside. Recurrence of disease is common in catteries and research colonies due to the short immunity to *C. felis*. *C. felis* may cause disease in humans; therefore, owners and technicians are advised to exercise care and observe strict hygiene when handling or treating infected cats. Vaccination may be necessary to prevent reoccurrence, particularly in catteries.

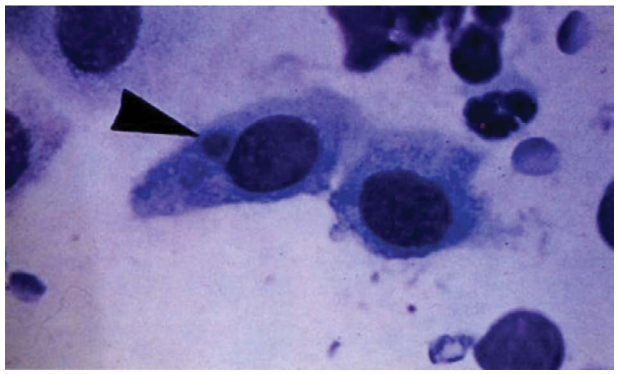


FIGURE 19.42 Chlamydial inclusion body (arrowhead) in epithelial cell from a kitten with acute conjunctivitis. Giemsa stain.

NEMATODIASIS

Dirofilariasis, caused by *Dirofilaria immitis*, is the most commonly reported intraocular nematode of dogs in North America. Ocular filariasis is associated with aberrant migration of immature (fourth-stage) canine heartworm larvae in the anterior chamber or vitreous with development into immature adults or fifth-stage larvae. Signs of anterior uveitis are evident, and the photophobic filarial larva may move from the anterior to posterior chamber. The immature heartworm must be surgically removed to be curative, and surgical removal has about a 90% success rate in removal and preservation of vision. The most commonly reported ocular complication is persistent corneal edema. Angiostrongylosis (French heartworm) caused by *Angiostrongylus vasorum* has been reported in dog and wild canids and may cause similar ocular signs as *Dirofilaria immitis*. Ocular larval migrans (*Toxocara canis* and *Baylisascaris procyonis*) causes anterior uveitis and focal chorioretinitis. Visual impairment is generally mild. Diagnosis is by serologic testing and larval identification. Onchocerciasis, caused by *Onchocerca lupi*, has been reported in dogs and cats. Affected animals may develop conjunctival, scleral, or periorbital masses but may also develop significant panuveitis and secondary glaucoma. Surgical removal may be curative, but chronic medical therapy may also be necessary, including oral steroids, oral doxycycline, oral ivermectin or selamectin, and oral melarsomine or emodepside. Microfilaria were recently identified in the corneal biopsies of seven dogs from Brazil with varying degrees of chronic vascular keratitis with corneal degeneration. The species of microfilaria was not identified, but case responded to oral doxycycline and ivermectin.

MISCELLANEOUS SYSTEMIC DISEASES

Ocular manifestations of hypercalcemia from hyperparathyroidism, neoplasia, renal failure, and hypoadrenocorticism may be associated with white, perilimbal calcium crystals on the conjunctiva, corneal calcification, corneal degeneration, and cataracts. Sustained hypocalcemia due to primary hypoparathyroidism, postparturient hypocalcemia, acute kidney injury or chronic kidney disease, acute pancreatitis, and intestinal malabsorption can cause focal punctate to linear cataracts to form in the anterior and posterior cortices of the lens of dogs and cats.

HYPERVISCOSITY SYNDROME

Definition/Overview

Hyperviscosity syndrome results from abnormal microcirculatory changes due to increased serum viscosity. The severity of hyperviscosity syndrome is linked to the size, shape, type, and concentration of large molecules (e.g., immunoglobulins [IgG and IgM]) in the bloodstream.

Etiology

The underlying cause is generally a malignancy but can also be due to infectious disease. Hyperviscosity may be caused by monoclonal gammopathy (multiple myeloma, macroglobulinemia, lymphocytic leukemia), polycythemia, renal disease, hepatic tumors, and infectious disease.

Pathophysiology

The hyperviscosity results in thromboembolism, sludging of plasma, and hemorrhages in the CNS and eye. Dilated and tortuous retinal vessels, retinal hemorrhages, and RD may be a result of sludging of blood in small vessels, hypertension, thrombocytopenia, coagulation abnormalities, and poor delivery of oxygen and nutrients.

Clinical Presentation

Ocular changes are noticed very early in disease and include retinal hemorrhage (Figure 19.43), retinal venous dilatation and segmentation, retinal vascular tortuosity, "boxcarring" of retinal vessels, microaneurysms of the retina, subretinal hemorrhage, RD (Figures 19.44–19.46), perivascular retinal folding, and papilledema. Anterior uveitis and secondary glaucoma may also be present.

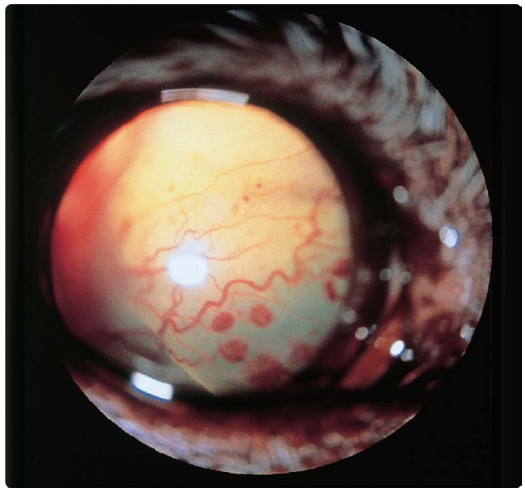


FIGURE 19.44 Dog with macroglobulinemia and hyperviscosity syndrome. Note the undulating retinal detachment with retinal hemorrhages in the dilated pupil.

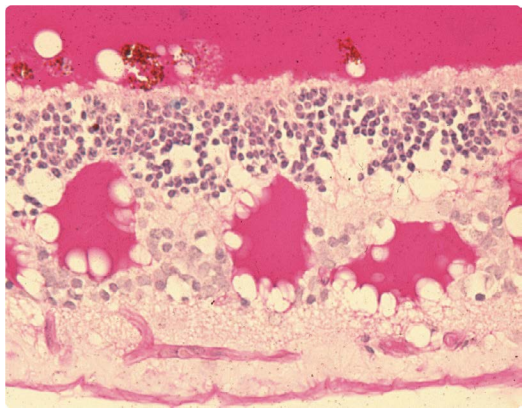


FIGURE 19.45 Histology. The right retina is detached with a large amount of PAS-positive subretinal fluid present. Intraretinal PAS-positive deposits, retinal vessel dilatation, and retinal pigment epithelium hyperplasia are noted (×250).



FIGURE 19.43 Multiple focal retinal hemorrhages and a small, peripheral, serous retinal detachment in an 18-year-old Siamese cat with hyperviscosity syndrome.

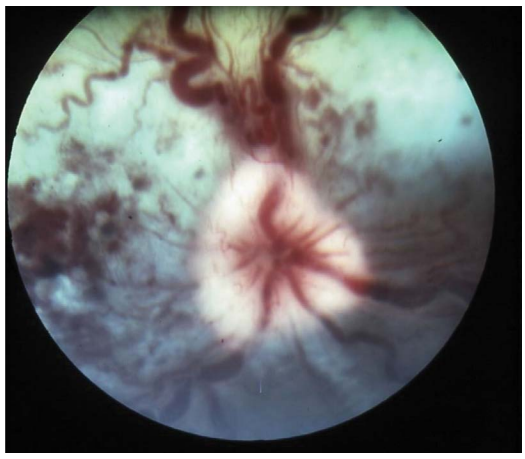


FIGURE 19.46 This dog has macroglobulinemia secondary to Waldenstrom macroglobulinemia. Note the thickened retinal vessels with sacculations as well as scattered retinal hemorrhages. (*Courtesy of M. Schaer.*)

Differential Diagnosis

See Tables 19.1 and 19.2.

Diagnosis

The diagnosis is made by demonstration of hyperproteinemia combined with serum and urine protein electrophoresis and immunoelectrophoresis. A coagulation assessment (platelet count, partial thromboplastin time, prothrombin time), serum protein electrophoresis, and serum viscosity measurements should be undertaken. Systemically affected animals should undergo a thorough anterior segment and funduscopic examinations.

Management

Plasmapheresis may be used to treat the hyperviscosity. Specific therapy directed at the diagnosed neoplastic or infectious disease is also indicated.

HYPERLIPIDEMIA

Definition/Overview

Hyperlipidemia is an increase in plasma concentration of triglycerides and/or cholesterol. Hyperlipidemia represents an abnormal finding in fasted dogs and cats and, when present, is indicative of either increased production or reduced degradation of lipoproteins. Hypothyroidism, diabetes mellitus, hyperadrenocorticism, pancreatitis, and renal (e.g., nephrotic syndrome) as well as hepatic (e.g., cholestasis) diseases can be associated with hyperlipidemia. Both primary and secondary hyperlipidemias may show ocular signs. Dogs and cats are commonly affected.

Etiology

Hyperlipidemia in dogs may be primary as an idiopathic hyperlipoproteinemia in the Beagle, Briard, Collie, Miniature Schnauzer, and Shetland Sheepdog or be secondary to diabetes mellitus, hypothyroidism, pancreatitis, lipoprotein lipase deficiency, renal and liver disease, or Cushing disease. Hyperlipidemia can occur in cats for several reasons, including postprandial hyperlipidemia, diabetes mellitus, exogenous corticosteroid administration, megestrol acetate administration, nephrotic syndrome, lipoprotein lipase deficiency, idiopathic hyperchylomicronemia, and familial hyperchylomicronemia.

Pathophysiology

Altered lipid metabolism may lead to lipemia of ocular blood vessels, corneal opacities, and lipemic aqueous. The term lipemia retinalis describes excess lipid within the retinal vessels, thus giving them a pale appearance. In both cats and dogs, it is the large, triglyceride-rich lipoproteins (e.g., low-density lipoproteins) that produce a visible lipemia. Hyperlipidemia may also manifest with lipids in the anterior chamber (lipemic aqueous). A prerequisite for gaining access to the anterior chamber by the large, lipid-laden molecules is breakdown of the blood–aqueous barrier secondary to pre-existing uveitis. Lipemic aqueous is commonly associated with systemic diseased that may cause hypertriglyceridemia as 95% of dog with lipemic aqueous have increased triglyceride levels.

Clinical Presentation

Increased triglycerides may result in brain dysfunction, acute pancreatitis, lipid-laden aqueous humor with anterior uveitis (Figure 19.47), and lipemia retinalis (Figure 19.48). Increased serum cholesterol has been

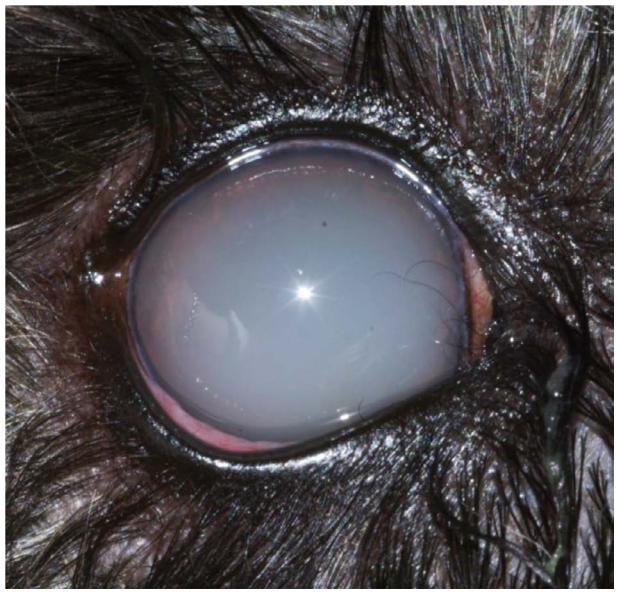


FIGURE 19.47 Lipemic aqueous in a lipemic dog with anterior uveitis. In more mild cases such as this, the lesion needs to be differentiated from diffuse corneal edema. As the lipemic aqueous worsens, it becomes more yellow in color.

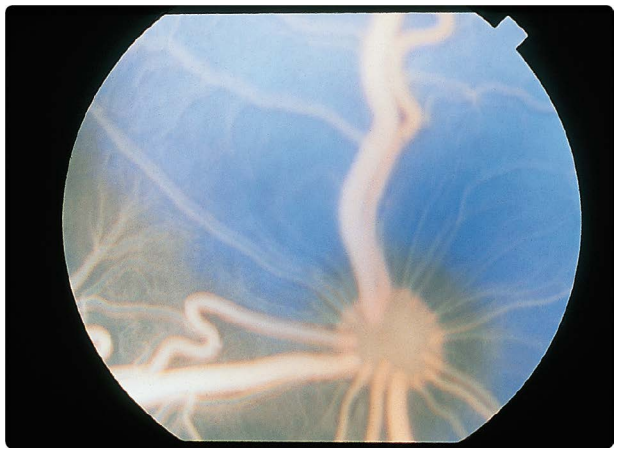


FIGURE 19.48 Lipemia retinalis in a kitten with a lipoprotein lipase deficiency. (*Courtesy of D. Brooks.*)

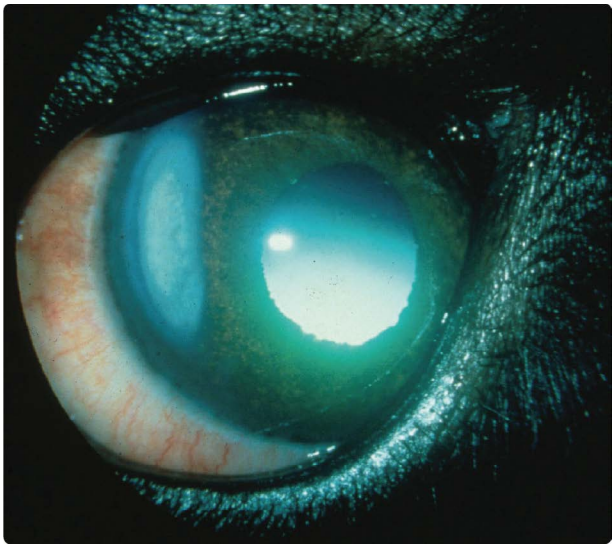


FIGURE 19.49 Lipidosis of the cornea in a hypercholesterolemic Dobermann.

suggested as a cause of lipid keratopathy, but most patients with increased cholesterol do not manifest with lipid keratopathy (Figure 19.49).

Differential Diagnosis

Other causes of corneal opacity, including corneal dystrophy, corneal ulcers, corneal scars, and inflammatory cellular infiltrates, must also be ruled out. It is reasonable to assess the lipid metabolism status of any patient presenting with lipemic aqueous, lipemia retinalis, or lipid keratopathy.

Diagnosis

Diagnosis is based on measurement of specific serum lipoproteins by electrophoresis or ultracentrifugation.

Management

Lipid-laden aqueous and lipemia retinalis resolve with resolution of the primary disorder and dietary modifications (low-fat diet), if necessary. Iridocyclitis should be treated if present. Untreated or severe uveitis may result in chronic inflammation and secondary glaucoma. Corneal lipid accumulation may not resolve. Only a limited number of lipid-lowering drugs have been used in dogs, with varying degrees of success for persistent hyperlipidemia. These include gemfibrozil, fish oils, cholestyramine, and lovastatin.

SYSTEMIC VASCULAR DISEASE

RDs associated with systemic hypertension due to chronic kidney disease are common in older cats and noticed in dogs (Figure 19.50). Complete RDs result in blindness, but vision may return if the hypertension responds to medical treatment and dietary adjustment.

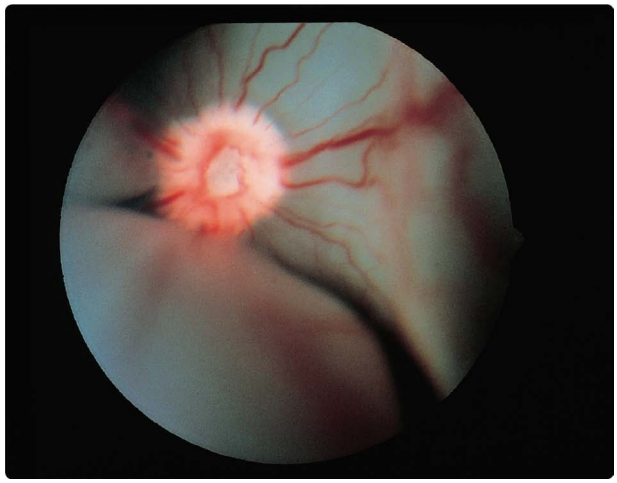


FIGURE 19.50 Exudative retinal detachment in a dog with nephrotic syndrome.

ANEMIA

Definition/Overview

Ocular manifestations of severe anemia in cats and dogs include conjunctival pallor, pale attenuated retinal vasculature, varying degrees of retinal hemorrhage, and subtle changes in tapetal reflectivity. Retinal hemorrhages are more likely to be observed, however, and are more dramatic if accompanied by thrombocytopenia (Figure 19.51). It has been suggested that anemia, alone is not a likely cause of retinal hemorrhage, but it is the diseases causing the anemia that result in retinal hemorrhage. It is postulated that the lack of red blood cells may render vascular endothelial cells hypoxic, thereby

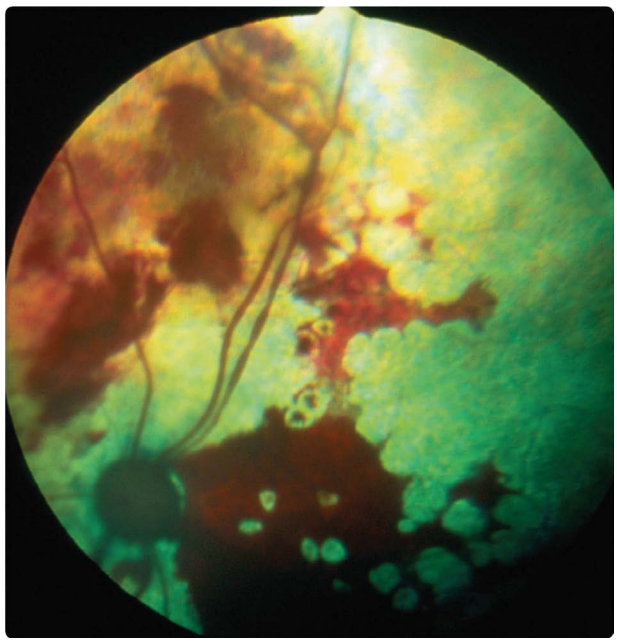


FIGURE 19.51 Vitreal and retinal hemorrhages in a cat with immune-mediated thrombocytopenia.

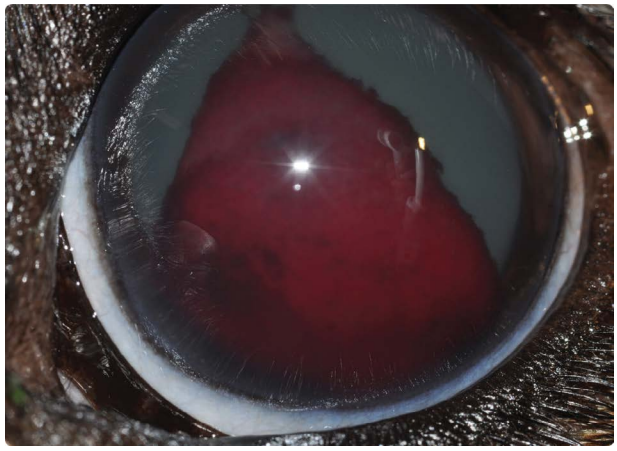


FIGURE 19.52 Hyphema shown in one of both eyes from a dog with immune-mediated hemolytic anemia and thrombocytopenia.

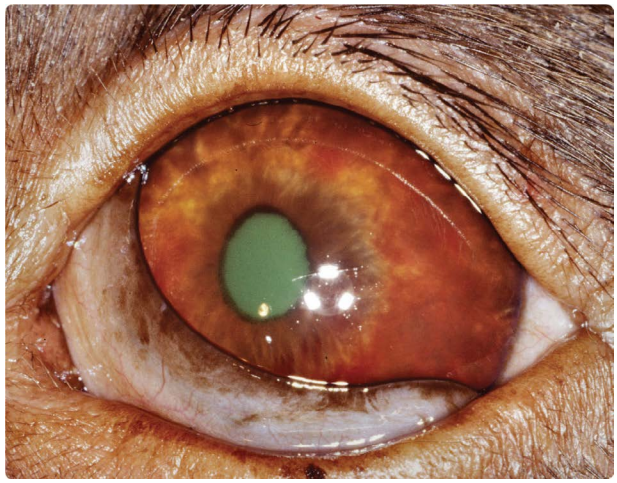


FIGURE 19.53 Iritis and iridal hemorrhage secondary to thrombocytopenia in a dog.

increasing vascular fragility and allowing retinal hemorrhages to occur in cats and dogs. The tapetal reflection is generally normal, which differentiates the retinal vessel attenuation from anemia from the attenuation found with retinal degeneration. Thrombocytopenia is more likely to cause ocular lesions such as hyphema and anterior uveitis in dogs (Figures 19.52 and 19.53).

SYSTEMIC ARTERIAL HYPERTENSION

See also Chapter 13.

Definition/Overview

Repeatable measurements of systolic pressure exceeding 160 mmHg and/or diastolic blood pressure measurements >100 mmHg are considered to indicate arterial hypertension. As any clinician knows, however, it can be challenging to accurately measure indirect blood pressure in both dogs and cats. Blindness is one of the most common presenting complaints with this disorder, as the eye is particularly sensitive to the effects of high blood pressure. Hypertensive retinopathy in many cats is a slow, insidious process. Vision may be spared if the process is identified and controlled before severe ocular disease develops. Consequently, old cats with diseases such as chronic kidney disease and hyperthyroidism should be screened for systemic hypertension. Old dogs with any systemic disease that is commonly associated with systemic hypertension should also be screened for systemic hypertension.

Etiology

Arterial hypertension in dogs and cats has been associated with old age, chronic anemia, hypercholesterolemia, atherosclerosis/arteriosclerosis, high-salt diets, obesity, and idiopathic essential hypertension. Secondary hypertension in dogs is now recognized as being a common complication of renal disease (60%–80% of cases), hyperadrenocorticism (59%–86% of cases), pheochromocytoma (>50% of cases), diabetes mellitus, primary hyperaldosteronism, hypothyroidism, and hyperthyroidism.

Hypertensive cats have been shown to have a greater prevalence of retinal lesions (48%) compared with normotensive cats (3%). In addition, cats with retinopathies had higher blood pressure (262 ± 34 mmHg) than hypertensive cats without retinal lesions (221 ± 34 mmHg). Cats over 8 years of age with chronic renal disease and with hyperthyroidism should have their fundi examined for lesions related to hypertension.

Pathophysiology

Renal pathology causes an increase in renin–angiotensin–aldosterone activity, which, in combination with increased plasma levels of norepinephrine, causes peripheral vasoconstriction. Incoming arterial and capillary blood at high pressure causes vasospasm, tissue hypoxia of the capillary beds allowing changes in vessel permeability, and exudation of fluid, plasma, or blood, resulting in development of infarcts and end-organ damage. The consequence of ocular vascular hypertensive changes is an initial vascular constriction in the retinal arterioles in response to increased blood pressure, which when sustained results in occlusion and ischemic necrosis of the vessel walls with resultant increased vascular permeability. The ocular circulation is not tolerant of such changes in its microcirculation.

Clinical Presentation

Ocular features in cats and dogs with hypertension include retinal arteriolar tortuosity, preretinal hemorrhage, retinal edema, perivasculitis, anterior uveitis, vitreal and anterior chamber hemorrhage, serous RDs, and retinal atrophy (Figures 19.54–19.66). In severe cases, irreversible blindness occurs. The severity of the lesions in cats has been correlated with the degree of systemic hypertension. In any dog or cat presenting with serous

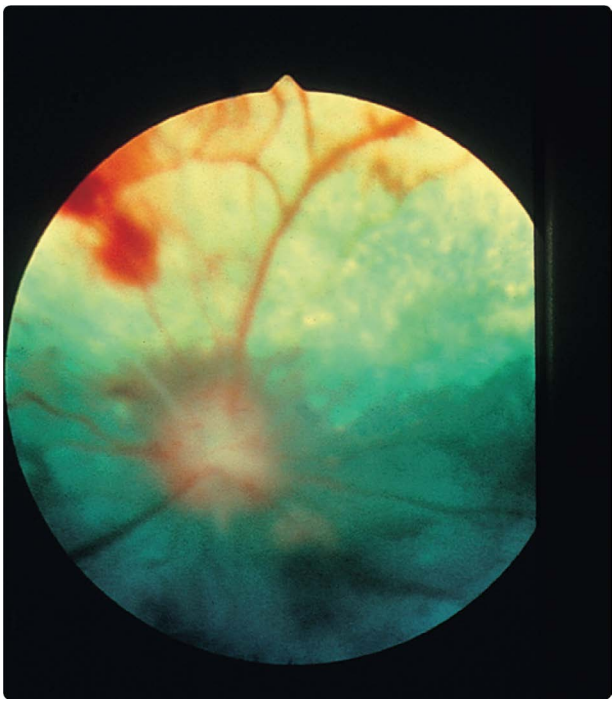


FIGURE 19.54 Retinal hemorrhages, vitreal haze, diffuse retinal edema, and optic neuritis in a dog with renal failure and hypertension.



FIGURE 19.56 Hyphema is present in this cat with systemic hypertension.



FIGURE 19.55 Extensive, serous retinal detachment with hemorrhages of the retinal and optic nerve vessels in a dog with systemic hypertension. The large, bright-white lesion in the lower left is a flash artifact.

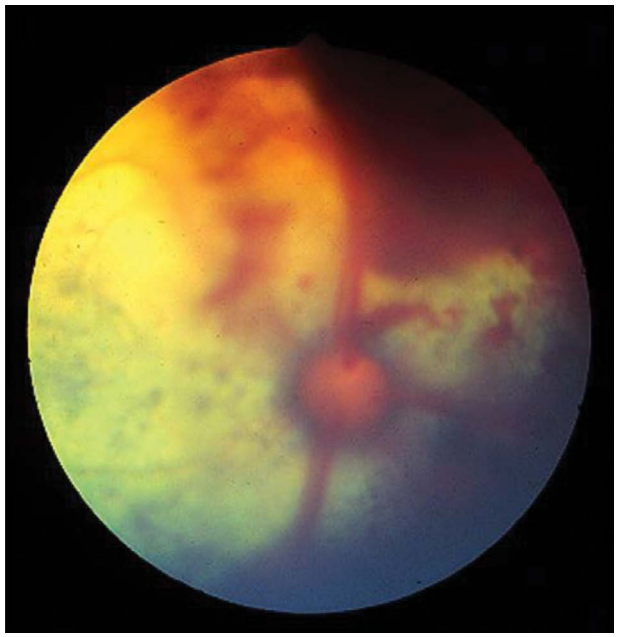


FIGURE 19.57 Hypertensive retinopathy manifested by dorsal vitreal hemorrhage, intraretinal hemorrhage, and retinal edema in a cat.

RDs and retinal or vitreal hemorrhage, systemic hypertension is the first syndrome that must be ruled out.

Differential Diagnosis

See Tables 19.1 and 19.2.

Diagnosis

Diagnosis is based on serial measurements of blood pressure along with typical clinical signs. A complete blood count (CBC), urinalysis, and serum biochemical profiles should be undertaken in all patients. All

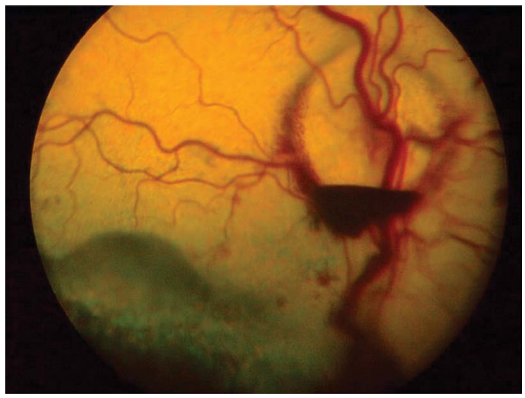


FIGURE 19.58 Preretinal "keel boat" hemorrhage in a dog with hypertensive retinopathy. An undulating, serous retinal detachment is noted in the lower left aspect of this image.



FIGURE 19.59 Arteriolar aneurysms are present in the retina of this dog with systemic hypertension.

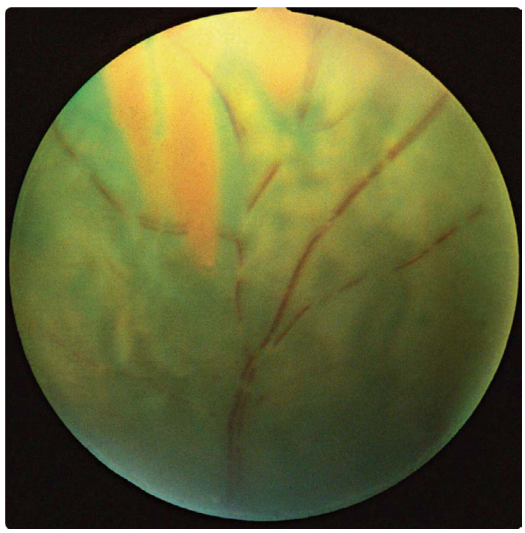


FIGURE 19.60 "Boxcarring" of retinal vessels indicates that the retinal tissue pressure is elevated and retinal perfusion reduced in this cat with systemic hypertension.

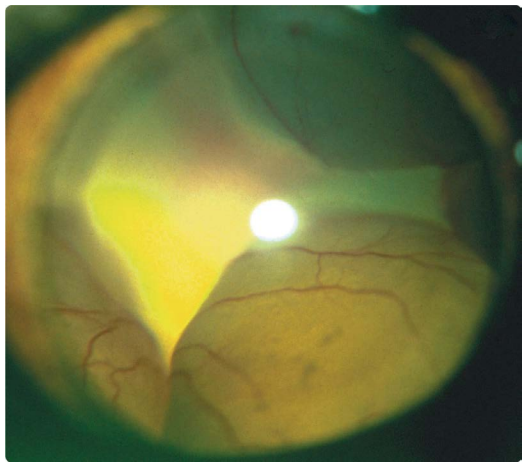


FIGURE 19.61 Bullous retinal detachment manifested as folds of opaque tissue posterior to the lens in a cat with hypertension.

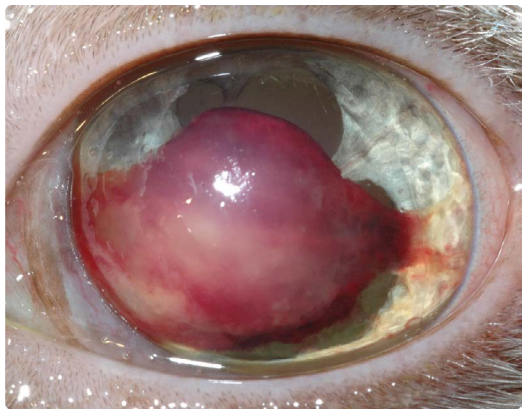


FIGURE 19.62 Hyphema is present in a dog with systemic hypertension.

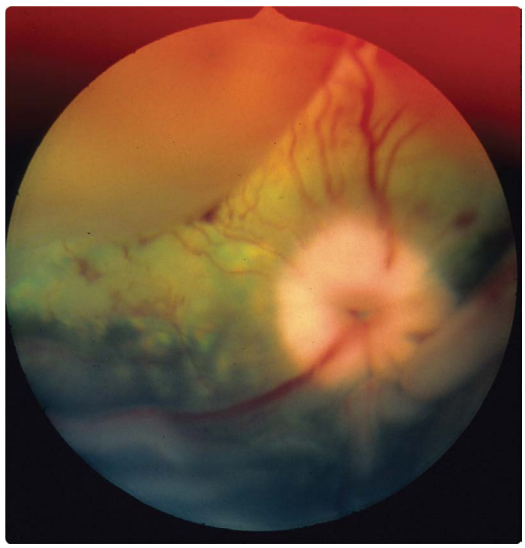


FIGURE 19.63 Retinal detachment and retinal hemorrhages in a dog with systemic hypertension.

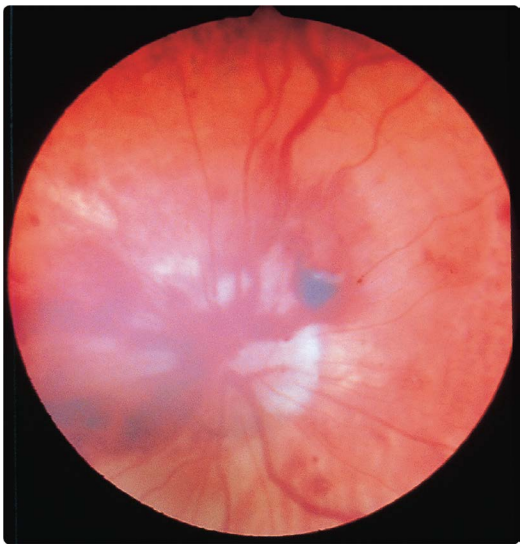


FIGURE 19.64 Vitreal and retinal hemorrhage obscure part of the optic disc in a dog with systemic hypertension.

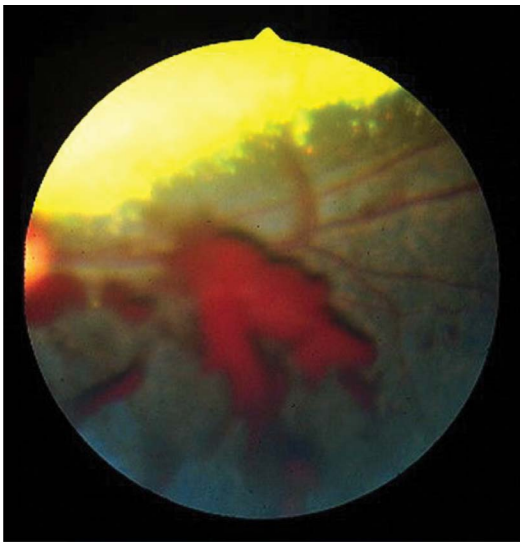


FIGURE 19.65 Preretinal hemorrhage in a dog with systemic hypertension.

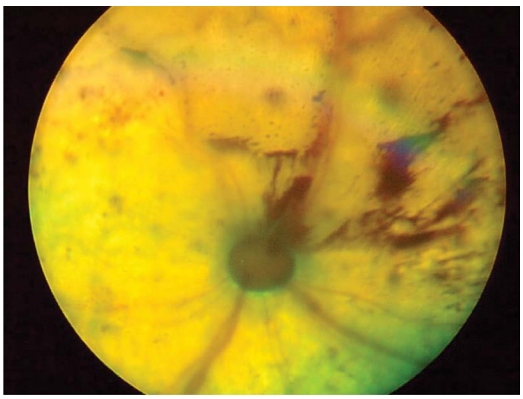


FIGURE 19.66 Multifocal retinal hemorrhages with serous retinal detachment in a cat with systemic hypertension.

affected patients should also have a complete physical examination and any other diagnostic tests as indicated in an attempt to rule in or rule out other systemic diseases associated with systemic hypertension.

Management

Treatment is based on the disease or diseases associated with the systemic hypertension. Unless these diseases are treated, the ocular lesions will not resolve and will worsen. The choice of antihypertensive drugs is left to the individual clinician as well as the other disease states for each patient. Patients with RDs and blindness may regain vision, particularly if the inciting cause and the concurrent systemic hypertension can be effectively treated or managed. The sooner the RDs are diagnosed and treated, the more likely it is that vision can be returned or spared. Chronic, complete RDs may never regain vision, even after treatment and retinal reattachment. In any patient diagnosed with systemic hypertension that has ocular lesions, serial ocular examination can be an effective tool to determine response to therapy. For example, if a patient's ocular signs are improving with treatment, but the indirect blood pressure measurements are still elevated, the improvement in ocular signs is strongly suggestive that the patient is on the correct therapy.

HORNER SYNDROME

Definition/Overview

Horner syndrome (sympathetic denervation) in the dog and cat is characterized by elevation of the third eyelid, ptosis, miosis (causing anisocoria), and enophthalmos.

Etiology

Sympathetic denervation to the eye can occur at the hypothalamus, brainstem/cervical cord, T1–T3 spinal cord segments, vagosympathetic trunk, cranial cervical ganglion, middle ear, ophthalmic branch of cranial nerve V, long ciliary nerve, and iris dilator muscle. The most common cause of Horner syndrome in the dog is secondary to an idiopathic, postganglionic lesion. Other causes of Horner syndrome include anterior mediastinal neoplasia, brachial plexus injury, otitis media, and cervical trauma.

Pathophysiology

Loss of sympathetic innervation causes a lack of tone in the orbital smooth muscle so that the eye retracts slightly, producing enophthalmos. Loss of innervation to the muscle of the upper eyelid (Muller's muscle) and sympathetically innervated tissue in the lower eyelid results in narrowing of the palpebral fissure and incomplete elevation of the upper eyelid or ptosis. Lack of sympathetic tone and enophthalmos results in elevation of the third eyelid. Reduction of normal sympathetic tone to the iris dilator muscle results miosis in the affected eye (Figure 19.67).



FIGURE 19.67 Miosis, third eyelid elevation, enophthalmos, and ptosis are found on the right side of a cat with Horner syndrome.

Clinical Presentation

The Horner miotic pupil is not pinpoint in room light. Constriction still occurs, and partial dilation in dark light occurs but not as much dilation as a normal pupil. The causative lesion can occur anywhere along the sympathetic chain. Intraocular pressure is normal, and vision is present.

Differential Diagnosis

Uveitis can cause miosis and elevation of the third eyelid. Painful eyes, such as an eye with corneal ulceration, can present with enophthalmos and blepharospasm that can be confused with Horner syndrome.

Diagnosis

Diagnosis is based on a complete physical examination and neurologic, otoscopic, and ophthalmologic examinations. Topically administered adrenergics such as 2.5% phenylephrine will restore the pupil to normal size, reposition the nictitans, and minimize the ptosis within about 20 minutes if the sympathetic lesion is postganglionic. If the patient has any other systemic signs, particularly additional neurologic abnormalities, evaluation by a neurologist is indicated.

Management

Idiopathic, postganglionic lesions may spontaneously resolve in some patients.

FELINE DYSAUTONOMIA OR FELINE DILATED PUPIL SYNDROME

Definition/Overview

Feline dysautonomia or feline dilated pupil syndrome (Key–Gaskell syndrome or feline autonomic neuropathy) is much more common in Europe than the United States. A similar syndrome is found in young, large-breed dogs living in rural areas of the Midwestern United States. Affected patients have widespread dysfunction of the autonomic nervous system.

Etiology

The cause is unknown, although lesions in the autonomic ganglia are consistent with a toxic cause. The bacterium *Clostridium botulinum* may be associated with the pathogenesis of feline dysautonomia.

Pathophysiology

Parasympathetic and sympathetic ganglia are equally affected. There is depletion of neuronal cell bodies, with many remaining neurons showing an atypical homogeneous cytoplasm, eccentric pyknotic nuclei, and dissolution of Nissl substance. Autonomic nerves show axonal degeneration, but peripheral nerves are comparatively spared. Ultrastructural changes include derangement of the rough endoplasmic reticulum, with cisternae lacking ribosomes and distended with flocculent material. Stacks of smooth membranous profiles are evident but no normal Golgi bodies.

Clinical Presentation

Ocular clinical signs include dilated, nonresponsive pupils, decreased tear production, and elevation of the third eyelid, but vision is not affected. Common systemic signs include dehydration, dysphagia, decreased appetite or anorexia, vomiting or regurgitation, xerostomia, constipation, bradycardia, and dysuria. Ataxia and poor proprioception may also occur.

Differential Diagnosis

Dilated pupils can be associated with glaucoma as well as retinal and optic nerve diseases. Significant iris atrophy may cause pupils (or one of the pupils) to appear dilated and nonresponsive to light.

Diagnosis

Diagnosis should be suspected from the characteristic clinical signs, and a definitive diagnosis can only be confirmed by the presence of lesions in the autonomic ganglia by histopathology. Urinary catecholamines are reduced. Pharmacologic testing can support the diagnosis. Pilocarpine (0.1%) topically constricts the pupil in affected cats, while topical echothiophate iodide (0.06%) and physostigmine (0.25%) will cause miosis in normal cats but not dysautonomic cats. Epinephrine at a concentration of 1:10,000 will induce retraction of the prolapsed third eyelid.

Management

Treatment includes supportive therapy with fluids, laxatives, and dietary management. Topical parasympathomimetics may be beneficial. The prognosis in affected patients is guarded to poor.

CANINE UVEODERMATOLOGIC SYNDROME

Definition/Overview

Ocular manifestations of canine uveodermatologic syndrome (UDS) are reported most often in "Arctic Circle" breeds such as Siberian Husky and Samoyed. Other breeds reported to be affected include the Australian Shepherd Dog, Beagle, Fila, Chow, Dachshund, Golden Retriever, Irish Setter, Old English Sheepdog, Saint Bernard, and Shetland Sheepdog. UDS appears to primarily affect young adult dogs, and ocular lesions generally precede dermatologic lesions.

Etiology

This is an autoimmune condition directed against melanin of neural crest (skin, hair, anterior uvea) and neuroectodermal (retina) origin.

Pathophysiology

This syndrome is considered to be an immune-mediated reaction to melanin that affects various organs containing melanocytes. It is similar to Vogt–Koyanagi–Harada (VKH) syndrome in people, although neurologic signs are rare in dogs as dogs' meninges are nonpigmented. Skin lesions are the result of a Th1-mediated inflammatory response, while ocular lesions are the result of a Th2-mediated inflammatory response. The role of certain dog leukocyte antigen class II gene alleles may be important regarding the pathogenesis of VKH-like syndrome in Akitas.

Clinical Presentation

Severe, bilateral panuveitis (Figures 19.68 and 19.69) and hypotony with secondary cataracts, glaucoma, RDs, and blindness are common. Iris and retinal depigmentation, poliosis/vitiligo, and ulceration of the face and muzzle are noticed (Figures 19.70 and 19.71). Dermal and hair depigmentation (vitiligo and poliosis, respectively) develop either gradually or rapidly, and they may be ulcerative in nature. The lesions are usually restricted to the mucocutaneous junctions of the face, involving the eyelids, nasal planum, and lips, but the scrotum and footpads are other areas of possible dermal involvement.

Differential Diagnosis

See Table 19.1.

Diagnosis

There is no specific diagnostic test for uveodermatologic syndrome. The diagnosis is made on the basis of clinical signs and histopathologic examination of skin biopsies. Skin biopsy specimens have lichenoid, interface dermatitis, histiocytes, and small mononuclear cells as well as

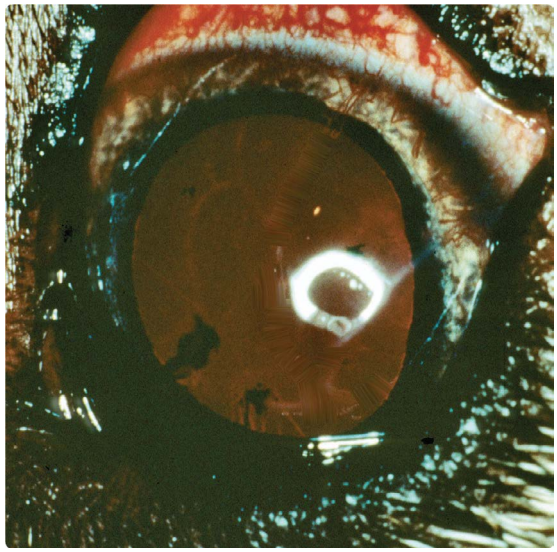


FIGURE 19.68 Husky dog with uveodermatologic syndrome (UDS). Anterior uveitis noted by scleral injection, iritis, and posterior synechia.

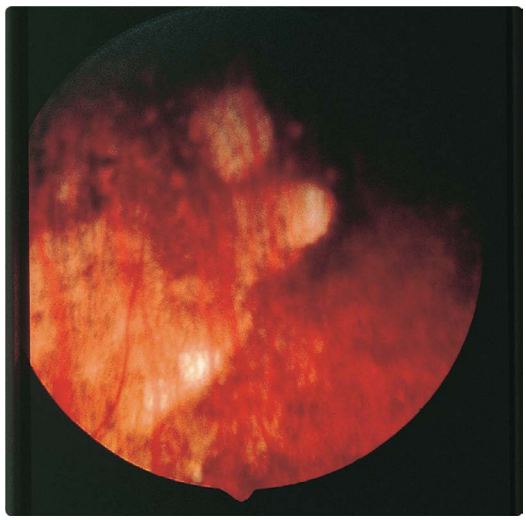


FIGURE 19.69 Focal depigmentation of the nontapetum due to previous chorioretinitis.



FIGURE 19.70 Dog with uveodermatologic syndrome prior to therapy. Note the depigmented and ulcerated lesions of the eyelid margins, nose, and lips.



FIGURE 19.71 Same dog with uveodermatologic syndrome as in Figure 19.70 after therapy.

giant cell infiltrations. The level of melanin in the epidermis and hair follicles is decreased. Special stains should be requested in the presence of granulomatous infiltrates in an attempt to identify microorganisms. Routine laboratory tests are typically normal. Skin biopsy should help to rule out other ulcerative skin diseases.

Management

Short-term success with systemically administered corticosteroids or azathioprine is good, but recurrence is common, particularly without chronic immunomodulatory therapy. Patients being treated with azathioprine must have bloodwork monitored, both acutely and chronically, to monitor for side effects in the liver and/or bone marrow. Other systemic immunomodulatory drugs such as cyclosporine may be beneficial in dogs that do not tolerate chronic azathioprine. Topical treatment of the uveitis with steroids is required.

GRANULOMATOUS MENINGOENCEPHALITIS AND MENINGOENCEPHALITIS OF UNKNOWN ETIOLOGY

See also Chapter 14.

Definition/Overview

Meningoencephalitis of unknown etiology (MUE) is a condition in which advanced diagnostic imaging and cerebrospinal fluid (CSF) analysis suggest an inflammatory, noninfectious disease process, but definitive histopathologic diagnosis is lacking. Granulomatous meningoencephalitis (GME) is diagnosed when the cause has been confirmed via histopathology, generally on postmortem examination. MUE/GME can be seen alone as a primary ocular disease or, more commonly, in conjunction with CNS disease. It is probably the most common inflammatory disease of the canine nervous system. The ocular signs may occur before CNS signs. The disease is typically seen in female, small-breed, middle-aged dogs, although any breed or age of dog may be affected.

Etiology

MUE/GME is an idiopathic, nonsuppurative inflammatory disease.

Pathophysiology

MUE/GME is characterized by the proliferation of reticuloendothelial elements and lymphoplastic infiltration of blood vessels of the CNS, the ciliary body, and the choroid. Perivascular infiltrates are composed of a heterogeneous population of major histocompatibility complex class II antigen-positive macrophages and mainly CD3 antigen-positive lymphocytes, supporting a hypothesis of T-cell-mediated, delayed-type hypersensitivity or an autoimmune disease.

Clinical Presentation

Ocular features include acute, unilateral, or bilateral blindness with a widely dilated, nonresponsive pupil in the affected eyes (Figure 19.72). Uveitis, optic neuritis (hyperemic, swollen, elevated optic disc, disc hemorrhage, peripapillary engorged vessels), retinal inflammation (white perivascular cuffs and yellow–white patches), and peripapillary RD are common (Figures 19.73 and 19.74). The optic disc may appear normal if the optic nerve involvement is posterior to the globe.

Differential Diagnosis

See Table 19.1. Any other infectious disease that can cause optic neuritis.



FIGURE 19.72 Dilated, nonresponsive pupils are present in a Miniature Pinscher with bilateral optic neuritis from granulomatous meningoencephalitis.



FIGURE 19.73 A swollen and hyperemic optic disc indicating optic neuritis that was associated with granulomatous meningoencephalitis.

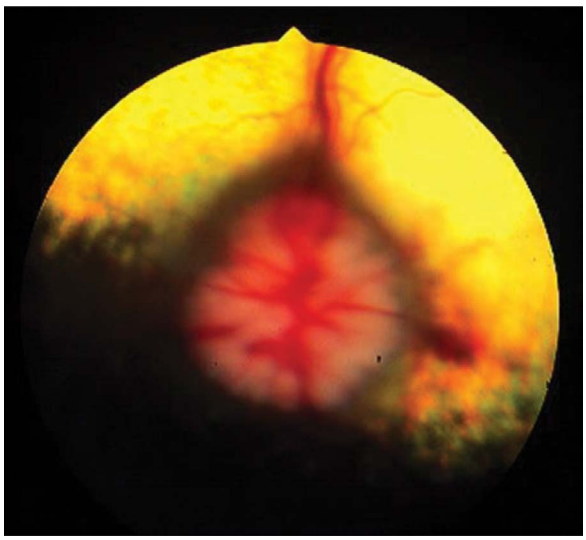


FIGURE 19.74 Swollen, hyperemic optic disc with peripapillary hemorrhages and peripapillary retinal detachment in a dog with meningoencephalitis of unknown etiology.

Diagnosis

Diagnosis of GME can only be confirmed at necropsy or by brain biopsy. MRI and analysis of CSF (increased CSF protein and pleocytosis) may enable a tentative diagnosis to be made (MUE).

Management

Treatment involves aggressive use of immunosuppressive corticosteroids often with added immunosuppression using cytosine arabinoside, azathioprine, leflunomide, or cyclosporine A. Gradual improvement and temporary remission are possible in about 30% of cases. Clinical signs tend to be progressive, and most dogs eventually lose vision permanently.

LYMPHOSARCOMA

Definition/Overview

Lymphosarcoma is the most common intraocular tumor of dogs and cats. It is usually a secondary ocular tumor and is usually bilateral. Presumed solitary ocular lymphoma (PSOL) has been reported in both dogs and cats. PSOL may be as common as systemic lymphoma in cats and is reported to have double the survival time compared to cats with systemic lymphoma. PSOL may also be more common that systemic lymphoma in dogs and is reported to have seven times the survival time compared to dogs with systemic lymphoma.

Etiology

This is generally a metastatic neoplastic disease to the eye and its adnexa. Cats may be positive for FeLV.

Pathophysiology

Systemic involvement generally precedes or accompanies ocular lymphosarcoma. Lymphosarcoma with secondary ocular involvement equates to advanced disease and translates to a shorter survival period for the patient.

Clinical Presentation

Lymphosarcoma in dogs and cats (Figures 19.75–19.82) may manifest as corneal edema, centrally migrating white bands of neoplastic cells, stromal hemorrhage, corneal vascularization, anterior uveitis with hyphema, hypopyon, keratic precipitates, secondary glaucoma, tortuous retinal vessels, retinal hemorrhages, perivascular sheathing, RD, or retinal tissue infiltration by tumor cells. Invasion of retinal tissue alone is very rare in dogs and cats but can occur. Cats more commonly have cranial nerve dysfunction. Exophthalmos secondary to orbital lymphoma may also occur.

Differential Diagnosis

See Table 19.1.



FIGURE 19.75 Miosis and diffuse iritis secondary to intraocular lymphosarcoma in a cat.



FIGURE 19.76 Focal and diffuse iritis and fibrin in a dog with lymphosarcoma.



FIGURE 19.77 Conjunctival lymphosarcoma in the right eye of this cat. An unrelated cataract is present in the left eye.

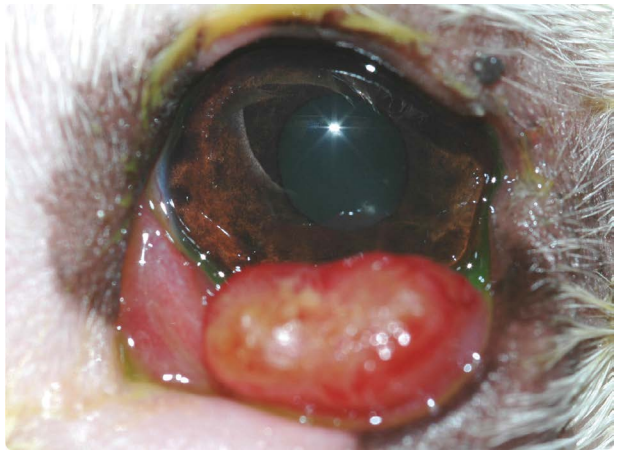


FIGURE 19.78 This mass on the third eyelid in a dog is lymphoma.



FIGURE 19.79 Lymphoma has effaced the entire anterior uveal tract of this cat.



FIGURE 19.80 Lymphosarcoma invasion of the choroid causes a focal retinal detachment in this cat.



FIGURE 19.81 Orbital lymphoma pressing on the globe indents the eye and distorts the ventral optic disc and nontapetal area of this dog's fundus.

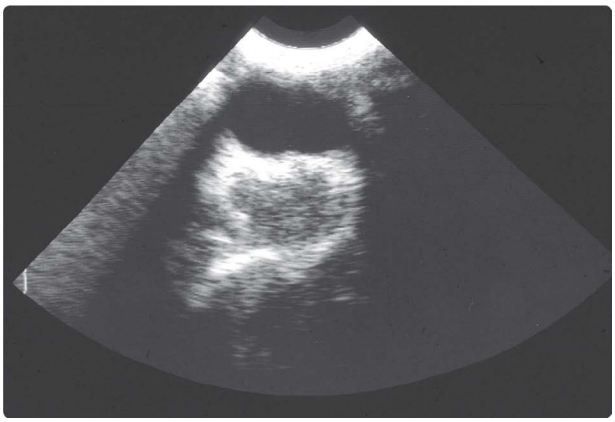


FIGURE 19.82 Ultrasound demonstrates the tumor presence behind the globe in the dog in Figure 19.81.

Diagnosis

Lymphadenopathy combined with bilateral anterior uveitis or intraocular hemorrhages should cause suspicion of lymphoma. Enlarged lymph nodes should be investigated by fine-needle aspiration.

Management

Anterior uveitis and hyphema should be treated by topical corticosteroids and atropine (if secondary glaucoma is not present). Medical protocols for treatment of lymphosarcoma should be instituted and are associated with the most rapid resolution of clinical signs.

DIABETES MELLITUS

See also Chapter 12.

Definition/Overview

There is a high incidence of cataracts in diabetic dogs, with many cataracts apparently developing rapidly over days to weeks. Most diabetic dogs form cataracts within 12–16 months after diagnosis.

Etiology

In dogs, inciting factors include obesity, immune-mediated insulitis, pancreatitis, infection, genetic predisposition, and insulin-antagonistic diseases. In cats, obesity-induced carbohydrate intolerance and amyloid deposition in islet cells are potential factors.

Clinical Presentation

The most common ocular manifestation of diabetes mellitus in small animals is acute formation of cataracts, often associated with sudden blindness (Figure 19.83). Diabetic cataracts in dogs begin at the lens equator and manifest as vacuoles that are best seen after pharmacologic dilation (Figure 19.84). Diabetic cataracts in cats are rare. Diabetic dogs may have KCS, reduced corneal sensitivity, and reduced tear film breakup times.

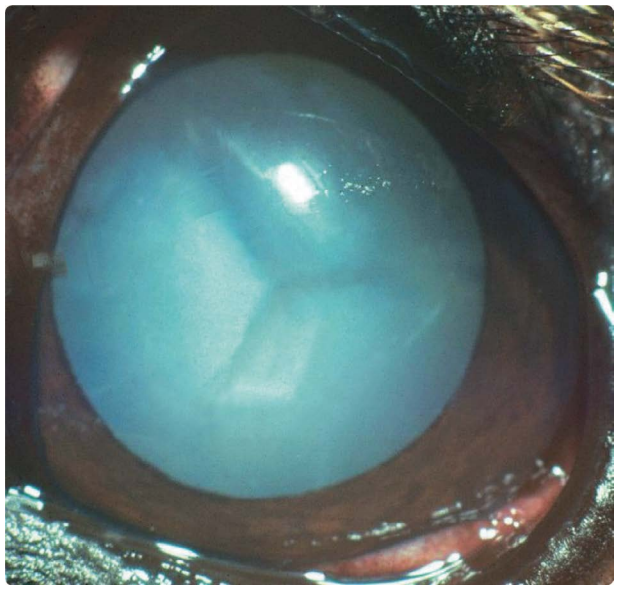


FIGURE 19.83 A mature cataract with prominent lens Y-suture involvement caused by diabetes mellitus in this dog.

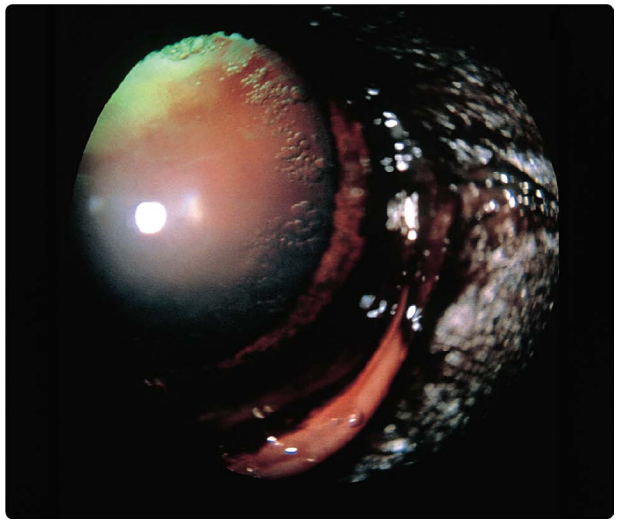


FIGURE 19.84 Lens fibers in the equatorial lens cortex swell and appear as vacuoles or bubbles at the equator of the lens in this dog with diabetes mellitus.

Pathophysiology

The cataracts form during periods of hyperglycemia when glucose enters the lens and is converted by the enzyme aldose reductase (AR) to sorbitol as the glycolytic enzyme hexokinase is saturated. Lens sorbitol dehydrogenase (SD) activity is also reduced, which allows sorbitol to accumulate in the lens. The sorbitol osmotically draws water into the lens, and the lens fibers swell and rupture to result in cataracts.

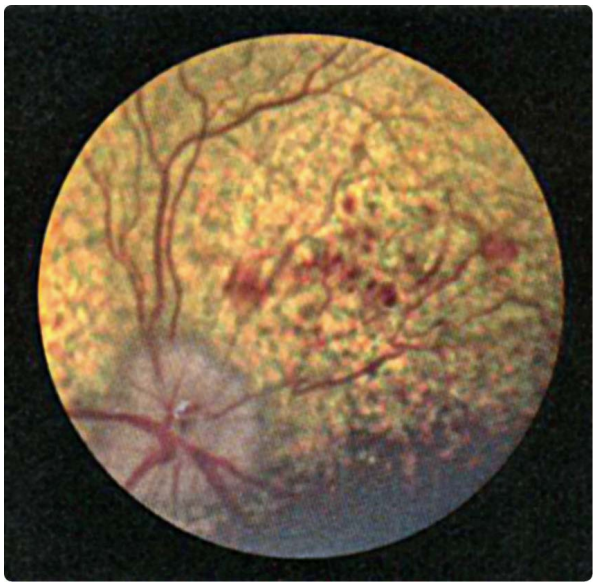


FIGURE 19.85 Retinal hemorrhages are present in this dog with diabetic retinopathy.

The cat lens generally has less age-matched activity of both AR and SD than that present in the lens of dogs, but the ratio of AR to SD is higher in the cat lens than the dog. Sorbitol should thus accumulate more quickly in diabetic cat lenses than in dogs, but the incidence of diabetic cataracts is actually lower clinically in diabetic cats than diabetic dogs. This may be a result of diabetes being primarily a disease of cats >7 years of age who have little AR activity in their aging lens. AR lens activity is highest in young cats (<4 years).

Ischemic changes in the retina of chronically diabetic dogs and cats can result in retinal vessel aneurysms and retinal hemorrhages (Figure 19.85). These changes may be masked by the rapid cataract formation.

Differential Diagnosis

Cataracts may be a hereditary condition in specific breeds. They may also be caused by aging, advanced retinal degeneration, anterior uveitis, diseases causing hypocalcemia, and radiation therapy.

Diagnosis

Early cataractous changes appear as vacuoles in the subepithelial equatorial cortex, which progress to mature, intumescent cataractous lenses with prominent Y-suture clefting. Anterior uveitis is also found in some canine diabetics. Diabetic retinopathy is slow to develop in diabetic dogs and cats.

Management

Surgery is necessary to treat the cataracts of controlled diabetic patients and is very successful at restoring sight. Topical aldose reductase inhibitors have shown promise to slow the development and advancement of diabetic cataract in dogs but are still experimental at this time.

LACRIMAL SYSTEM MANIFESTATIONS OF SYSTEMIC DISEASE

ACUTE AND CHRONIC KERATOCONJUNCTIVITIS SICCA

Definition/Overview

Keratoconjunctivitis sicca (KCS) is a disease associated with reduced aqueous secretions from the lacrimal and third eyelid glands. Most cases of chronic conjunctivitis in dogs are caused by KCS.

Etiology

The most common cause of KCS is immune-mediated dacryoadenitis. KCS in dogs may be associated with canine distemper, trauma, irradiation, and drug toxicity. Canine immune-mediated KCS has also been associated with atopy, hypothyroidism, hyperadrenocorticism, systemic lupus erythematosus (SLE), rheumatoid arthritis, diabetes mellitus, chronic active hepatitis, and pemphigoid disorders. FHV infection is associated with KCS in cats.

Pathophysiology

The trilayered precorneal tear film is critical for maintaining optical clarity and providing nutrition to the cornea. Lack of tears results in chronic and painful conjunctival and corneal degeneration. Left untreated, KCS may result in blindness.

Clinical Presentation

Blepharospasm, conjunctivitis, chemosis, mucoid to mucopurulent ocular discharge, superficial corneal pigmentation and vascularization, and corneal ulcers can be present (Figure 19.86). Cats seem less affected by low tear levels than dogs.

Differential Diagnosis

KCS is often confused with bacterial conjunctivitis. While it does occur, bacterial conjunctivitis in dogs in not common.

Diagnosis

Decreased Schirmer tear test levels (<10 mm per minute), along with appropriate clinical signs, are diagnostic. The presence of concurrent corneal ulcers should be identified and treated aggressively to prevent infection and/or collagenolysis.

Management

Topically administered cyclosporine A, tacrolimus, pimecrolimus, artificial tears, and antibiotics are effective



FIGURE 19.86 Chronic KCS in a dog. Note the mucoid ocular discharge, diffuse conjunctivitis, superficial vascularization, and superficial pigmentary keratitis.

at controlling KCS in up to 80% of dogs. If medical therapy is not working, adjunctive surgical options, including parotid duct transposition and canthoplasty, can be beneficial in that management of KCS.

SJÖGREN'S-LIKE SYNDROME

Definition/Overview

Sjögren's syndrome is a systemic autoimmune disease directed against glandular tissues. It is characterized by KCS, xerostomia, lymphoplasmacytic dacryoadenitis, and lymphocytic sialadenitis.

Etiology

Sjögren's syndrome is frequently associated with human autoimmune disease (rheumatoid arthritis, SLE, thyroiditis). A similar syndrome to Sjögren's syndrome has recently been recognized in dogs (KCS associated with SLE, hypothyroidism, diabetes mellitus, other immune disorders, and xerostomia) and cats.

Pathophysiology

There is immune-mediated destruction of the lacrimal and salivary glands.

Clinical Presentation

Sjögren's syndrome is characterized by KCS (xerophthalmia) and xerostomia (dry mouth).

Differential Diagnosis

Any chronic keratitis or keratoconjunctivitis.

Diagnosis

Clinical signs (KCS, keratitis, conjunctivitis), presence of other immune-mediated systemic diseases (e.g., pemphigus) associated with salivary signs, positive ANA test.

Management

Treatment is the same as for KCS with additional identification and management of concurrent autoimmune diseases.

SYSTEMIC DISEASE ASSOCIATED WITH INFLAMMATORY MYOPATHY

MASTICATORY MUSCLE MYOSITIS

See also Chapter 9.

Definition/Overview

Eosinophilic masticatory muscle myositis is an inflammatory disorder involving the muscles of mastication. Masticatory myositis typically affects young to middle-aged adult dogs and predominantly medium- to large-breeds dogs.

Etiology

The cause is unknown, but an immune-mediated reaction is possible. Neutrophils and eosinophils infiltrate the temporalis and pterygoid muscles to cause pronounced masticatory muscle fiber swelling and subsequent fibrosis.

Pathophysiology

The 2M muscle fibers in the masticatory muscles contain a unique type of myosin, which is specifically involved in immune-mediated reactions. The pathogenesis is not understood, although autoantibodies against type 2M muscle fibers are present in the circulation and tissue. Bacteria containing antigens similar to type 2M muscle fibers may initiate the myositis. Exophthalmos results from inflammatory swelling of the muscles of mastication forcing orbital fat and the globe anteriorly to cause the exophthalmos.

Clinical Presentation

Ocular lesions are present in about 45% of cases (Figure 19.87). Masticatory muscle myositis of the masseter,



FIGURE 19.87 Bilateral exophthalmos and third eyelid elevation secondary to masticatory muscle myositis in a Shetland Sheepdog.

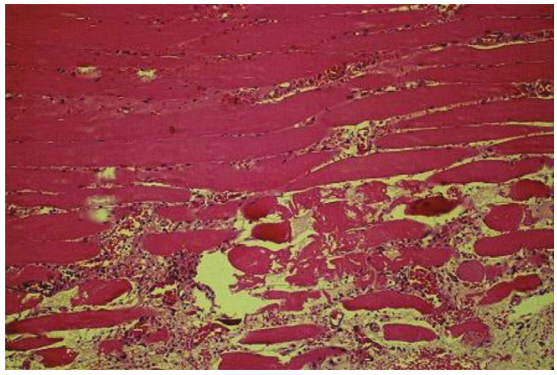


FIGURE 19.88 Histopathology of a muscle biopsy of the same dog in Figure 19.87 demonstrating muscle necrosis, inflammatory cells, and mild fibrosis.

pterygoid, and temporalis muscles may cause acute, painful exophthalmos that is followed by chronic muscle atrophy with enophthalmos and third eyelid elevation. Pain is elicited when opening the mouth. Most dogs present with anorexia and depression, although tonsillitis, submandibular and prescapular lymphadenopathy, and pyrexia may occur.

Differential Diagnosis

Orbital cellulitis and orbital neoplasia.

Diagnosis

Diagnosis is based on electromyography (which reveals abnormal spontaneous pathologic activity in the temporal and masseter muscles), peripheral eosinophilia, elevated serum creatine kinase, temporalis muscle biopsy, and the demonstration of serum 2M autoantibodies. MRI detects widespread, symmetrical, and in homogeneously hyperintense areas in the masticatory muscle. Histopathologic findings found are cellular infiltration of affected muscles with varying degrees of lymphocytes and/or macrophages and/or eosinophils; muscle atrophy, necrosis, and fibrosis; presence of fibrosis in chronic cases; and immune complexes bound to type 2M muscle fibers (Figure 19.88).

Management

Systemically administered corticosteroids are indicated in acute disorders. Uncontrolled myositis leads to painful masticatory muscle atrophy. Therapy may be life-long.

EXTRAOCULAR MUSCLE MYOSITIS

Definition/Overview

Extraocular muscle myositis is common in young, large-breed dogs such as Golden Retrievers.

Etiology

The specific cause of this focal inflammatory myositis is unknown at present.

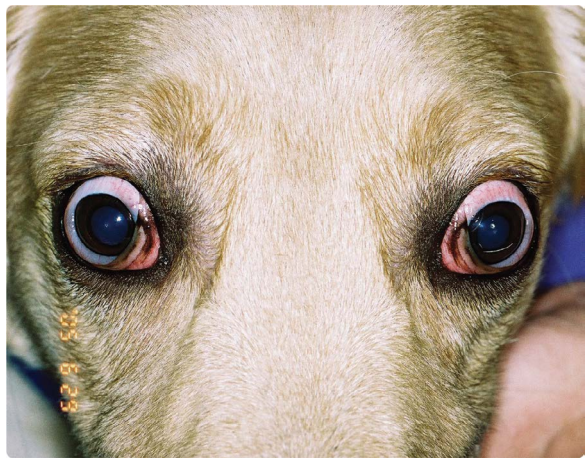


FIGURE 19.89 Young Golden Retriever with extraocular muscle myositis. Bilateral exophthalmos due to the extraocular muscle myositis.

Pathophysiology

Extraocular muscle myositis is an immune-mediated disease directed against the type 1 myofibers of the extraocular muscles. The pressure on the optic nerve from the swollen extraocular muscles can severely reduce optic nerve axoplasmic flow and cause visual deficit.

Clinical Presentation

The clinical signs are bilateral in most dogs, and most dogs are not painful. A generally nonpainful chemosis precedes exophthalmos in 81% of cases, and optic nerve impingement with optic neuritis may occur to cause blindness (Figures 19.89–19.92). Chronic inflammation may result in restrictive strabismus.

Differential Diagnosis

Orbital cellulitis and orbital neoplasia.

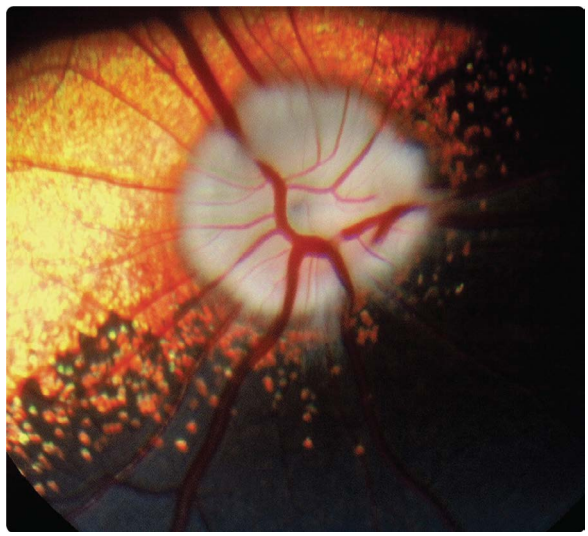


FIGURE 19.90 Same Golden Retriever as Figure 19.89. The optic disc is slightly swollen.



FIGURE 19.91 Same dog as Figure 19.89. MRI shows bilateral extraocular muscle swelling (arrowheads).

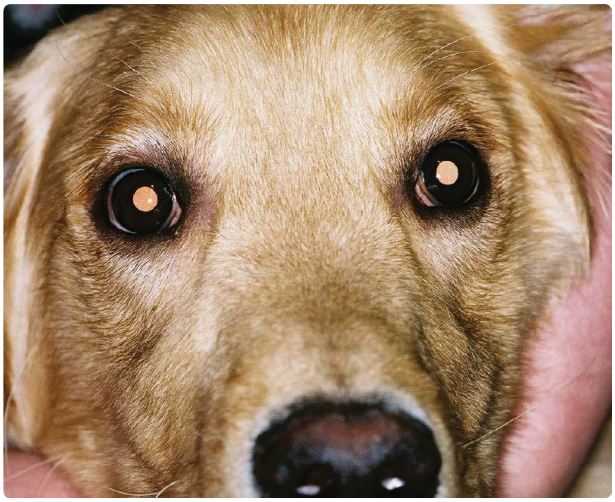


FIGURE 19.92 Same dog as Figure 19.89 4 months later. Therapy for the extraocular myositis has reduced the exophthalmos.

Diagnosis

Diagnosis is by serum and muscle biopsy for detection of type 1 myofiber antibodies.

Management

Treatment is the same as for masticatory muscle myositis.

NEOPLASIA OF THE ORBIT

Definition/Overview

Both primary and secondary neoplasia of the orbit occur in dogs and cats.

Etiology

Reports differ whether most orbital tumors are primary or secondary. Most orbital tumors are malignant in dogs and cats.

Pathophysiology

As the orbit contains almost all tissue types found in the body, a wide variety of tumors are reported involving all of those tissue types present within the orbit. Malignant cell types predominate with any widely metastatic tumor potentially involving the orbit.

Clinical Presentation

Progressive, usually nonpainful, slow exophthalmos with varying amounts of strabismus and exposure keratitis are the most common clinical signs (Figures 19.93 and 19.94). Acute-onset exophthalmos is most commonly associated with orbital inflammatory diseases such as retrobulbar abscesses/cellulitis. Exophthalmos with pain on attempting to open the mouth usually indicates a retrobulbar abscess or cellulitis, with swelling



FIGURE 19.93 A retrobulbar lipoma causing exophthalmos, third eyelid elevation, and dorsolateral displacement of the left globe within the orbit of this dog.



FIGURE 19.94 Bilateral third eyelid elevation, exophthalmos, and globe deviation in a dog with a brain tumor.

behind the last upper molar on the affected side also often observed. Dogs with orbital tumors undergoing necrosis can have the same clinical signs as dogs with orbital abscesses/cellulitis.

Differential Diagnosis

Orbital abscesses/cellulitis, masticatory myositis, salivary gland mucoceles, orbital varices.

Diagnosis

Cytologic examination and culture of discharge or aspirates from the orbit, biopsy of masses, exploration of fistulous tracts, ultrasonography, MRI, and CT are very valuable in evaluating orbital diseases (Figures 19.95–19.97). Of these, advanced imaging with CT or MRI followed by biopsy is the best way to establish a tissue diagnosis as well as to determine the potential invasiveness of the neoplasia. Histopathology is superior to cytology to determine a definitive diagnosis. Ultrasound-guided core biopsies are a safe and effective method to collect histopathologic samples. Affected patients should also undergo complete staging with CBC, serum biochemistry, urinalysis and imaging of the orbit, chest, and abdomen to check for evidence of potential metastasis.

Management

Early diagnosis and intervention may allow treatment along with salvage of the globe (Figures 19.98 and 19.99). In advanced or chronic cases, orbital exenteration (removal of the mass and the globe) is generally the therapy of choice unless the orbital tumor is well circumscribed. The prognosis for affected dogs and cats with orbital neoplasia is dependent on the type of tumor and when the tumor is diagnosed. Unfortunately, many cases are advanced prior to clinical signs and diagnosis.

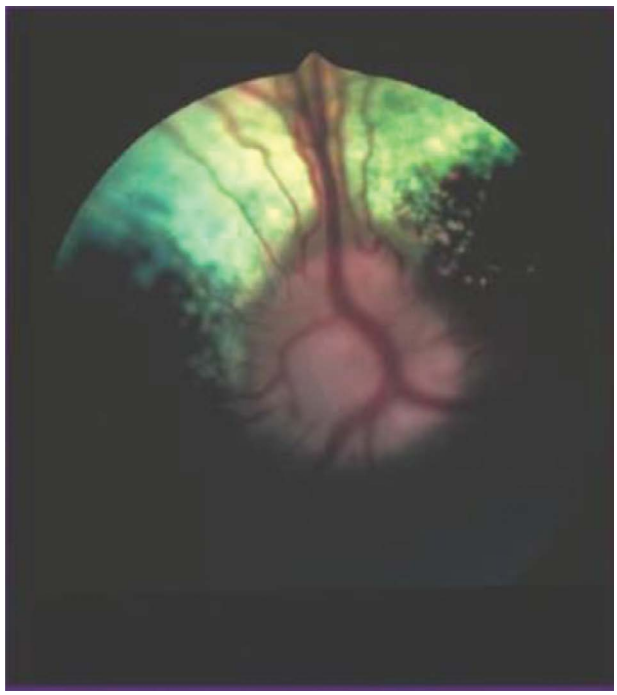


FIGURE 19.95 An optic nerve meningioma in the orbit has caused papilledema and scleral indentation of the optic disc in a mixed-breed dog.



FIGURE 19.96 Ocular and orbital ultrasound of the same dog in Figures 19.95 and 19.97. Note the circular mass indenting the globe.

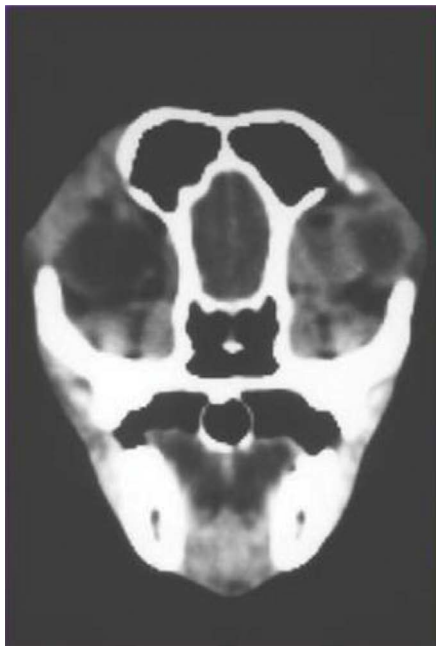


FIGURE 19.97 Orbital CT scan of the same dog in Figures 19.95 and 19.96. Note the mass behind the globe that is indenting the globe and has pushed the globe forward.



FIGURE 19.98 Exophthalmos, strabismus, and subconjunctival hemorrhage on the left side of this dog with lobular orbital adenoma.

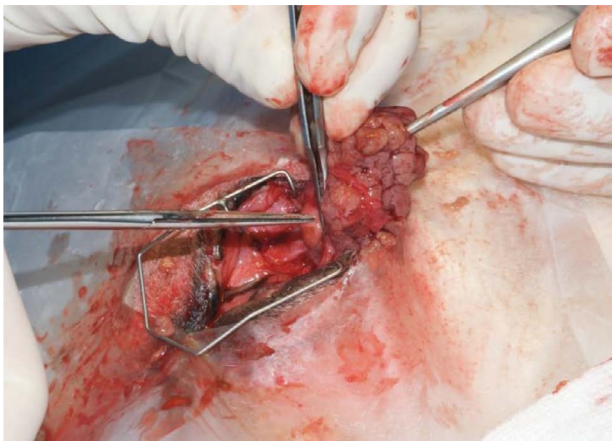


FIGURE 19.99 Surgical exploration and debulking of the retrobulbar lobular adenoma in the dog in **Figure 19.98**. The dog was visual before and after surgery.

The patient should be evaluated carefully for the ability to completely close the lids over the globe. Many patients with exophthalmos develop secondary exposure keratitis from lagophthalmos. Corneal ulceration may occur in patients with lagophthalmos. All patients with exophthalmos should be evaluated carefully for the presence of a corneal ulceration. If corneal ulceration is present, it should be treated like any other corneal ulcer. In addition, topical lubricating ointments should be applied every 2–6 hours to prevent desiccation of the ocular surface. A temporary tarsorrhaphy may be necessary if the exophthalmos is severe or prolonged.

CELLULITIS/ABSCESSATION OF THE ORBIT

Definition/Overview

Orbital cellulitis/abscessation occurs when there is infectious, inflammatory, traumatic, and potentially neoplastic disease within the orbit.

Etiology

The causes of orbital cellulitis include trauma, penetrating foreign body, extension of tooth root abscess or sinonasal disease, and hematogenous dissemination of infection or neoplasia. In some cases, an underlying cause may not be identifiable.

Pathophysiology

The canine and feline orbit lacks a bony floor, which leaves it vulnerable to penetrating injury or puncture if the patient chews a bone or a stick. Foreign bodies often are implicated as the cause of orbital cellulitis but rarely are identified definitively.

Clinical Presentation

The onset of clinical signs generally is rapid. These signs may include exophthalmos, periorbital swelling, chemosis, conjunctivitis, third eyelid elevation, fever, and pain upon opening the mouth (**Figure 19.100**). A soft, fluctuant swelling, hyperemia, or drainage may be present caudal to the last molar on the same side as the exophthalmos (**Figures 19.101** and **19.102**). Tooth root abscesses of the fourth premolar can erupt through the skin causing a draining tract ventral to the orbit.

Differential Diagnosis

Masticatory myositis, salivary gland mucoceles, orbital varices, orbital neoplasia with an inflammatory focus, or extraocular polymyositis.

Diagnosis

Diagnostic evaluation for orbital cellulitis or abscess should include a complete physical examination, a complete blood count, and a thorough oral examination. Due to the pain upon opening the mouth, most dogs will require heavy sedation or general anesthesia for a thorough evaluation and diagnostic sampling. Dental radiography may be indicated to rule out dental disease.



FIGURE 19.100 This dog has orbital and retrobulbar cellulitis. This patient has dramatic, severe conjunctivitis and chemosis, subconjunctival hemorrhage, third eyelid elevation, and significant periorbital swelling. (*Courtesy of M. Schaer.*)

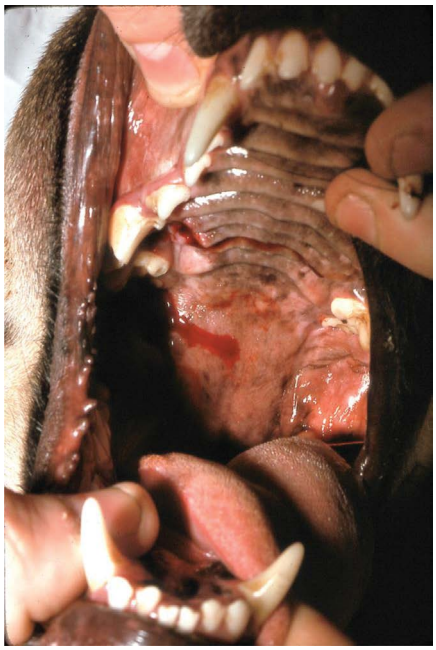


FIGURE 19.101 This is the same dog as in **Figure 19.100**. Note the hemorrhage coming from a draining tract behind the last upper molar on the right side. There is also a wound more rostrally on the soft palate, suggesting that the cause of the orbital cellulitis may have been from the dog chewing on a stick or other foreign material. (*Courtesy of M. Schaer.*)

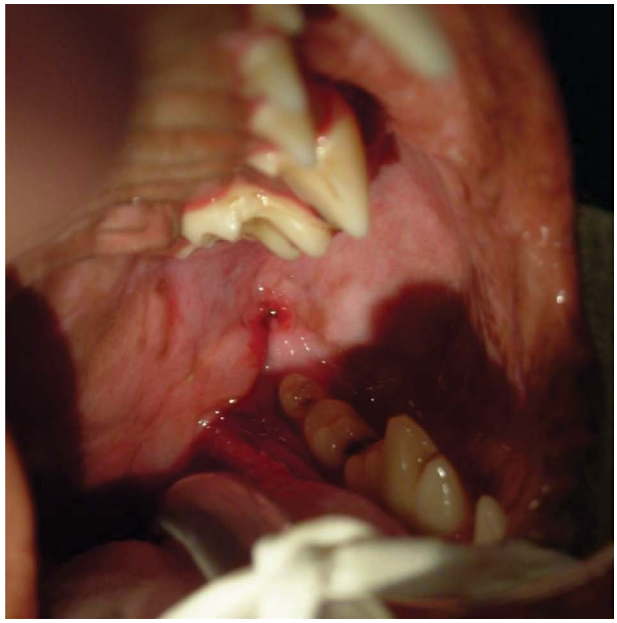


FIGURE 19.102 This dog with orbital cellulitis also has a small draining tract behind the last upper molar. (*Courtesy of M. Schaer.*)

Skull radiographs may demonstrate radiodense foreign bodies, show evidence of extension of inflammation from adjacent sinuses, or reveal orbital fractures. Orbital ultrasonography may demonstrate diffuse hyperechogenicity posterior to the globe or a discrete hypoechoic mass. Ultrasonography of the fellow normal orbit may be useful for comparison and aid in the identification of subtle lesions. Advanced imaging (including magnetic resonance imaging MRI and computed tomography CT) provides the most detailed and accurate images of the orbit and retrobulbar tissue. Fine-needle aspirates for cytologic evaluation and culture and sensitivity testing may be obtained from the retrobulbar space through the conjunctiva, skin, or oral cavity. Ultrasonographic, CT, or MRI guidance may be useful to improve localization when aspiration is performed. CT has not been shown to be an effective imaging modality to differentiate inflammatory versus neoplastic orbital disease, particularly when dealing with soft tissue lesions.

Management

In appropriate cases, therapy consists of establishing surgical drainage under general anesthesia, performing gentle, local irrigation, and administering systemic antibiotics. Before any of these procedures is performed, the operator should ensure that the cuff of the endotracheal tube is well inflated to prevent aspiration of any exudates. The mucosa may be incised behind the last upper molar using a #10 or #15 Bard-Parker scalpel blade, and a closed blunt mosquito hemostat should be inserted to enlarge the opening. The closed hemostat then should be opened gently to create a tract to allow drainage. Purulent material may not be immediately evident after establishment of a drainage tract. Samples should be procured for aerobic and anaerobic culture and sensitivity testing if purulent material is obtained. The tract then may be flushed gently with sterile saline solution. Systemic antibiotics should be administered after drainage has been established or when drainage cannot be established. Mixed aerobic and anaerobic bacterial infections occur most commonly in the dog and cat, and cephalosporins, extended-spectrum penicillins, potentiated penicillins, and carbapenems are recommended for initial antimicrobial treatment of orbital abscesses in dogs and cats. A recent study demonstrated that no bacteria cultured from dogs with orbital cellulitis/abscessation was susceptible to cefovecin, so this medication should not be utilized for treatment of canine orbital cellulitis/abscessation. Administration of systemic nonsteroidal anti-inflammatories and analgesics, including oral opioids such as tramadol hydrochloride, also is recommended until clinical signs resolve. Anti-inflammatory dosages of oral corticosteroids may also be effective; however, immunosuppressive dosages should be avoided. The patient should be evaluated carefully for the ability to completely close the lids over the globe. Many patients with exophthalmos develop secondary exposure keratitis from lagophthalmos. Corneal ulceration may occur in patients with lagophthalmos. All patients with exophthalmos should be evaluated carefully for the presence of a corneal ulceration. If corneal ulceration is present, it should be treated like any other corneal ulcer. In addition, topical lubricating ointments should be applied every 2–6 hours to prevent desiccation of the ocular surface. A temporary tarsorrhaphy may be necessary if the exophthalmos is severe or prolonged.

CONJUNCTIVAL MANIFESTATIONS OF SYSTEMIC DISEASE

Definition/Overview

Many systemic diseases of dogs and cats have nonspecific conjunctival manifestations. Mild hypoxia in cardiovascular disorders is manifested as conjunctivitis with dilation and darkening of conjunctival vessels. Conjunctival petechiation may be seen in any patient with a coagulopathy. Conjunctival venous engorgement may be noticed with congestive heart failure. Anemia may be seen as pallor or hemorrhage of the conjunctiva. Hyperviscosity syndromes are associated with conjunctival congestion. Icterus of the conjunctiva can be seen with any disease syndrome that causes icterus. Systemic tumors such as lymphoma may initially masquerade as conjunctivitis.

LIPID KERATOPATHY

Definition/Overview

Lipid keratopathy may be induced in hypercholesterolemic states by corneal trauma, ulcers, and surgery. Corneal lipidosis is reported in Shelties, Collies, German Shepherd Dogs, and Dobermanns.

Etiology

Lipid keratopathy in the dog is associated with hyperlipidemia, hypothyroidism, pancreatitis, diabetes mellitus, and spontaneous hyperlipidemia but can occur in the absence of any of these disease processes.

Pathophysiology

Lipid keratopathy is characterized by peripheral and central crystalline corneal stromal opacities (Figure 19.103). Corneal lipidosis generally does not completely regress.

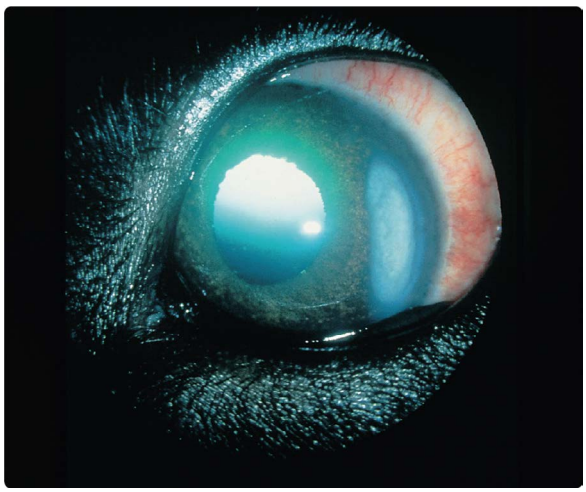


FIGURE 19.103 A limbal infiltrate of lipids accompanies elevated serum triglycerides in this dog with hypothyroidism.

Clinical Presentation

Lipid keratopathy appears as a bilateral, silver or blue–gray, complete ring at the limbus. The central cornea may be affected in advanced cases. Vascularization of the cornea may speed lipid deposition.

Differential Diagnosis

Rule out causes of corneal opacity, including corneal ulcers, edema, scars, and inflammatory cellular infiltrates from inflammatory, infectious, or neoplastic disease.

Diagnosis

Dogs with lipid keratopathy should have a serum lipid profile performed and be screened for thyroid function, pancreatitis, and diabetes mellitus. However, most affected dogs have normal lipid profiles.

Management

Low-fat diets may be beneficial in reducing the corneal opacity. If any inflammation is associated with the lesion, topical immunomodulators such as cyclosporine may be beneficial. Keratectomy may be utilized if vision is significantly affected by the opacification.

EYELID MANIFESTATIONS OF SYSTEMIC DISEASE

Definition/Overview

Chronic blepharitis may be associated with systemic endocrine imbalances such as hypothyroidism. Bacterial, fungal, parasitic, allergic, and neoplastic (lymphoma and mast cell tumors) diseases may affect the eyelids (Figures 19.104–19.108). Atopy, exposure to contact allergens, and autoimmune conditions are reported. Juvenile pyoderma can affect the lids of puppies. Predisposed breeds include the Dachshund, Golden Retriever, Labrador Retriever, Gordon Setter, and Lhasa

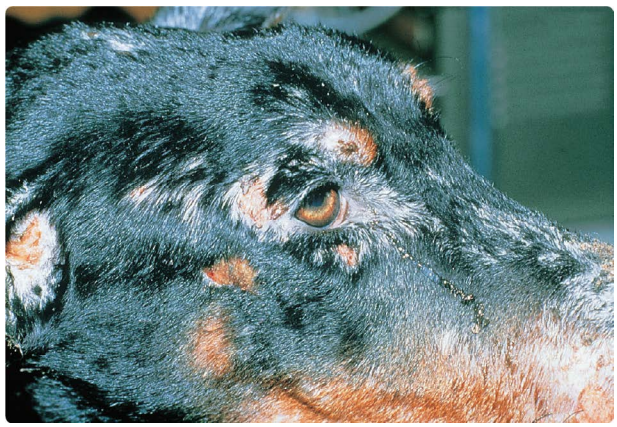


FIGURE 19.104 Alopecia and crustiness of the face and eyelids in a dog with systemic lupus erythematosus.

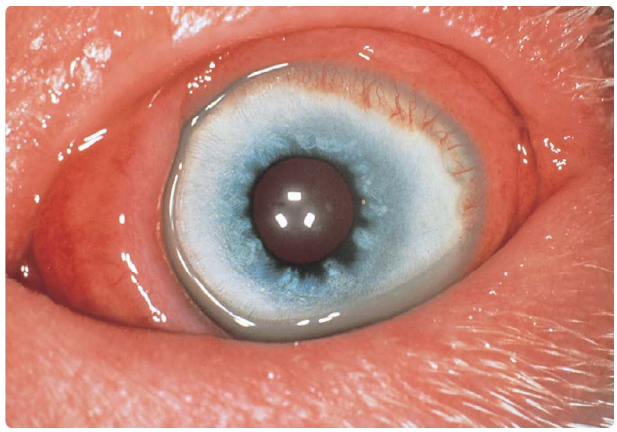


FIGURE 19.105 Blepharoconjunctivitis in a dog with demodicosis.



FIGURE 19.106 Blepharitis in a cat due to *Demodex* spp. infestation. (*Courtesy of K. Gelatt.*)



FIGURE 19.107 Zinc-responsive dermatosis in a Husky dog with bilateral blepharitis.

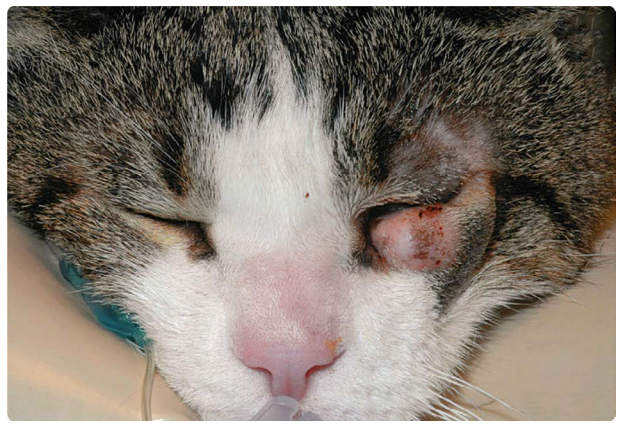


FIGURE 19.108 This mast cell tumor of the left lower lid of a cat was responsive to strontium radiation.

Apso. Papillomatous eyelid growths in young dogs may be associated with oral papillomatosis. Demodicosis causing deep lid pyoderma is reported in dogs and cats.

Bilateral and symmetrical hyperkeratotic "crustiness" of the lids is found in Huskies and Malamutes with zinc-responsive keratosis. An inherited inability to absorb zinc from the intestines causes the problem. Oral and parenteral elemental zinc supplementation is beneficial and will be required for the life of the patient.

Ocular manifestations of Ehlers–Danlos syndrome reported in the dog and the cat have been linked to excessive laxity of the eyelid skin and include entropion with secondary blepharospasm and keratoconjunctivitis (Figure 19.109). Cataract and lens luxation have been reported in the dog. The mode of inheritance in the dog and the cat is considered to be autosomal dominant.

Pemphigus foliaceus is the most common immune-mediated dermatologic condition affecting the feline eyelid and is also found in dogs. Pemphigus foliaceus,

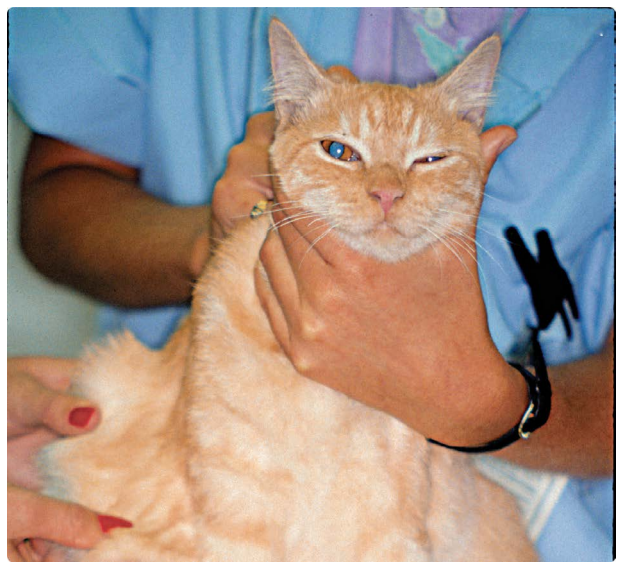


FIGURE 19.109 This cat has left-sided blepharospasm and Ehlers–Danlos-associated cataracts.

pemphigus erythematosus, pemphigus vulgaris, food hypersensitivity, and atopy may also affect the lids of cats and dogs.

UVEAL MANIFESTATIONS OF SYSTEMIC DISEASES

INFLAMMATION OF THE ANTERIOR UVEA

Definition/Overview

Inflammation of the anterior uvea (iris and ciliary body) is termed anterior uveitis or iridocyclitis. Inflammation of the posterior uvea or choroid is termed choroiditis. It is often useful to discuss inflammation of the anterior uvea as a distinct entity from the choroid, but inflammation of one region is generally associated with some degree of inflammation of the other region. Panuveitis is inflammation of the entire uveal tract, with endophthalmitis also involving the anterior chamber and vitreous. Anterior and posterior uveitis disrupt the protective blood–ocular barrier and allow blood and blood-derived compounds access to transparent nonvascular regions of the eye such that vision can be compromised.

Etiology

The most common cause of uveitis in dogs and cats is idiopathic. Patients with idiopathic uveitis are more likely to respond to therapy than patients diagnosed with infectious or neoplastic uveitis. Infectious and noninfectious neoplastic, immune-mediated, and metabolic systemic diseases can cause uveitis. Uveitis in cats is caused by systemic diseases such as FIP, FHV, FeLV-associated disorders, FIV, feline sarcoma virus (FeSV), toxoplasmosis, systemic mycotic infections, and neoplasms. Other causes for feline uveitis include bacteria (tuberculosis) and hypersensitivity reactions. Uveitis in dogs is caused by algae, bacteria, fungi, immune-mediated diseases, metabolic diseases, parasites (Figure 19.110), neoplasms, viruses, and rickettsiae.

Pathophysiology

Inflammatory mediators are released that disrupt the blood–ocular barrier and also cause the pupillary sphincter muscles and ciliary muscles to constrict.

Clinical Presentation

Miosis, conjunctival hyperemia, corneal edema, hypotony, hyphema, hypopyon, iris color change, iridal swelling, keratic precipitates (adherence of clusters of mononuclear inflammatory cells to the corneal endothelium), and pain may be found with anterior uveitis. Cataracts, deep corneal stromal vascularization, endophthalmitis, lens luxation, rubeosis iridis, iris bombé, and secondary glaucoma are adverse sequelae.

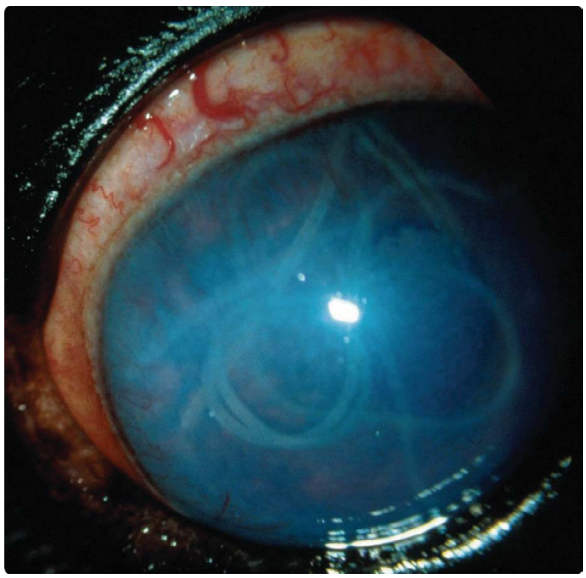


FIGURE 19.110 Heartworm larvae are motile and causing uveitis in this dog.

Choroiditis is associated with decreased vision, choroidal effusion, choroidal granulomas, optic neuritis, exudative RD, retinal hemorrhage, and vitreal opacification (Figures 19.111–19.115).



FIGURE 19.111 Keratic precipitates and hyphema in a cat with anterior uveitis from FIP.



FIGURE 19.112 Iridal neovascularization in a cat with thrombocytopenia.

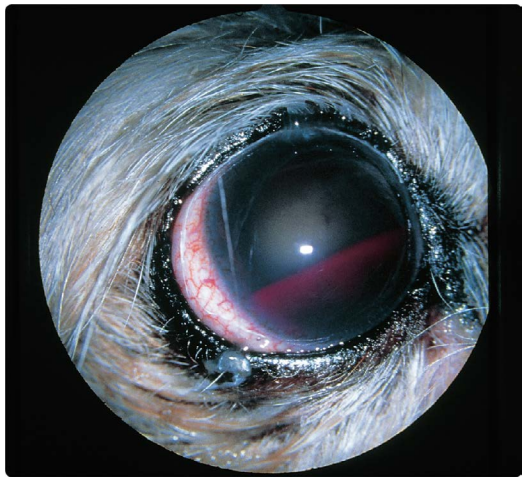


FIGURE 19.113 Hyphema due to renal hypertension indicates anterior uveitis in this dog.



FIGURE 19.114 An iris color change from blue to brown in the right eye of this cat is caused by anterior uveitis as the inflammatory or neoplastic cells infiltrate the iris stroma along with iridal neovascularization.



FIGURE 19.115 Cataracts may occur secondary to uveitis, or they may induce uveitis.

Differential Diagnosis

See Table 19.1.

Diagnosis

Complete physical and ocular examinations are important in animals with uveitis since they may provide diagnostic clues to the etiology. Other diagnostic considerations are a CBC, blood chemistries, serologic tests, and aqueous humor analysis. Cytologic evaluation and bacterial culture of aqueous and vitreous aspirates may help characterize the etiology of the uveitis. The uveitis may be unilateral or bilateral in multiple system diseases.

Management

Acute unilateral uveitis can be treated empirically. Bilateral or chronic uveitis, particularly posterior uveitis, is more likely due to infection and should be treated accordingly.

RETINAL AND OPTIC NERVE MANIFESTATIONS OF SYSTEMIC DISEASES

Definition/Overview

Neuronal ceroid lipofuscinosis (Batten disease) is reported in the English Setter, Tibetan Terrier, American Bulldog, American Cocker Spaniel, Australian Blue Heeler, Border Collie, Chihuahua, Dachshund, Dalmatian, Miniature Schnauzer, Polish Owczarek Nizinny, and Saluki. Ceroid is deposited in neurons of the CNS and in the retina and retinal pigment epithelium. Blindness and neurologic signs occur concurrently. Ophthalmoscopic lesions have not been noted in the English Setter and Tibetan Terrier, but mild tapetal hyperreflectivity, mild retinal vascular attenuation, and optic disc pallor have been noted as early as 2.5 years of age in affected Miniature Schnauzers.

Fucosidosis is an autosomal recessive glycoproteinosis occurring in the English Springer Spaniel. The disease is produced by a deficiency of the lysosomal enzyme α-L-fucosidase. While retinal ganglion cells are vacuolated from the accumulation of substrate, ophthalmoscopic lesions have not been reported with the visual impairment in the affected English Springer Spaniels.

The retinal dystrophy of the Briard dog is caused by a defect in polyunsaturated fatty acid metabolism. Plasma arachidonic acid levels are elevated to twice normal levels in American Briards with this congenital night blindness.

CHORIORETINITIS

Definition/Overview

Posterior uveitis involves the choroid and cannot be clinically distinguished from retinitis. It is therefore usually described as chorioretinitis.

Etiology

Chorioretinitis in the cat is frequently caused by toxoplasmosis, FIP, cryptococcosis, histoplasmosis, and blastomycosis. Toxoplasmosis and cryptococcosis commonly involve only the posterior segment, although anterior and

posterior uveitis may occur. Granulomatous choroiditis in cats can also be associated with several *Mycobacterium* species. Chorioretinitis in dogs is caused by distemper, leptospirosis, brucellosis, Rocky Mountain spotted fever, aspergillosis, blastomycosis, coccidioidomycosis, histoplasmosis, protothecosis, toxoplasmosis, leishmaniasis, and primary and secondary neoplasia. Potentially toxic drugs such as ivermectin can also cause chorioretinitis.

Clinical Presentation

The signs of retinal or chorioretinal inflammation include edema, infiltration with inflammatory cells and granuloma formation, hemorrhage, and possible exudative detachment (Figure 19.116). In dogs, retinal exudates, hemorrhage, and RD are a sequelae to chorioretinitis (Figure 19.117).



FIGURE 19.116 Focal areas of chorioretinitis in a cat.

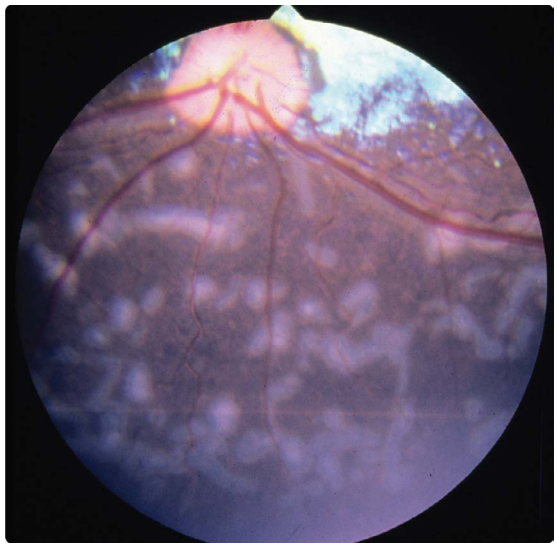


FIGURE 19.117 Chorioretinitis post ivermectin ingestion is present in this Border Collie.

Differential Diagnosis

See Table 19.1.

Diagnosis

Active chorioretinitis causes hyporeflective lesions in the tapetal region. Chorioretinal scars, characterized by hyperreflective areas in the tapetal region or depigmented areas in the nontapetal region, may be observed in normal healthy cats and dogs and are an indication of a previous subclinical inflammatory process (Figures 19.118 and 19.119). If the interior of the globe cannot be visualized due to clinical signs such as fibrin, hypopyon, hyphema, and/or secondary cataract, an ocular ultrasound may be



FIGURE 19.118 Inactive chorioretinitis is manifested with two areas of hyperreflectivity of the retina (more bright yellow areas) over the green tapetum of this dog.

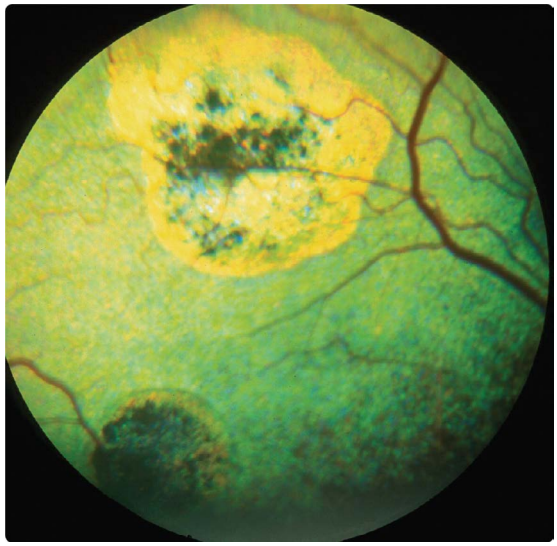


FIGURE 19.119 Hyperreflective areas of retinal atrophy with pigmentation from inactive chorioretinitis in a cat.

beneficial to diagnose a mass lesion or a retinal detachment with subretinal exudate.

Management

Treatment is determined by the inciting cause. Systemic therapy is necessary for treatment of retinal diseases.

UVEAL AND CHORIORETINAL MANIFESTATIONS OF SECONDARY NEOPLASIA

Definition/Overview

Secondary neoplasia may have similar ocular manifestations as both idiopathic or infectious uveitis. It may also present as a more solitary mass rather than diffuse uveitis. Neoplastic uveitis of the dog has been reported to occur in between 4% and 24% of cases. In a recent retrospective study, neoplasia was the cause of the uveitis in 5% of cats.

Etiology

The most common secondary neoplasm to affect both dogs and cats is lymphosarcoma. Numerous other secondary neoplasms have been reported in the dog, including hemangiosarcoma, malignant melanoma, osteosarcoma, mastocytoma, malignant histiocytosis, seminoma, transmissible venereal tumor, transitional cell carcinoma, neurogenic sarcoma, rhabdomyosarcoma, anaplastic fibrosarcoma, pheochromocytoma, and adenocarcinoma of the mammary gland, thyroid gland, parotid salivary gland, adrenal gland, sweat gland or renal, nasal, pancreatic, and pulmonary origin. Other systemic neoplasms reported in the cat include adenocarcinoma of lung, mammary or uterine origin, pulmonary carcinoma, soft-tissue fibrosarcoma, plasmacytoma, and multiple myeloma.

Pathophysiology

As many secondary neoplasms spreads hematogenously, the uveal tract is a site of predilection. The uveal tract is also an area where this hematogenous spread can often be visualized with a complete ophthalmic examination.

Clinical Presentation

Secondary neoplasms tend to have similar clinical signs and mimic anterior uveitis, posterior uveitis, and/or panuveitis secondary to idiopathic or infectious diseases (Figures 19.120 and 19.121). It is more likely for clinical signs of a secondary neoplasm to present bilaterally versus unilaterally, but this is not always the case. Secondary neoplasms often present with clinical signs affecting the choroid, but lymphosarcoma is most commonly associated with signs of anterior uveitis. Patients may have systemic disease related to that specific neoplasm, or the signs may be initially limited to the globe.

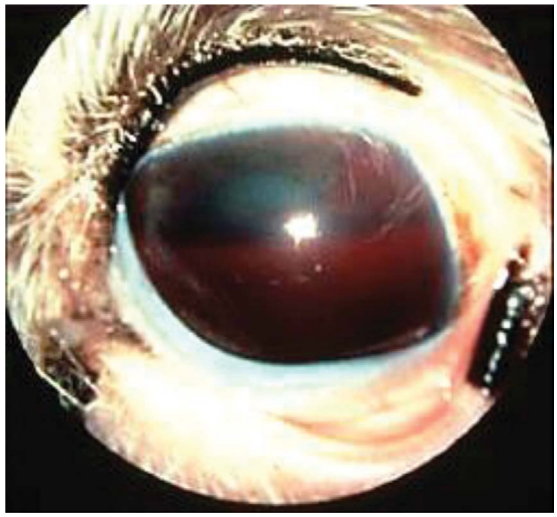


FIGURE 19.120 Hyphema in a dog with metastatic hemangiosarcoma.

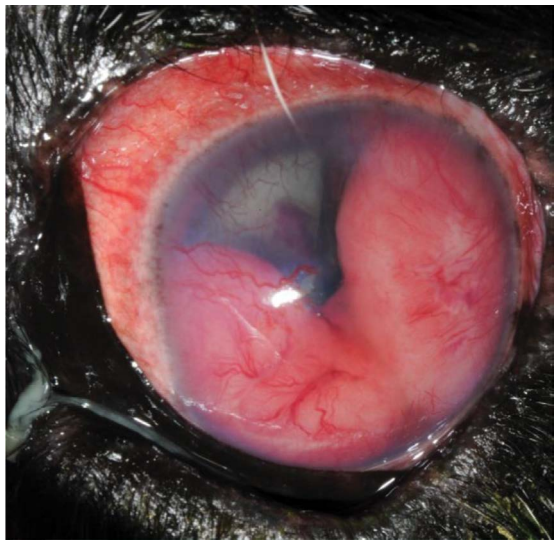


FIGURE 19.121 Scleral injection and iridal masses in a dog with histiocytic sarcoma.

Differential Diagnosis

See Tables 19.1 and 19.2.

Diagnosis

If systemic neoplasia is suspected, it is recommended to perform complete staging of the patient, including physical examination, CBC, serum chemistry panel, urinalysis, thoracic imaging (radiographs or CT), and abdominal imaging (ultrasound or CT). If the interior of the globe cannot be visualized due to clinical signs such as fibrin, hypopyon, hyphema, and/or secondary cataract, an ocular ultrasound may be beneficial to diagnose a mass lesion or a retinal detachment with subretinal exudate. It is also possible for inflammatory or infectious disease to also show similar lesions on ocular ultrasound. Aspirates of masses or mass lesions can

be attempted but may result in exacerbation of anterior uveitis. In most cases, histopathology is the best way to diagnose the secondary neoplasm, and the globe may be the simplest organ to obtain tissue.

Management

The treatment of systemic neoplasia affecting the globe is based on the diagnosis and generally directed at systemic treatment for that specific neoplasm. The treatment of the uveitis is based on the clinical signs present and is similar to uveitis of idiopathic or infectious etiologies.

RETINAL DETACHMENT

Definition/Overview

Retinal detachment (RD) occurs with separation of the inner nine layers of the neurosensory retina from the single outer retinal pigment epithelium (RPE).

Etiology

Bilateral RD suggests a systemic problem. Optic nerve colobomas, severe retinal dysplasia, systemic hypertension due to renal or cardiac failure, intraocular neoplasia, and chorioretinitis may cause RD. Infectious disease and neoplasia generally are associated with exudative retinal detachments. Hypertension can lead to serous retinal detachments with retinal and vitreal hemorrhage. Vitreoretinal dysplasia occurs in certain breeds (Jack Russell Terriers and Shih Tzus) that may lead to spontaneous, rhegmatogenous retinal detachment.

Pathophysiology

The neurosensory retina may be pushed away from the RPE by accumulation of chorioretinal inflammatory or neoplastic exudate in the subretinal space (exudative RD), or the retinal tissue may be torn, with retinal holes forming, and the retina can be pulled away from the RPE by vitreal traction from vitreal inflammation or hemorrhage (rhegmatogenous RD).

Clinical Presentation

The pupils are fixed and dilated if the RD is complete. Small detachments are not associated with blindness, but total RD is a serious problem with a poor visual outcome in most cases.

Differential Diagnosis

See Tables 19.1 and 19.2.

Diagnosis

Ophthalmic examination reveals dilated pupils (if bilateral), visible blood vessels behind the lens, leukocoria, vitreous degeneration and/or hemorrhage, and an opaque, folded retina. Ocular ultrasound is diagnostic of RD in eyes with cataracts or other opacity of the anterior segment that precludes direct visualization of the retina.

Management

The inciting systemic cause of the RD must be identified and treated. Systemic medical therapy may be curative in RD of short duration (e.g., cats with systemic hypertension-induced RD). Rhegmatogenous RD requires advanced microsurgery.

OPHTHALMOMYIASIS

Definition/Overview

Ophthalmomyiasis interna refers to the presence of dipteran fly larva in the eye.

Etiology

Ophthalmomyiasis is caused by the sheep nasal botfly (*Oestrus ovis*), warble fly (*Cuterebra* spp.), or the cattle warble fly (*Hypoderma bovis*). Larvae gain access to the eye via the blood or via direct migration through the tissues of the eye.

Pathophysiology

Larval migration and/or death incite mild-to-severe inflammation of the ocular tissues.

Clinical Presentation

Anterior uveitis and RDs may also occur with ophthalmomyiasis. Cats are more commonly affected than dogs. The presence of arcuate or linear areas of depigmentation in the tapetal and nontapetal fundus may be due to traumatic, degenerative, or inflammatory disease of the retina, RPE, and choroid (Figure 19.122). Clinical findings of ophthalmomyiasis are usually incidental.

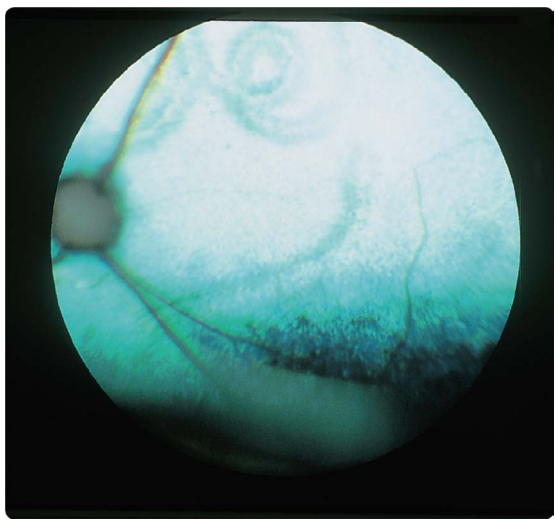


FIGURE 19.122 Curvilinear tracks due to ophthalmomyiasis in a cat.

Differential Diagnosis

See Table 19.1.

Diagnosis

Ophthalmomyiasis is evident as curvilinear tracks of retinal degeneration and retinal hemorrhage in dogs and cats. Larvae may be noticed floating in the vitreous or actively migrating in the retina.

Management

Most cases are incidental findings and require no therapy. Surgical removal of vitreal larvae can be done to remove a source of inflammation.

FELINE NUTRITIONAL RETINAL DEGENERATION OR TAURINE RETINOPATHY

Definition/Overview

Diets deficient in the amino acid taurine cause retinal degeneration and dilated cardiomyopathy in cats.

Etiology

Feline nutritional retinal degeneration occurs in cats that are fed commercial dog food or special diets formulated for dogs. Improperly formulated vegetarian cat diets can result in blindness in cats.

Pathophysiology

Taurine is an essential amino acid for cats with long-term deficiency causing severe retinal lesions. A taurine intake of 110 mg/kg body weight per day is needed to maintain normal retinal structure and function.

Clinical Presentation

Early lesions appear as bilateral, focal, hyperreflective regions in the area centralis. If taurine continues to be deficient in the diet, the retinal lesions progress to symmetrical, horizontal, band-shaped hyperreflective areas dorsal to the optic disc (Figures 19.123–19.126), with advanced stages appearing as diffuse generalized retinal atrophy and complete blindness.

Differential Diagnosis

Any inflammatory or infectious disease can leave a scar, but the location and orientation of the lesions in this disease are rather pathognomonic. Similar lesions can be found in cats that are reported to have only been fed diets with appropriate taurine levels, so it is possible that another syndrome/disease causes similar lesions, but this has not been documented.

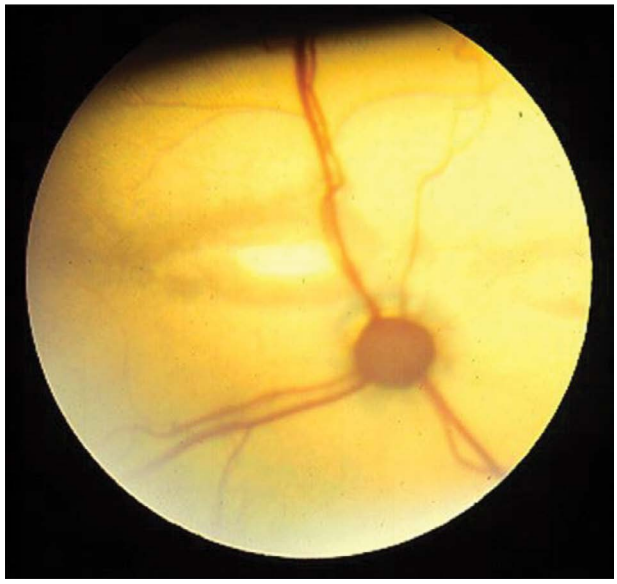


FIGURE 19.123 An oval area of tapetal hyperreflectivity over the area centralis of this cat with taurine retinopathy. This cat appeared to have normal vision.

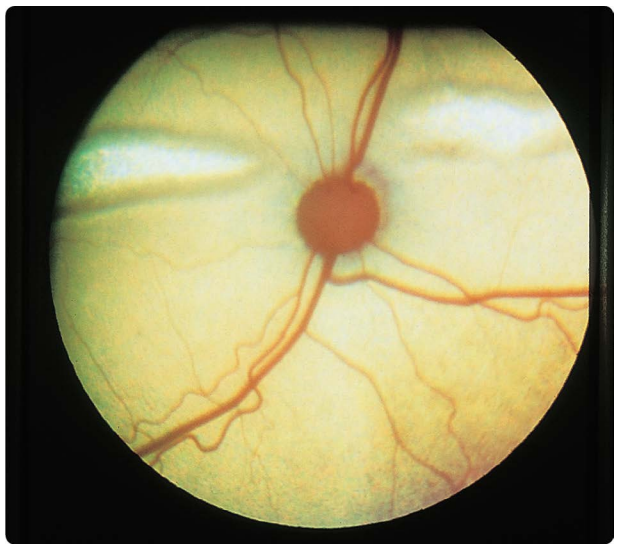


FIGURE 19.124 Two separate areas of hyperreflectivity dorsal to the optic disc in a cat with more advanced taurine retinopathy than the cat in Figure 19.123. This cat appeared to have normal vision.

Diagnosis

Measurement of plasma taurine levels is necessary to determine if taurine deficiency is present (a level less than 20 nmol/mL is critically low). Similar lesions can be found incidentally in cats that are fed appropriate diets and are not taurine deficient.

Management

Restoration of vision with taurine supplement is dependent on the degree of damage. The degeneration in early cases can be arrested if adequate amounts of taurine are

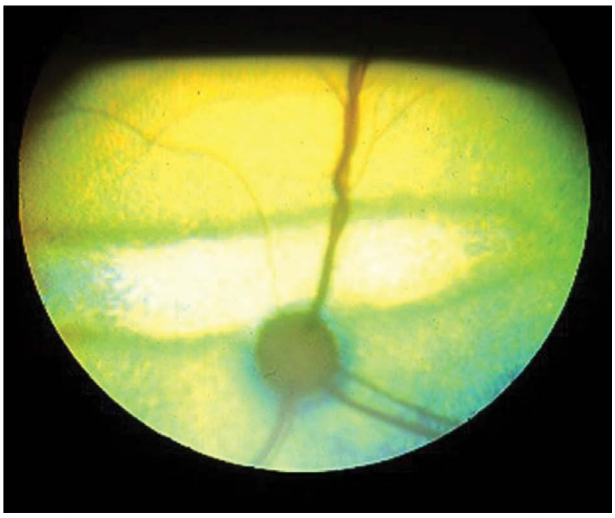


FIGURE 19.125 A complete band of hyperreflectivity dorsal to the optic disc in a cat with more advanced taurine retinopathy than the cat in **Figure 19.124**. This cat appeared to have normal vision.

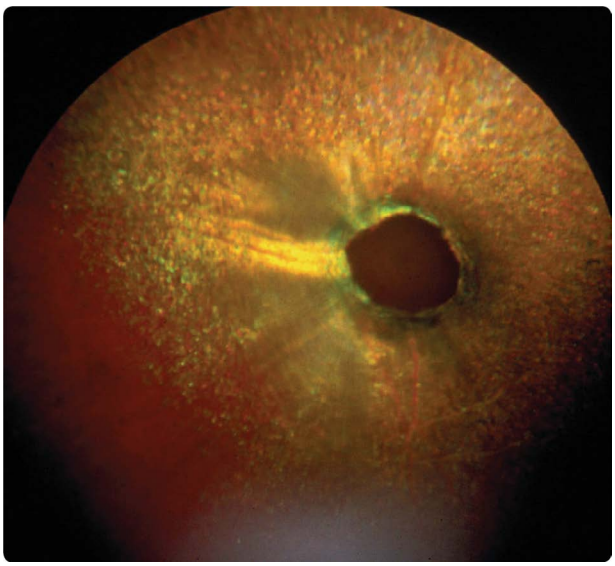


FIGURE 19.126 Diffuse retinal and optic nerve atrophy secondary to chronic taurine deficiency in a cat. This cat will be permanently nonvisual.

included in the diet. However, taurine supplementation is of no value restoring vision in eyes with advanced retinal degeneration and blindness.

ENROFLOXACIN RETINOPATHY

Definition/Overview

Enrofloxacin, a fluoroquinolone antibiotic, has been associated with a rare adverse ophthalmic reaction causing an acute, irreversible, retinal degeneration in cats. Pupils are fixed and dilated, and the retina demonstrates diffuse, severe retinal degeneration. The tapetum is diffusely hyperreflective, and there is significant vascular attenuation. Vision loss is acute and follows enrofloxacin administration. The reported estimated incidence of this adverse reaction is 1 in 122,414 treated cats, or 0.0008%. Toxicity more commonly occurs with parenteral administration. Adherence to the manufacturer's current recommendation for enrofloxacin dosage in cats is advisable but may still be too high for some cats.

OPTIC NEURITIS

Definition/Overview

Optic neuritis is inflammation of the intraocular or intraorbital optic nerve. It may be a manifestation of systemic illness. Optic neuritis is seen more commonly in male, middle-aged, and medium-to-large breeds of dogs. See previous section in this chapter on GME and MUE.

Etiology

Causes include idiopathic, immune-mediated, infectious, inflammatory, and neoplastic disorders.

Pathophysiology

Optic neuritis is more of a clinical syndrome than a single disease. Inflammation of the nerve or adjacent tissue causes damage to the optic nerve axons, vision loss, and optic nerve atrophy.

Clinical Presentation

The optic disc, when affected, appears swollen, with the peripapillary retina displaying evidence of RD. Retinal and optic disc hemorrhages and a vitreal haze may be present. The pupil is fixed and dilated, and vision is absent.

Differential Diagnosis

Intraorbital or retrobulbar optic neuritis must be differentiated from glaucoma, RD, cataracts, and sudden acquired retinal degeneration (SARD), a retinal disease associated with sudden blindness and a normal-appearing retina early in the disease process.

Diagnosis

Diagnosis is based on elimination of possible causes, a CBC, serum chemistry profile, urinalysis, screening for infectious diseases, heartworm antigen test, thoracic radiography, and analysis of CSF. An electroretinogram (ERG) can differentiate acute retinal disease, such as SARD, from intraorbital or retrobulbar optic neuritis. With SARD, the ERG will be flatline, but with intraorbital or retrobulbar optic neuritis, the ERG will be within normal limits.

Management

Oral corticosteroids are the drugs of choice in idiopathic cases. Other immunosuppressive agents, such as cytosine

arabinoside, azathioprine, leflunomide, or cyclosporine A, are also utilized. Many cases, however, relapse.

PAPILLEDEMA

Definition/Overview

Papilledema is noninflammatory swelling of the optic nerve head. Papilledema can result in optic nerve atrophy and blindness if the inciting condition cannot be eliminated.

Etiology

Papilledema is caused by partial obstruction of axoplasmic flow associated with increased intracranial pressure and is not commonly reported in dogs. Vision is present, particularly early in the disease process. Papilledema is seen in dogs with compression of the optic nerve by retrobulbar tumors and in dogs with elevated intraocular pressure in early glaucoma.

Pathophysiology

Sustained mechanical trauma to the optic nerve axons or ischemia to any part of the optic nerve can reduce axoplasmic flow. Axoplasmic flow of both fast and slow components becomes reduced at the lamina cribrosa in papilledema.

Clinical Presentation

Dilated pupils and optic nerve head swelling are present, but vision is maintained.

Differential Diagnosis

Must be differentiated from any cause of optic neuritis.

Diagnosis

Elevation/swelling of the optic disc, blurring of the disc margin, filling in of the optic cup, and protrusion of the disc into the vitreous are found ophthalmoscopically with papilledema. In contrast to optic neuritis, the optic disc is not usually hyperemic, and there are not associated peripapillary and retinal hemorrhages, inflammatory exudates, or peripapillary RD.

Management

Resolution of the elevated intracranial pressure can aid animals with papilledema.

LYSOSOMAL STORAGE DISEASES

Definition/Overview

Several lysosomal storage diseases have been identified in cats and dogs. Storage diseases are characterized by an accumulation of metabolic by-products within lysosomes, the cellular organelles that degrade complex macromolecules. Specific lysosomal storage diseases are normally named according to the specific accumulated product. Because this excess material is a normal cellular component, the histopathologic changes result from physical distortion of affected cells rather than from a toxic effect. Most lysosomal storage diseases with known modes of inheritance are inherited as an autosomal recessive trait.

ALPHA-MANNOSIDOSIS

Definition/Overview

Alpha-mannosidosis is a member of the inherited oligosaccharidoses described in Persian, Domestic Shorthair, and Domestic Longhair cats that results from a deficiency in acidic alpha-mannosidase. Ocular abnormalities described in affected cats include progressive corneal and lenticular opacification and resting nystagmus.

GLOBOID CELL LEUKODYSTROPHY

Definition/Overview

Globoid cell leukodystrophy, or Krabbe disease, is a member of the inherited sphingolipidoses described in the cat that result from a deficiency in galactocerebrosidase activity. The substrate galactocerebroside (i.e., galactosylceramide), a constituent of myelin, and another metabolite of myelin turnover, psychosine (galactosylsphingosine), accumulate. Ocular manifestations of this disease in cats include lack of vestibular ocular reflexes and signs associated with visual deficits, including diminished pupillary light reflexes and reduced menace responses. Galactocerebrosidosis is an autosomal recessive trait in West Highland White and Cairn Terriers. Clinical signs of globoid cell leukodystrophy in dogs are generally rapidly progressive and develop at a young age (2–6 months). Visual deficits and blindness may result late in the course of disease, but ophthalmoscopic lesions have not been observed.

GM1-GANGLIOSIDOSIS

Definition/Overview

GM1-gangliosidosis is caused by a deficiency of a lysosomal hydrolase, beta-galactosidase, which produces an accumulation of GM1-ganglioside in the cerebral cortex and visceral organs. Ganglion cell swelling is the main ocular sign in cats. With respect to dogs, GM1-gangliosidosis is an autosomal recessive condition seen in Alaskan Huskies, English Springer Spaniels, mixed-breed Beagles, Portuguese Water Dogs, and Shiba Inus. Abnormal ocular findings in dogs with this disease are limited to: (1) Central corneal clouding, as

has been observed in Shiba Inus and Portuguese Water Dogs; (2) vision disturbances, as seen in Shiba Inus and Portuguese Water Dogs; (3) strabismus, as has been observed in mixed-breed Beagles and Huskies; and (4) nystagmus, as has been observed in English Springer Spaniels, Portuguese Water Dogs, and Huskies.

GM2-GANGLIOSIDOSIS

Definition/Overview

GM2-gangliosidosis is caused by a deficiency of hexosaminidase. Clinical signs include ataxia, immobility, blindness, dysphagia, and finally seizures or generalized myoclonus (5 months of age), quadriplegia (6 months of age), and death prior to 8 months of age in cats. Variant forms of GM-2 gangliosidosis have been reported in the Japanese Spaniel, the German Shorthair Pointer, and the Golden Retriever.

MUCOLIPIDOSIS II

Definition/Overview

Mucolipidosis II, or inclusion cell disease, is caused by deficient activity of the enzyme N-acetylglucosamine-1-phosphotransferase. Ocular abnormalities detected in cats affected with mucolipidosis II include early-to-late lesions, absent menace response, diminished pupillary light reflexes, and dilated pupils by 4 months of age. Initially, retinal development appears normal until 2.5 months of age, at which time dorsal retinal degeneration develops followed by progressive end-stage generalized retinal degeneration and blindness by 3.5 months of age.

MUCOPOLYSACCHARIDOSES

Definition/Overview

The mucopolysaccharidoses (MPS) are a group of diseases characterized by defective metabolism of mucopolysaccharides (glycosaminoglycans). Three types of MPS have been identified in cats (MPS I, VI, and VII). Corneal clouding is the most debilitating ocular manifestation. Five types of MPS have been identified in dogs (MPS I, II, III, VI, and VII). Corneal opacities are also seen with these conditions in dogs.

RECOMMENDED FURTHER READINGS

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SECTION

IV

MULTISYSTEMIC DISORDERS



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CHAPTER

20

Clinical Toxicology

Tina Wismer

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This chapter will begin with the methods of decontamination followed by a discussion of intoxicants that affect specific organ systems in the body.

DECONTAMINATION

Decontamination is the cornerstone of treating toxicoses. With decontamination, we can change the kinetics of the toxin by reducing absorption and increasing excretion. Decontamination is performed in the asymptomatic patient. It is important that the ABCs (airway, breathing, circulation) are assessed before treating any toxicosis.

Decontamination of ocular exposures includes flushing the eyes with tepid water or saline solution for 20–30 minutes. The severity of ocular exposure can range from mild irritation to corrosion of the ocular tissues depending on the substance, concentration, and contact time.

Dermal exposures can occur to a large variety of substances. Damage to the skin can range from mild irritation to severe burns. Bathing with a mild liquid hand dishwashing detergent and warm water is recommended.

Oral ingestion is the most common route of toxicant exposure in pets. Dilution with milk or water is recommended for irritants and corrosives. Emetics can be used to evacuate the stomach if there are no contraindications. Contraindications include ingestion of corrosives or hydrocarbons, uncontrolled seizure disorders, cardiac failure, significant clinical signs, and previous vomiting. Emetics generally empty 40%–60% of the stomach contents. Potential complications from emesis induction may include aspiration, gastritis, and transient bradycardia (due to vagal stimulation). Emesis is most productive if performed within 1–2 hours post ingestion. Chocolate, grain-based rodenticides, and plant material can stay in the stomach longer (**Figure 20.1**). Feeding a small meal prior to inducing vomiting can increase chances of an adequate emesis. Apomorphine a centrally acting emetic agent is the emetic of choice in the dog. It can be given IV or conjunctivally. It works by antagonizing dopamine in the chemoreceptor trigger zone (CRTZ) quickly (i.e., within 5–10 minutes), resulting in vomiting. Potential adverse effects include

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FIGURE 20.1 Chocolate emesis, several hours after ingestion. (*Courtesy of Mike Lucroy*.)

central nervous system (CNS) and respiratory depression and protracted vomiting. Naloxone can be used to reverse the CNS and respiratory depression. Naloxone will not block the emetic effect. If the toxicant affects the CRTZ, a locally acting emetic such as 3% hydrogen peroxide can be used in dogs. The dosage is 2 mL/kg (1 teaspoon/5 pounds) body weight, not to exceed 45 mL (3 tablespoons). Vomiting usually occurs within 10–15 minutes, and the dose can be repeated once if not initially successful. Overdosing with hydrogen peroxide should be avoided, as it may result in severe hemorrhagic gastritis. Recently, the Food and Drug Administration (FDA) approved the use of a new emetic, Clevor (ropinirole 30 mg/mL ophthalmic solution), which specifically antagonizes dopamine D2-type receptors in the CRTZ causing emesis.

The CRTZ in cats is regulated by alpha receptors and xylazine or dexmedetomidine can be used as an emetic. Yohimbine or atipamezole are used to reverse the CNS and cardiovascular (CV) signs.

Activated charcoal adsorbs toxicants in the gastrointestinal (GI) tract and facilitates excretion via the feces. Xenobiotics that are not effectively adsorbed by activated charcoal include ethanol, methanol, fertilizer, fluoride, petroleum distillates, heavy metals, iodides, nitrates, nitrites, sodium chloride, and chlorates. The recommended dose of activated charcoal for all species is 1–2 g/kg body weight.

Cathartics enhance elimination of substances bound to activated charcoal by moving them through the gastrointestinal tract. Cathartics are not to be used if the animal has diarrhea or is dehydrated. Osmotic cathartics, like sorbitol, pull electrolyte-free water into the gastrointestinal tract. Excessive dosing can lead to hypernatremia (see Sodium Toxicosis).

In situations where emesis cannot be performed, enemas can be helpful to eliminate toxicants from the lower gastrointestinal tract. Plain warm water or soapy warm water (10 mL/kg) is preferred.

Gastric lavage can also be used in mammals to remove recently ingested toxicants. Lavage is contraindicated with caustic substances or hydrocarbons. Gastric lavage is generally considered to be less effective than emesis in removing toxicants from the stomach. Patients are anesthetized and intubated with a cuffed endotracheal tube to protect the airway. Water used at body temperature (5–10 mL/kg) is instilled through a large-bore fenestrated gastric tube. Multiple lavages are performed until the lavage fluid becomes clear. Drainage of the lavage fluid is facilitated by the gravity method, with the patient's head being kept lower than the chest for fluid recovery. Recovered lavage fluid is collected and examined for evidence of ingested toxic substance(s).

Gastrotomy or endoscopy may be indicated for agents that will not readily pass through the gastrointestinal tract (coins, metal objects, expandable polyurethane glues, large amounts of toxic plant material, etc.).

Intravenous lipid emulsions are used to treat lipid soluble toxicants. The mechanism of action is unknown, but the working theory is the "lipid sink/lipid shuttle" theory. Lipophilic drugs are bound in the expanded plasma lipid volume, decreasing free (active) drug. The lipid emulsion of choice for treating lipid soluble toxicosis is the 20% solution and may be given through a peripheral catheter. Veterinary dosing guidelines have been extrapolated from human literature and are considered extra-label. Dosing is at 1.5 mL/kg initial IV bolus, followed by a constant rate infusion (CRI) of 0.25 mL/kg/min for 30–60 minutes. This can be repeated in 4–6 hours if no lipemia is present and the animal is still symptomatic. Uncommon adverse effects of lipids include allergic reactions, lipemia, hypertriglyceridemia, hemolysis (oxidative damage), and elevated liver and pancreatic values. Fat overload syndrome is caused by excessive lipid volumes overwhelming the endogenous lipid clearance mechanisms. Another deleterious side effect is that lipids can also bind antidotes or other therapies being used to treat the patient, resulting in a worsening of the clinical condition. Lipid therapy should be considered when traditional therapies have failed if the toxin is lipid soluble. Intravenous lipid emulsion therapy has been used successfully in the treatment of lidocaine, permethrins, baclofen, ivermectin, diltiazem, and ibuprofen intoxications among others.

Cholestyramine is an anion exchange resin used to lower cholesterol in humans who have not responded to normal therapies. It binds with bile acids in the intestine, preventing their reabsorption and stopping enterohepatic recirculation. This increases the excretion of the toxicant. Cholestyramine has been used in the treatment (off label) of several toxicity is both humans and animals. These include amiodarone, digitoxin, methotrexate, piroxicam, vitamin D, warfarin, blue-green algae, indomethacin, naproxen, and sago palm. The dose is 300 mg/kg p.o. t.i.d. with duration depending on the toxin ingested. For veterinary patients, the powder should be given with or mixed in canned food.

Advanced therapies such as hemodialysis, hemoperfusion, and therapeutic plasma exchange may be available. These procedures should be chosen based on the toxicant (molecule size, distribution, protein binding) and the size of the patient.

NERVOUS SYSTEM

The nervous system can be affected by various toxins, and clinical signs will vary depending on the dose and route of exposure. While the blood–brain barrier and blood–cerebrospinal fluid barrier help protect the brain from toxins, it is still susceptible to injury as it receives a high percentage of cardiac output (20%–25%) and requires a continuously high level of oxygen and nutrients. Refer to Table 20.1 for a list of selected toxicants.

ALCOHOLS (METHANOL, ETHANOL, ISOPROPYL)

Definition/Overview

Alcohols include ethanol (alcoholic beverages [Figure 20.10] liquid medications, hand sanitizers, yeast bread dough), methanol (wood alcohol, windshield washer fluid [Figure 20.11]), and isopropyl alcohol (isopropanol; flea sprays, rubbing alcohol [Figure 20.12]).

Pathophysiology

Alcohols are CNS depressants that act by enhancing the inhibitory effects of neurotransmitters in the CNS. Alcohols are rapidly absorbed orally, and some have dermal absorption (isopropyl).

TABLE 20.1 Selected toxicants and organ system(s) affected

Toxicant	Organ system(s)	Comments
Acetaminophen (paracetamol)	Hepatic, hematologic	See chapter for details
Acids	Dermal, GI	See chapter for details
Aflatoxins	Hepatic	Acute hepatic necrosis
Albuterol	Cardiovascular	See chapter for details
Alcohols (methanol, ethanol, isopropyl)	CNS	See chapter for details
Alkalis	Dermal, GI	See chapter for details
Allium spp. (onions, garlic)	Hematologic	See chapter for details
Alpha-lipoic acid (thioctic acid)	CNS, hepatic, renal	Hypoglycemia and organ failure
Amitraz	CNS, cardiovascular	Atipamezole is antidotal
Amatoxins (mushrooms)	Hepatic	See chapter for details
Aminoglycosides	Renal	Renal tubular necrosis
Amphetamines	CNS, cardiovascular	See chapter for details
Anatoxin-a (blue–green algae)	CNS	Respiratory paralysis
Anatoxin-a(s) (blue–green algae)	CNS	Naturally occurring organophosphate
Anticholinergic insecticides (organophosphates, carbamates)	CNS, PNS	See chapter for details
Anticoagulant rodenticides	Hematologic	See chapter for details
Antihistamines (diphenhydramine)	CNS	Sedation at low doses, stimulation at high doses
Arsenic, arsenical anthelmintics	Gastrointestinal	Hemorrhagic gastroenteritis, hypovolemic shock
Avermectins (ivermectin, moxidectin, selamectin, milbemycin)	CNS	See chapter for details
Baclofen	Musculoskeletal	Centrally acting skeletal muscle relaxant, death from respiratory paralysis
Barbiturates (phenobarbital, pentobarbital)	CNS	Treat with lipids
Benzodiazepines (diazepam, alprazolam)	CNS, hepatic (cats)	Flumazenil is antidotal
Bleach	Gastrointestinal	Vomiting, ulcers with concentrated products
Bromethalin	CNS	See chapter for details

(*Continued*)

TABLE 20.1 Selected toxicants and organ system(s) affected (*Continued*)

Toxicant	Organ system(s)	Comments
Bromide	CNS, gastrointestinal	Vomiting and CNS depression; sodium is antidotal
Brunfelsia spp. (yesterday, today, and tomorrow)	CNS	Tremors can last for weeks
Cannabis spp. (marijuana)	CNS	See chapter for details
Calcium channel blockers (diltiazem, verapamil)	Cardiovascular	Severe hypotension, bradycardia, treat with lipids
Carbon dioxide	Respiratory	Asphyxiation
Carbon monoxide	Respiratory	See chapter for details
Cardiac glycosides – *Nerium* spp. (oleander [**Figure 20.2**]) – *Digitalis* spp. (foxglove [**Figure 20.3**]), kalanchoe, *Convallaria majalis* (lily of the valley [**Figure 20.4**]), digoxin, toads, fireflies	Cardiac	Arrhythmias, digoxin FAB fragments are antidotal
Cholecalciferol rodenticides, calcipotriene and related vitamin D compounds	Renal	See chapter for details
Cyanide (cyanogenic glycosides—apple, cherry, peach, cassava, bamboo shoots, etc.)	Respiratory	– Stops oxygen utilization, cherry red blood (smell of almonds) – Rare in monogastrics
Cycad palm, sago palm (**Figure 20.5**) (*Cycas* spp., *Zamia* spp.)	Hepatic	Hepatic necrosis
DEET	CNS	Seizures
Detergents (nonionic, anionic, cationic)	Dermal, gastrointestinal	– Cationic—chemical burns – Nonionic, anionic—mild GI
Elapids (coral snakes)	PNS	Ascending paralysis
Essential oils	CNS, hepatic	Signs will vary depending on concentration and type of oil
Estrogens	Hematopoietic	Aplastic anemia
Ethylene glycol	Renal, CNS	See chapter for details
5-fluorouracil	CNS, gastrointestinal, hematopoietic	Chemotherapeutic agent—seizures are hard to control
5-hydroxytryptophan (5-HTP)	CNS	See serotoninergic medications for details
Fluoride	Gastrointestinal	Hemorrhagic gastritis
Gold salts	Renal	Glomerulopathy
Grayanotoxin-containing plants – Rhododendrons, azaleas (*Rhododendron* spp.), Laurels (*Kalmia* spp.) – Japanese pieris (*Pieris* spp.)	Cardiac, gastrointestinal	Arrhythmias GI signs are most common in nonruminants
Humulus lupulus (hops)	CNS, musculoskeletal	Severe hyperthermia, dantrolene is antidotal (dogs only)
Hydrogen sulfide	Respiratory	Paralyzes respiratory center
Imidazoline decongestants (oxymetazoline, xylometazoline, tetrahydrozoline, naphazoline)	Cardiovascular	Atipamezole is antidotal
Ionophores	PNS	Paralysis (dogs), neuropathy (cats)
Insoluble calcium oxalates	Gastrointestinal	See chapter for details
Iron	Gastrointestinal, hepatic	Deferoxamine is antidotal
Isocyanates (polyurethane glue)	Gastrointestinal	Foreign body
Isoniazid	CNS	Pyridoxine is antidotal
Isoxazole mushrooms	CNS	Alternating agitation and sedation
Ketoconazole	Hepatic	Cats (rare)

(*Continued*)

TABLE 20.1 Selected toxicants and organ system(s) affected (*Continued*)

Toxicant	Organ system(s)	Comments
Latrodectus spp. (widow spiders)	PNS	Painful muscle cramping
Lead	CNS, PNS, gastrointestinal	See chapter for details
Lectin plants – *Abrus precatorius* (Rosary pea) – *Ricinus communis* (castor bean [Figure 20.6]) – *Robinia* spp. (black locust)	Gastrointestinal, liver, renal	Vomiting most common, can see multiorgan failure
Lilium and *Hemerocallis* spp.	Renal	See chapter for details
Local anesthetics (benzocaine, lidocaine)	Cardiac, CNS, hematologic	Arrhythmias, seizures, methemoglobinemia (esp. cats)
Loxosceles spp. (recluse spiders)	Dermal, hematologic	Necrotic lesions (dogs rarely affected), slow to heal, hemolysis (rare)
Macadamia nuts	Musculoskeletal	Tremors, weakness (only dogs)
Metaldehyde	CNS	Molluscicide, tremors, seizures
Methionine	CNS	Hepatic encephalopathy-type signs
Methylene blue	Hematologic	– For treating methemoglobinemia – Can cause Heinz body anemia (cats)
Methylxanthines (chocolate, caffeine, coffee)	Gastrointestinal, CNS, cardiac	See chapter for details
Metronidazole	CNS	Most common with chronic large doses
Microcystins (blue–green algae)	Hepatic	Hepatic necrosis, hypovolemic and hemorrhagic shock
Minoxidil	Gastrointestinal, cardiac	Vomiting, hypotension, pulmonary edema, death
MAOIs (monoamine oxidase inhibitors)	CNS	Serotonin syndrome—see chapter for details
Muscarinic mushrooms (*Amanita muscaria*)	PNS	SLUDDE signs
Naphthalene	Hematologic	Hemolysis
Nicotine	CNS, gastrointestinal	See chapter for details
NSAIDs	Gastrointestinal, renal, CNS (some), liver (rare)	See chapter for details
Ochratoxin	Renal	Mycotoxin (rare)
Opioids, opiates	CNS	See chapter for details
Paraquat	Respiratory	Herbicide, pulmonary fibrosis
Petroleum distillates, hydrocarbons (gasoline, paint thinner, mineral spirits, oil, wax) (Figure 20.7)	Respiratory, CNS, dermal	Aspiration risk, defatting of skin, light hydrocarbons have CNS effects
Phenazopyridine	Hepatic, hematologic	Converted to acetaminophen, see chapter for details
Phenylpropanolamine (PPA)	Cardiovascular	See chapter for details
Pit vipers	Hematologic, vasculotoxic	Coagulopathy, rarely neurologic (Mojave A-toxin)
Propylene glycol	CNS, renal, hematologic	CNS depression, Heinz body anemia (chronic ingestion)
Pseudoephedrine (Figure 20.8)	CNS, cardiac	See amphetamines for details
Psilocybin mushrooms	CNS	See serotoninergic medications for details
Pyrethrins, pyrethroids	CNS	See chapter for details
Salicylates (aspirin)	Gastrointestinal, hepatic, hematopoietic, CNS	See chapter for details

(*Continued*)

TABLE 20.1 Selected toxicants and organ system(s) affected (*Continued*)

Toxicant	Organ system(s)	Comments
SSRIs (selective serotonin reuptake inhibitors)	CNS	See serotoninergic medications for details
SNRIs (serotonin and norepinephrine reuptake inhibitors)	CNS	See serotoninergic medications for details
Sodium	CNS	See chapter for details
Sodium fluoroacetate (1080)	CNS	Seizures
Spinosad	CNS, gastrointestinal	Makes animals susceptible to ivermectin toxicosis (even when used at appropriate dose)
Strychnine	CNS	Seizures, death from inability to expand chest
Sulfonamides	Hepatic, renal, hematologic	
Tacrolimus	Gastrointestinal	Vomiting, intussusception (up to day 6)
Taxus spp. (yew) (**Figure 20.9**)	Cardiovascular	Arrhythmias, death
Thiaminase (raw fish)	CNS	Cats Thiamine is antidotal
Tremorgenic mycotoxins (penitrem A, roquefortine)	CNS	See chapter for details
Tricyclic antidepressants (TCAs) (amitriptyline, clomipramine)	CNS	See serotoninergic medications for details
Turpentine	CNS, respiratory	Depression, aspiration
Vitis spp. (grapes, raisins)	Renal	See chapter for details
Xylitol	CNS, liver	See chapter for details
Zinc	Hematologic, renal (secondary)	See chapter for details
Zinc phosphide	CNS, respiratory	– Rodenticide, releases phosphine gas – Dangerous to veterinary personnel



FIGURE 20.2 *Nerium oleander*—Oleander.



FIGURE 20.3 *Digitalis* spp.—Foxglove. (*Courtesy of Laura Stern.*)



FIGURE 20.4 *Convallaria majalis*—Lily of the Valley. (*Courtesy of Laura Stern*.)



FIGURE 20.5 *Cycas* spp.—Sago or cycad palm.



FIGURE 20.6 *Ricinus communis*—Castor bean. Plant is much more toxic with parenteral exposure. If beans are swallowed whole, no problems are expected.

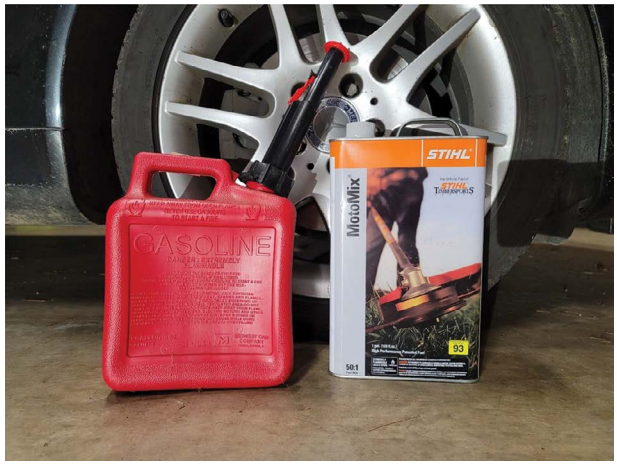


FIGURE 20.7 Light petroleum distillates are volatile and can cause CNS depression, dermal lesions, and aspiration pneumonia. (*Courtesy of Tim Williams*.)



FIGURE 20.8 Pseudoephedrine acts like an amphetamine stimulant in pets. (*Courtesy of Tim Williams*.)



FIGURE 20.9 *Taxus* spp.—Yew. (*Courtesy of Laura Stern*.)



FIGURE 20.10 Alcoholic beverages are a common source of ethanol. (*Courtesy of Tim Williams*.)



FIGURE 20.11 Windshield washer fluid contains methanol. The label reads "can cause blindness and death." This does not happen in nonprimates. (*Courtesy of Tim Williams*.)



FIGURE 20.12 Isopropyl alcohol can be absorbed dermally as well as orally.

Alcohols are all metabolized in the liver (95%) by alcohol dehydrogenase (ADH) to acetaldehyde and then by aldehyde dehydrogenase to an acid. With methanol, primates can develop blindness and seizures. This does not happen in dogs and cats.

Clinical Presentation

Clinical signs develop within 30 minutes to 2 hours post ingestion. Alcohol is irritating to the stomach, and high blood levels will also stimulate emesis. Vomiting, CNS depression, and ataxia (drunkenness) are common. In severe cases, hypothermia, hypotension, hypoglycemia, tremors, seizures, respiratory depression, coma, and death can occur. The risk of aspiration is increased as high blood levels slow the muscles that control the epiglottis.

Diagnosis

History and clinical signs; ethanol levels may be determined from blood, serum, plasma, and urine, but they are seldom done in pets.

Management

The amount of ethanol needed to cause intoxication will vary depending on the type of alcohol ingested (Table 20.2). Emesis may be induced if asymptomatic (risk of aspiration). Activated charcoal is not indicated. Heart rate (HR), blood pressure (BP), and body temperature should be monitored. In animals demonstrating clinical signs, acid–base status and glucose should be monitored for the development of metabolic acidosis

TABLE 20.2 Ethanol concentrations in alcoholic beverages and other household products

	Proof	Percent ethanol v/v
Light beer	5–7	2.5–3.5
Beer	8–12	4–6
Ale	10–16	5–8
Wine, craft beer (barley wine, imperial stouts)	20–40	10–20
Mouthwash		14–27
Amaretto	34–56	17–28
Aftershave		19–90
Schnapps	40–100	20–50
Coffee liqueurs	42–53	21–26.5
Brandy	70–80	35–40
Bourbon, whiskey	80–90	40–45
Rum, cognac, vodka	80–82	40–41
Tequila	80–92	40–46
Gin	80–94	40–47
Cologne/perfume		50
Hand sanitizers		60–95

and hypoglycemia. Intravenous fluids should be given to prevent dehydration and to support the cardiovascular system. Maropitant, dextrose, and sodium bicarbonate should be used as needed. In severely affected comatose patients, the patient's oxygen status should be monitored, and the airway should be protected. Yohimbine, atipamezole, and naloxone have been tried to reverse coma with variable results. Hemodialysis can increase excretion of alcohols.

Prognosis

There are no published minimum lethal oral doses of alcohols in dogs or cats, with most animals recovering within 12–24 hours. Animals that are comatose or who develop aspiration pneumonia have a guarded to grave prognosis. Isopropyl is thought to be 3x more toxic than ethanol.

AMPHETAMINES

Definition/Overview

Amphetamines can be found in both prescription forms (attention deficit hyperactivity disorder [ADHD], weight loss medications) and illicit forms (methamphetamine, methylenedioxymethamphetamine [MDMA], crack).

Pathophysiology

Amphetamines are sympathomimetic alkaloids that stimulate alpha- and beta-adrenergic receptors, causing the release of endogenous catecholamines at synapses in the brain and the heart. This causes peripheral vasoconstriction and cardiac stimulation resulting in hypertension, tachycardia, ataxia, agitation, tremors, and seizures. Amphetamines also increase serotonin and dopamine release in the CNS.

Clinical Presentation

Agitation, tachycardia, hypertension, tremors, and seizures can occur. The time frame will vary with the form of amphetamine ingested. Peak plasma concentrations of amphetamine occur 1–3 hours after ingestion of immediate release or illicit products. Extended-release products (ADHD medications) may have a lag of up to 8 hours before clinical signs are seen.

Diagnosis

History and clinical signs; urine drug screens are not validated in animals but can be used to help with diagnosis.

Management

Asymptomatic animals can have emesis induced and activated charcoal administered. Fluid therapy is important to enhance elimination and for cardiovascular support. Phenothiazines (acepromazine, chlorpromazine) are the drugs of choice for controlling agitation. Diazepam can worsen dysphoria. Cyproheptadine may aid in managing some of the CNS effects secondary to increased serotonin (see Serotoninergic Medications). If tachycardia persists, propranolol or atenolol may be used. Signs may last up to 48–72 hours in severe cases.

Prognosis

Most animals do well if their cardiovascular signs are controlled.

AVERMECTINS

Definition/Overview

Avermectins are macrocyclic lactone parasiticides and include ivermectin, milbemycin, selamectin, doramectin, abamectin, and moxidectin (Figure 20.13).

Pathophysiology

Avermectins bind to glutamate-gated chloride channels in nematodes and arthropods causing hyperpolarization by enhancing the movement of chloride ions into the cell. This results in paralysis. In mammals, avermectins potentiate the release and binding of gamma-aminobutyric acid (GABA) in the CNS. In dogs with the ABCB1 (MDR1) mutation, more avermectin remains in the CNS, resulting in neurologic signs. Labeled preventative doses for moxidectin and ivermectin are safe even in ABCB1 mutation patients.

Clinical Presentation

The most common clinical signs include depression, weakness, recumbency, ataxia, and coma. Other



FIGURE 20.13 Avermectins are commonly used in heartworm medications.

reported signs include tremors, seizures, transient blindness, bradycardia, and hyperthermia. Most severe cases are secondary to veterinary miscalculation with injections or dogs ingesting horse dewormers.

Diagnosis

History and clinical signs; laboratory diagnosis is usually delayed.

Management

If the exposure has just occurred (oral) and the animal is asymptomatic, induce vomiting. Activated charcoal can be given. If the animal becomes comatose, use lipids. Treatment can take days to weeks, and supportive care is very important.

Prognosis

Clinical signs in ivermectin "sensitive" and "nonsensitive" breeds start at 150 mcg/kg and 2,000 mcg/kg, respectively. Prognosis depends on the dose and speed of onset of clinical signs, with animals developing clinical signs within the first 4 hours having a worse prognosis.

BROMETHALIN

Definition/Overview

Bromethalin is a neurotoxic rodenticide (Figure 20.14).

Pathophysiology

Bromethalin uncouples oxidative phosphorylation in CNS mitochondria. This reduction of adenosine triphosphate (ATP) leads to insufficient energy for maintaining sodium-potassium ion channel pumps. Loss of pump activity causes cerebral and spinal cord edema, retention of water in the myelin lamellae, and demyelination injury to long nerves. Continued swelling of the lamellae results in increased intracranial and cerebrospinal fluid (CSF) pressure that is typically unresponsive to therapy.



FIGURE 20.14 Bromethalin baits have become very common with the restrictions placed on second generation anticoagulants. (*Courtesy of Tim Williams.*)

Clinical Presentation

There are two syndromes, high dose (acute) and low dose (chronic). The acute syndrome is seen at doses higher than the lethal dose (LD). Signs can begin within 12–24 hours and include severe tremors, hyperthermia, seizures, coma, and death. With the chronic syndrome, signs may not appear for 72–96 hours and include hindlimb ataxia and paresis, decreased proprioception, CNS depression, and fine muscle tremors.

Diagnosis

History and clinical signs; histopathology is used for confirmation.

Management

For acute intoxication, decontamination is very important. Once significant clinical signs occur, they are difficult to control. Emesis and activated charcoal (multiple doses may be needed) should be performed in the asymptomatic patient. Treatment (mannitol, corticosteroids, diazepam) is directed at controlling the clinical signs and decreasing cerebral edema. Since most of the drug is located within myelin, efficacy is poor. Animals with sublethal doses will require symptomatic and supportive care, with improvement being noted over several weeks.

Prognosis

Once clinical signs occur, prognosis is guarded to grave. Cats are far more sensitive to bromethalin than dogs. Dogs under 16 weeks of age appear to be more at risk, with an LD as low as 0.9 mg/kg.

Cannabis sativa (MARIJUANA)

Definition/Overview

Marijuana (*Cannabis sativa*) is used both recreationally and medicinally in people. As the societal stigma with its use has decreased, more animals are presenting to veterinarians with intoxication. Historically, most pet exposures to marijuana were ingestions of plant material. Now edibles (cookies, brownies, etc., [Figure 20.15]) and concentrates (oils, waxes, shatters) are more common sources for intoxication.

Pathophysiology

The main toxic principle of marijuana is a resin called tetrahydrocannabinol (THC). THC levels have increased in cannabis over the years due to selective



FIGURE 20.15 Edibles are attractive to pets. A "normal" human dose is 10 mg THC. (*Courtesy of Tim Williams.*)

breeding. THC levels in plant material range from 1% to 8%, extracts 28%, and hash oil up to 50%. THC affects various types of neurotransmitters, including dopaminergic, cholinergic, noradrenergic, serotonergic, and GABA.

Clinical Presentation

Clinical signs are dependent on the type of exposure, with inhalational producing signs within 6–12 minutes. Absorption is unpredictable with oral ingestion, with clinical signs often being delayed. Clinical signs can last up to 72 hours with common clinical signs exhibited being lethargy, disorientation, bradycardia, hypothermia, mydriasis, urinary incontinence, as well as CNS signs (ataxia, hyperesthesia, and tremors). Exposure to concentrates may result in patients becoming hypotensive and comatose.

Diagnosis

History and clinical signs. Over-the-counter urine drug screening tests have not been validated for use in dogs.

Management

For acute intoxications in asymptomatic patients, emesis is induced with hydrogen peroxide, since marijuana is an antiemetic at the CRTZ. Activated charcoal is generally not needed. Many cases with plant material ingestion can be managed at home with confinement and monitoring. Symptomatic and supportive care for more severely affected patients consists of intravenous fluids, sedatives (acepromazine 0.05–0.1 mg/mg IV) and muscle relaxants (diazepam 0.25–0.5 mg/kg slowly IV). While receiving in hospital treatment, heart rate (HR), respiratory function, blood pressure, and body temperature should be monitored. Intravenous lipid therapy may be helpful for severely affected (hypotensive, comatose) animals.

Prognosis

Most animals recover well from acute intoxications. Patients that are more severely affected or that consume edibles or concentrates carry a worse prognosis.

CHOLINESTERASE INHIBITORS (ORGANOPHOSPHORUS AND CARBAMATES)

Definition/Overview

These compounds are commonly used as insecticides but are also found in chemical warfare agents (VX, sarin, soman, tabun). Common organophosphates (OPs) include chlorpyrifos, malathion, and tetrachlorvinphos. Common carbamates are aldicarb, carbaryl, methomyl, and propoxur. Cholinesterase inhibitors are being replaced by more insect-specific insecticides.

Pathophysiology

Acetylcholine (ACh) is a neurotransmitter released at synapses and neuromuscular junctions. It facilitates nerve transmission at preganglionic to postganglionic neurons of parasympathetic and sympathetic nervous systems and postganglionic parasympathetic and sympathetic fibers to effector organs and sweat glands. It also facilitates nerve transmission at the motor nerves to skeletal muscle. The enzyme acetylcholinesterase (AChE) found in the synapse rapidly hydrolyzes ACh to control the level and duration of synaptic transmission. Acetylcholinesterase inhibitors bind to and inhibit function of AChE. Without functional AChE, ACh accumulates and causes excessive postsynaptic stimulation. This leads to muscarinic and nicotinic clinical signs.

OPs phosphorylate the enzyme by binding to an esteratic site, while carbamates carbamylate the enzyme. This means that OPs are often referred to as irreversible inhibitors of AChE, and carbamates are reversible. As OPs "age" (chemical change that strengthens the bond to the AChE enzyme), the enzyme will not regain activity, and new enzymes must be synthesized.

Clinical Presentation

Clinical signs appear within a few minutes to several hours after exposure. Signs can be associated with either the muscarinic or nicotinic effects. The muscarinic signs include SLUDDE signs (salivation, lacrimation, urination, defecation, dyspnea, emesis) as well as miosis and bradycardia. Dyspnea is the result of increased bronchial secretions, bronchoconstriction, and decreased contraction of the respiratory muscles. Nicotinic signs are muscle tremors, twitching, weakness, and paresis progressing to paralysis. Central nervous system signs are hyperactivity, tremors, and seizures.

Diagnosis

Whole blood AChE activity (<25% normal activity confirms toxicosis).

Management

Emesis is not recommended due to the potential for rapid onset of clinical signs. Activated charcoal with a cathartic can be given in cases of recent ingestions if asymptomatic. Monitor respiratory effort and HR. Atropine (0.2 mg/kg, one-quarter IV, rest IM or SQ) is an anticholinergic and can be used if animal is bradycardic or has harsh lung sounds. Pralidoxime (2-PAM) is used to treat the nicotinic effects. It reactivates the AChE enzyme. It is not indicated for carbamates and will not work with OPs once aging has occurred. Diazepam or methocarbamol can be used for the nicotinic signs if needed. Because carbamates bind with acetylcholine on a reversible basis, the inhibition of acetylcholinesterase is temporary. Therefore, carbamates have a shorter duration of action that organophosphate insecticides.

Prognosis

There is a wide range of toxicity for these products, and prognosis depends on the dose and clinical signs. Animals suffering from seizures and/or respiratory distress have a guarded prognosis. Cats are especially sensitive to cholinesterase inhibitors.

LEAD

Definition/Overview

Lead is a heavy metal found in various forms (elemental, inorganic, and organic) and from varied sources. Dogs and cats may be exposed to automotive batteries, bone meal supplements, ceramic glazes, lead weights (fishing sinkers, curtain weights), lead-based paints (old houses, artist's paints), lead bullets/shot, lead solder, putty and caulk, linoleum, electronic equipment, roofing felt, and decorative objects. Animals that are shot can develop lead poisoning only if the retained bullet is in an acidic environment (synovial joint, area of inflammation [Figure 20.16]).

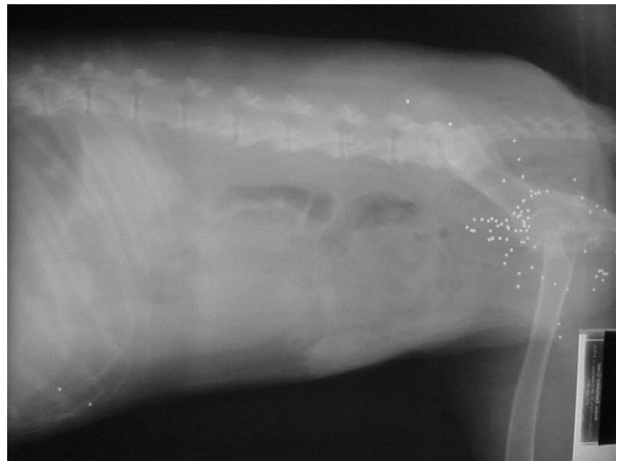


FIGURE 20.16 Lead shot remaining in muscle tissue of dog.

Pathophysiology

Lead can be absorbed from the gastrointestinal or respiratory tract. Lead interferes with multiple organ systems, cell types, enzymes, and tissues within the body.

Young animals absorb lead more readily than adults. Lead is especially toxic to the fetus and young as it inhibits brain development and disrupts the blood–brain barrier. Lead affects central and peripheral neurotransmission by inhibiting calcium. It also interferes with enzymes involved in heme synthesis, resulting in red blood cell abnormalities (basophilic stippling) and anemia. Alterations in synaptic transmission in visceral smooth muscle can alter intestinal motility and tone leading to lead colic. Lead is stored long term in bone.

Clinical Presentation

While lead can affect various body systems, dogs and cats show neurologic and gastrointestinal signs most commonly. Acute lead poisoning is characterized by colic, anorexia, behavior changes, ataxia, tremors, and seizures. Chronic lead poisoning can present with abdominal discomfort, vomiting, diarrhea, anorexia, lethargy, weight loss, anemia, behavior changes, intermittent seizures, and megaesophagus (cats; rare).

Diagnosis

While radiographs with radiopaque objects and findings such as anemia, NRBCs, and basophilic stippling can suggest lead intoxication, whole blood lead levels are the preferred diagnostic test (more than 90% of circulating lead is bound to erythrocytes). Blood lead levels above 0.3–0.35 ppm (30–35 ug/dL) indicate significant lead exposure. With appropriate clinical signs, these levels support the finding of lead toxicosis. Blood lead levels greater than 0.6 ppm (60 ug/dL) are diagnostic for lead toxicosis. With chronic lead poisoning radiopaque lines can be seen in the metaphyseal regions.

Management

Once stabilized, any lead remaining in the GI tract should be removed (emesis, lavage, endoscopy, surgery, enema). Activated charcoal does not bind to heavy metals. Chelation therapy can be started afterwards if indicated. There are several choices of chelation agents: Calcium disodium ethylene diamine tetraacetate (Ca-EDTA), British anti-Lewisite (BAL), d-penicillamine (cuprimine) and succimer (dimercaptosuccinic acid [DMSA]). Refer to Table 20.3 for advantages and disadvantages in chelator selection. Shot or bullets in synovial joints should be surgically removed.

TABLE 20.3 The pros and cons of various lead chelators

Chelator	Pros	Cons
Ca-EDTA	– Most efficient	– Nephrotoxic – Painful injections if undiluted – Chelates essential minerals
BAL	– Removes lead from brain	– Nephrotoxic – Painful injections
Penicillamine	– Oral	– Vomiting – Nephrotoxic – Chelates essential minerals
DMSA	– Oral (rectally if vomiting) – Does not chelate essential minerals – Can use with lead in GI tract	– Expensive

Prognosis

Good in most cases with an early diagnosis and appropriate therapy. The source of the lead must be removed from environment.

METHYLXANTHINES (CHOCOLATE, TEA, COFFEE, GUARANA)

Definition/Overview

Methylxanthines (caffeine, theobromine, theophylline) are stimulants. Chocolate (Figure 20.17), coffee (Figure 20.18), tea, colas, and some human stimulant drugs (NoDoz®, Vivarin®) are common sources of methylxanthines.



FIGURE 20.17 Chocolate will vary in darkness. The darker the chocolate, the more methylxanthines it contains by weight. (*Courtesy of Tim Williams*.)



FIGURE 20.18 Chocolate-covered espresso beans contain both theobromine and caffeine, while coffee only contains caffeine. (*Courtesy of Tim Williams*.)

Pathophysiology

Methylxanthines are thought to antagonize adenosine receptors and stimulate the sympathetic nervous system, resulting in gastrointestinal, cardiac, and neurologic signs. Methylxanthines stimulate the CNS, act on the kidney to stimulate diuresis, and increase the contractility of cardiac and skeletal muscle.

Clinical Presentation

Depending on the form in which the methylxanthine is ingested, onset can be quick (i.e., within 30 minutes) or delayed (i.e., up to 12 hours post ingestion e.g., chocolate). Mild signs, including agitation, polyuria, polydipsia, vomiting, and diarrhea, have been seen with methylxanthine levels over 20 mg/kg. Doses over 40 mg/kg have cardiac signs, with sinus tachycardia being most common. Doses over 60 mg/kg of methylxanthines can cause neurologic signs like tremors and seizures. Death is generally due to cardiac arrhythmias or respiratory failure. Refer to Table 20.4 for theobromine and caffeine content of various types of chocolates.

TABLE 20.4 Caffeine and theobromine content of chocolate

Compound	Caffeine (mg/g)	Theobromine (mg/g)
White chocolate	0.03	0.01
Milk chocolate	0.2	2.04
Semi-sweet (dark) chocolate	0.77	4.86
Unsweetened (baking) chocolate	1.65	13.86
Cocoa powder	2.46	25.99

Diagnosis

History and clinical signs.

Management

Management will vary depending on the dose ingested and clinical signs exhibited. If the patient is asymptomatic, emesis can be induced. Activated charcoal should only be given if over a lethal dose of methylxanthines were ingested. Intravenous fluid therapy should be used as methylxanthines are diuretics. Monitor HR and rhythm, body temperature, and BP as needed. Acepromazine is the drug of choice to treat agitation and mild hypertension. Methocarbamol can be used for tremors, propranolol for tachycardia, and diazepam for seizures. Depending on which type of methylxanthines were ingested (half-life [dog]: Caffeine = 4.5 hours; theobromine = 16.5 hours) signs may persist up to 72 hours.

Prognosis

Prognosis in most cases is good with appropriate care. The lethal dose of theobromine and caffeine is 100–300 mg/kg.

NICOTINE, *Nicotiana tabacum* (TOBACCO)

Definition/Overview

Nicotine is an alkaloid derived from both cultivated (*Nicotiana tabacum*) and wild tobaccos (*N. attenuata*, *N. trigonophylla*). It is found in cigarettes, cigars, other tobacco products (stuff, chewing), patches, gums, nasal sprays, vape liquids, and some insecticides. Refer to Table 20.5 for nicotine content.

Pathophysiology

Nicotine mimics acetylcholine (ACh) at sympathetic and parasympathetic ganglia, neuromuscular junctions of skeletal muscle, and at some synapses in the CNS. Low doses cause depolarization and stimulation of receptors, while higher doses cause stimulation followed by blockade at autonomic ganglia and myoneural junctions of skeletal muscle. Nicotine is poorly absorbed from the stomach but well absorbed from the small intestine. Death is usually due to respiratory failure.

TABLE 20.5 Nicotine amounts

Product	Amount of nicotine
Gum	2–4 mg/piece (Caution: Some contain xylitol)
Low-yield cigarettes	3–8 mg each
Snuff	4.6–32 mg/g (moist) or 12.4–15.6 mg/g (dry)
Nasal spray	10 mg/mL
Cigarettes	13–30 mg each
Patches	15–144 mg each
Cigars Cigar butt	15–40 mg each 5–7 mg each
Liquid nicotine (vape liquid)	0–250 mg/mL

Clinical Presentation

Vomiting is most common as nicotine effects the CRTZ. Other signs include initial excitation, tachypnea, salivation, emesis, and diarrhea, with larger doses causing lethargy, muscle weakness, hypotension, slow respirations, collapse, coma, cardiac arrest, and death.

Diagnosis

History and clinical signs; nicotine can be detected in urine, blood, liver, kidney, or GI contents but not in a timely manner.

Management

If asymptomatic, induce emesis and potentially give activated charcoal. Monitor HR and BP. Symptomatic care includes IV fluids, oxygen, and/or artificial ventilation. Atropine can be given if parasympathetic effects are present. Antacids are contraindicated because they enhance absorption of nicotine. The duration of signs is dose dependent and can vary from 1 to 2 hours following mild exposure up to 24 hours for severe exposures.

Prognosis

Prognosis is most cases is good; it becomes poor if depressive signs occur. The oral LD_{50} (dog) is 9.2 mg/kg.

OPIOIDS, OPIATES

Definition/Overview

Opioids and opiates are synthetic or natural compounds used for pain control in human and veterinary medicine (Figure 20.19). There are both prescription and illicit substances (buprenorphine, butorphanol, codeine, fentanyl, heroin, hydrocodone, hydromorphone, loperamide, methadone, morphine, naloxone, oxycodone, oxymorphone, and tramadol).

Pathophysiology

Opioids act in the CNS to elevate the pain threshold. Opioids are well absorbed from the GI tract, but bioavailability is variable. Some opioids have a large first pass effect (i.e., fentanyl) and must be administered by other routes (CRI, buccal, transdermal) to reach therapeutic blood levels.

Clinical Presentation

Depression and ataxia are most common, but bradycardia and hypotension may be seen with larger doses.



FIGURE 20.19 Many opioids are in combination with acetaminophen. The APAP is usually more dangerous than the opioid.

Respiratory depression is rare in dogs and cats. Cats may show excitatory behavior and urinary retention.

Diagnosis

History and clinical signs; opioids can be detected in urine or serum.

Management

Naloxone (0.04–0.1 mg/kg IV, inhalation [IN], IM) is antidotal. It may need to be repeated as the duration of action is only 60–90 minutes. Treatment times will vary with the half-life of the opioid.

Prognosis

If cardiovascular function can be maintained, then prognosis is good.

PYRETHRINS AND PYRETHROIDS

Definition/Overview

Pyrethrins and pyrethroids are insecticides. Common names include allethrin, bifenthrin, cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, esfenvalerate, etofenprox, permethrin, phenothrin, tetramethrin, and tralomethrin. They are found in shampoos, dips, foggers, spot-ons, granules, and sprays. Concentration is a key factor in determining the risk of toxicosis.

Pathophysiology

Pyrethrins bind to sodium channels on nerves, causing them to remain open and repetitively fire. Most animals are exposed orally or dermally. Cats which interact with recently spot-on treated dogs may be at risk of toxicosis during the period where the product spreads on the haircoat.

Clinical Presentation

Exposures to the low concentration products rarely cause more than GI upset or drooling (the exception is bifenthrin in dogs which can cause tremors). Ear twitching and paw flicking is sometimes seen in cats. Dermal hypersensitivity reactions can be seen with the topical concentrated spot-on products (pruritus, erythema, fasciculations). Concentrated products can also cause vomiting, hypersalivation, muscle tremors, seizures, and possibly death. Onset of signs is within 24 hours.

Diagnosis

History and clinical signs.

Management

Treatment includes bathing with liquid dish washing detergent for dermal exposures and controlling the tremors. High-dose methocarbamol (55–220 mg/kg IV) works best for tremor control. For dermal hypersensitivity reactions, antihistamines or steroids are sometimes needed. Pyrethrins have no direct action of the liver or kidneys, but fluids are needed to protect the kidneys from myoglobinuria secondary to tremors. Diazepam can be used for seizure control. Lipid therapy may be used if there is no response to traditional therapies. Treatment may last 24–48 hours.

Prognosis

Cats are more sensitive to concentrated pyrethrins than dogs but have a good prognosis with appropriate treatment.

SALT TOXICOSIS (WATER DEPRIVATION)

Definition/Overview

Hypernatremia from salt poisoning can be due to either ingestion of excess sodium (direct sodium ion toxicosis), water deprivation (indirect sodium ion toxicosis), or fluid shifts (indirect sodium ion toxicosis secondary to free water loss). With direct sodium ion toxicosis, there is excess sodium intake (brine, homemade playdough, rock salt, bouillon cubes, seawater). With indirect sodium ion toxicosis, there is either decreased water intake or osmotic agents in the GI tract that cause a loss of free water from the vasculature.

Pathophysiology

Sodium acts as a mucosal irritant stimulating vomiting. As sodium is absorbed from the GI tract, the serum sodium increases. Sodium then passively diffuses into the CSF, increasing its sodium concentration. Elevations in brain sodium leads to neurologic signs (ataxia, tremors, seizures). Sodium uses ATP for active transport out of the CSF. Unfortunately, elevated sodium levels in

the CNS inhibit glycolysis, so there is no ATP production, and the removal of sodium from the brain does not occur. The brain protects itself from dehydration by producing idiogenic osmoles (amines). This takes about 24 hours to occur. The danger with these osmoles is that blood levels of sodium fall more rapidly than brain levels, so a concentration gradient is established. Water will follow the concentration gradient and enter the CSF, resulting in cerebral edema and severe neurologic signs. It is very dangerous to quickly rehydrate animals with chronic hypernatremia.

Clinical Presentation

Vomiting generally occurs within 2 hours of ingestion. Polyuria, polydipsia, tremors, seizures, hyperthermia, and death can occur.

Diagnosis

Serum sodium >160 mEq/L.

Management

Management changes depending on the timeframe of hypernatremia. If acute hypernatremia (<24 hours), the sodium can be dropped quickly with low-sodium IV fluids (D5W) and plain water enemas. With chronic hypernatremia (>24 hours), idiogenic osmoles have formed in the brain, and the sodium must be dropped slowly to prevent cerebral edema. The hypernatremia is corrected over 48–72 hours using fluids that most closely match the serum sodium.

Prognosis

The prognosis is good for acute hypernatremia but guarded for chronic. The minimal lethal dose for sodium chloride in dogs is 4 g/kg.

SEROTONERGIC MEDICATIONS

Definition/Overview

There are several classes of pharmaceuticals that affect serotonin levels in the CNS (5-hydroxytryptophan [5-HTP], monoamine oxidase inhibitors [MAOIs], serotonin and norepinephrine reuptake inhibitors [SNRIs], selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants [TCAs], and novel antidepressants). Refer to Table 20.6 for more information.

TABLE 20.6 Serotoninergic medications

Classification	Common generics
Amphetamines	Amphetamine, dextroamphetamine, lisdexamfetamine, methylphenidate
MAOI	Phenelzine, selegiline, tranylcypromine
SSRI	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline
SNRI	Desvenlafaxine, duloxetine, venlafaxine
TCA	Amitriptyline, clomipramine, doxepin, imipramine, nortriptyline
Novel antidepressants	Bupropion, trazodone, vilazodone

Pathophysiology

Different class of drugs have different mechanisms to increase serotonin in the CNS: Increased production (5-HTP), increase release (amphetamines, MAOIs, cocaine), inhibit metabolism (MAOIs), inhibit serotonin reuptake (SSRI, SNRI, TCA, amphetamines, cocaine, dextromethorphan) and serotonin agonists (buspirone, sumatriptan, LSD). High levels of serotonin in the CNS result in "serotonin syndrome" and are characterized by gastrointestinal, cardiovascular, neurologic, and respiratory signs.

Clinical Presentation

Lethargy and ataxia are common with low-dose exposures. As the doses rise, serotonin syndrome occurs and is characterized by vomiting, vocalization, mydriasis, disorientation, tremors, tachycardia, hypertension, blindness, and hyperthermia. Seizures, coma, and death are rare with most serotonergic medications (more common with 5-HTP).

Diagnosis

History and clinical signs.

Management

Emesis can be attempted in asymptomatic pets with recent exposures. Activated charcoal binds to serotonergic medications and can be given if asymptomatic. Monitor body temperature. Start IV fluids to support the cardiovascular system, aid in thermoregulation, and maintain renal blood flow. Phenothiazines (acepromazine, chlorpromazine) work well for controlling agitation. The use of cyproheptadine (1.1 mg/kg p.o. dogs; 2–4 mg p.o. cats), a nonselective serotonin antagonist, has shown to be a helpful adjunct in managing the stimulatory signs. Propranolol also has some serotonin blocking effect and may be of benefit if animals are tachycardic. Diazepam can be used for seizures.

Prognosis

Good for most serotoninergic medications. 5-HTP ingestion is more serious and has a guarded prognosis.

TREMORGENIC MYCOTOXINS

Definition/Overview

Tremorgenic mycotoxins are indole alkaloid compounds produced by molds. These toxins are produced from a variety of different fungi that grow on dairy products,

grains, nuts, and legumes. Compost piles and fruit/nut trees in the environment may provide a source of tremorgens.

Pathophysiology

Tremorgenic mycotoxins inhibit glycine leading to full-body tremors.

Clinical Presentation

Signs start as fine muscle tremors and can progress to more severe full-body tremors when stimulated. Vomiting is common. Hyperactivity, seizures, tachycardia, and death are rare.

Diagnosis

History and clinical signs; laboratory confirmation is available but not timely.

Management

Asymptomatic animals exposed to moldy foods should be decontaminated via emesis. Activated charcoal may be given. Tremors respond best to large doses of methocarbamol (55–220 mg/kg IV to effect). Supportive care includes intravenous fluids and thermoregulation. Signs may persist for several days.

Prognosis

Good in most cases, guarded if seizures occur.

Hepatic

The liver is the largest organ in the body and metabolizes almost every xenobiotic introduced into the body. There are various mechanisms of hepatic injury, and the liver can respond to toxic insults with hepatic lipidosis, hepatocellular necrosis (centrilobular, midzonal, periportal, massive), nodular regeneration, pigmentation, megalocytosis, biliary system damage, neoplasia, and liver atrophy. Refer to Table 20.1 for a list of selected heptatotoxicants.

ACETAMINOPHEN (PARACETAMOL)

Definition/Overview

Acetaminophen (paracetamol, nonaspirin pain reliever, APAP) is a synthetic nonopiate derivative of p-aminophenol.

Pathophysiology

APAP acts primarily in the CNS to increase the pain threshold. The metabolism of acetaminophen occurs primarily in the liver. There are three major pathways: Glucuronide conjugation, sulfate conjugation, and oxidation by cytochrome P450 enzymes. Glucuronide and sulfate conjugation form nontoxic metabolites. Cats, unfortunately, have only about one-tenth the acetaminophen biotransformation ability of dogs due to decreased microsomal uridine 5'-diphospho (UDP)-glucuronosyltransferase enzyme activity. Cats mostly use the sulfate conjugation pathway, but it can be saturated due to the limited availability of inorganic sulfates. Acetaminophen-induced hepatoxicity is due to the formation of the oxidative metabolite, N-acetyl-para-benzoquinone imine (NAPQI). This is produced by the cytochrome P450s as the other pathways become saturated. Centrilobular hepatic necrosis is most common due to the concentration of P450s in that area. If glutathione (GSH) is available, NAPQI will be bound and inactivated. GSH stores become depleted 16–24 hours after exposure to acetaminophen, increasing the risk of cellular damage. Another acetaminophen metabolite is para-aminophenol (PAP). It has been implicated in causing methemoglobinemia. GSH becomes depleted in erythrocytes, and hemoglobin is oxidized to methemoglobin, which cannot carry oxygen. Methemoglobin values increase within 2–4 hours, followed by Heinz body formation (Figure 20.20).

Clinical Presentation

Depression, weakness, tachypnea, tachycardia, and chocolate-colored gums are seen most commonly. Facial or paw edema can occur, along with death. Liver necrosis is less common in cats than in dogs. Clinical signs of methemoglobinemia may last 3–4 days. Hepatic injury may not resolve for several weeks.

Diagnosis

History and clinical signs; laboratory confirmation is not timely.

Management

Emesis can be induced, but peak blood levels are reached in 10–120 minutes. Activated charcoal can

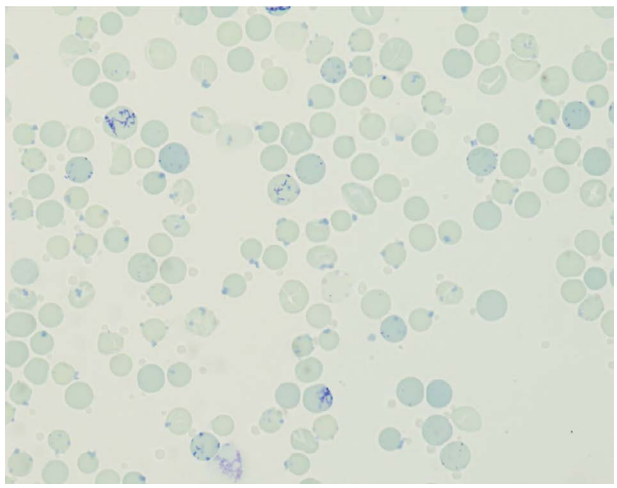


FIGURE 20.20 Heinz body anemia. Canine blood, 100x, new methylene blue stain. (*Courtesy of Amy Schnelle, University of Illinois Urbana-Champaign.*)

be given if the pet is asymptomatic. Monitor liver values for 48 hours and give liver protectants (SAMe) as needed. Symptomatic patients need initial stabilization, including oxygen if dyspneic. N-acetylcysteine (Mucomyst®, NAC) is antidotal as it is a precursor in the synthesis of glutathione, provides sulfhydryl groups for sulfate conjugation, and it can bind directly with NAPQI. NAC decreases the half-life of methemoglobinemia in cats from 10 to 5 hours. An initial loading dose of 140 mg/kg (dilute to 5% in dextrose or sterile water) is given, followed by 70 mg/kg p.o. q.i.d. for 7 treatments. Continue treatment until normal. Ascorbic acid provides a slow-acting, nonenzymatic reduction of methemoglobin back to hemoglobin.

Prognosis

Prognosis is good if the animal is treated promptly. Animals with severe signs of methemoglobinemia or with hepatic damage have a guarded-to-poor prognosis.

HEPATOTOXIC MUSHROOMS

Definition/Overview

Amanita, *Galerina*, and *Lepiota* spp. mushrooms have been associated with liver necrosis.

Pathophysiology

Hepatotoxic mushrooms contain amatoxins. Amatoxins are bicyclic octapeptides that inhibit ribosomal protein synthesis and cause loss of cytoskeletal function, resulting in hepatocyte necrosis. Amatoxins are first taken up by cells in the GI tract, causing vomiting. Then, following systemic absorption, the amatoxins are taken up into hepatocytes via OATP1B3, where they cause liver damage.

Clinical Presentation

Vomiting (6–24 hours) is usually the first sign followed by lethargy and diarrhea. The hepatic phase (icterus, hypoglycemia, coagulopathy, coma) begins 36–48 hours after ingestion. Many humans require liver transplantation.

Diagnosis

History and clinical signs; cage side tests and laboratory confirmation from urine are available.

Management

Emesis and activated charcoal are recommended in witnessed exposures for the first 1–2 hours. Later implementation can worsen the situation. Monitor serum glucose, liver and renal values, acid/base, electrolytes, packed cell volume/total protein (PCV/TP), and coagulation parameters. Significant amounts of amatoxin are eliminated in the urine during the first 48 hours, so a diuretic rate of intravenous fluids is helpful. The goal is to sequester amatoxins in the gallbladder to decrease the risk of liver necrosis. The animal should be n.p.o. to limit gallbladder contraction. This should be continued until the liver values begin to improve. Octreotide (10–20 ug bolus IV then 10–20 ug/h CRI) will inhibit gallbladder contraction and inhibit the OATP1B3 transporter molecule (decrease hepatocyte amatoxin exposure). Silibinin (milk thistle) reduces the uptake of amanitin into hepatocytes, but it is not available in the United States in the injectable form (oral has poor bioavailability). Percutaneous bile drainage (ultrasound-guided needle aspiration) will remove the amatoxins from the body. Historically, treatment with acetylcysteine, penicillin G, and cimetidine has had poor results. Because amatoxins are cleared from the serum in the first 24–48 hours either by the kidneys or via uptake into hepatocytes, extracorporeal elimination techniques are not likely to be useful.

Prognosis

Prognosis is guarded to grave.

XYLITOL

Definition/Overview

Xylitol is a sugar alcohol used as a natural sweetener. It is found in sugar-free products from gums, candies, pudding, high-protein peanut butter, toothpaste, quick dissolve and chewable medications, as well as in powdered form for baking.

Pathophysiology

In humans, xylitol does not cause a significant increase in blood glucose or insulin secretion. However, in dogs, xylitol causes rapid, dose-dependent insulin release followed by hypoglycemia. With larger doses, liver necrosis can occur. It is thought that xylitol uses the pentose phosphate pathway (PPP) instead of the tricarboxylic acid (TCA; Krebs cycle) for metabolism. This means there is a shortage of ATP. Hypoglycemia can start at 100 mg/kg and liver effects around 400 mg/kg.

Clinical Presentation

Initial signs fit with hypoglycemia, vomiting, weakness, ataxia, depression, hypokalemia, seizures, and coma.

Diagnosis

History and clinical signs.

Management

Emesis can be induced if asymptomatic. Activated charcoal is not efficacious. Depending on the form of xylitol ingested, dogs can show signs of hypoglycemia in as few as 30 minutes (powder, candy, medications), or it may be delayed for several hours (gum). Dextrose (bolus +/- CRI) can be administered to treat hypoglycemia. It may

also be used to support the liver. Treatment should continue until blood glucose normalizes. Other liver protectants such as SAMe or n-acetylcysteine may be started, but it is unknown how efficacious they are. With liver necrosis, monitoring of coagulation values and plasma transfusions may be needed.

Prognosis

Good in most cases, guarded when liver necrosis occurs.

Renal

The kidney is susceptible to toxicants because of its high relative blood flow (~25% of cardiac output) compared with its low percentage of total body weight. The proximal tubule is the most sensitive portion the nephron to both hypoxia and toxicosis. There are many toxicants that can directly and indirectly affect the kidneys (refer to Table 20.1).

CHOLECALCIFEROL AND VITAMIN D_3 ANALOGS

Definition/Overview

Vitamin D and vitamin D analog toxicoses (calcipotriene, calcitriol) are becoming more common. In addition to prescription-strength vitamin D capsules (50,000 IU) and psoriasis creams (Dovonex®, Taclonex®), over-the-counter (OTC) vitamin D has become more popular, and there has also been an increase in cholecalciferol-containing rodenticides.

Pathophysiology

Cholecalciferol and vitamin D analogs cause elevations of serum calcium and phosphorus, leading to soft tissue mineralization and renal failure. Cholecalciferol is metabolized to 25-hydroxycholecalciferol (calcifediol) and then to 1,25-dihydroxycholecalciferol (calcitriol = active metabolite). Calcitriol increases intestinal absorption of calcium, stimulates bone resorption, and increases renal tubular reabsorption of calcium. Elevated serum calcium causes heart issues and bleeding secondary to mineralization of the vessels, kidneys, stomach wall, and lungs.

Clinical Presentation

As serum calcium begins to rise, vomiting, depression, polyuria, and polydipsia begin by 12–18 hours post ingestion. Elevations in phosphorus can be seen within 12 hours, with elevations in calcium, BUN, and creatinine being noted within 24 hours. As soft tissue mineralization progresses, the pet will become oliguric, then anuric. Problematic doses can be as low as 0.1 mg/kg.

Diagnosis

Elevated calcium with confirmatory clinical signs.

Management

Timing of emesis varies depending on the form ingested. If tablets or creams have been ingested, emesis should occur within 60 minutes; for bait, within the first 4 hours. Decontamination should continue with one dose of activated charcoal followed by cholestyramine (300 mg/kg q.8 h. for 4 days). Obtain baseline (<8 hours post exposure) calcium, phosphorus, blood urea nitrogen (BUN), and creatinine for future comparison. Monitor calcium daily for 4 days. If no elevations of calcium are seen by 4 days, no further treatment is needed. If calcium is rising, bisphosphonates (pamidronate, zoledronate) can be used to inhibit osteoclasts. Other treatments to reduce calcium include 0.9% sodium chloride (NaCl) fluids, furosemide, and prednisolone (adjust fluids accordingly). Sodium chloride and furosemide increase calcium excretion in the urine. Steroids reduce bone resorption, decrease intestinal absorption, and increase renal excretion of calcium. Phosphate binders should also be administered. The animal should be maintained on a low-calcium diet. Monitor blood values frequently for 5–6 weeks. Treatment may be prolonged because of the long half-life of calcifediol (16–30 days).

Prognosis

Prognosis decreases with prolonged elevations in calcium. Lesions from soft tissue mineralization (renal, cardiac, GI) are not reversible and may result in long-term sequelae or sudden death. Anuria is a poor prognostic factor.

ETHYLENE GLYCOL

Definition/Overview

Ethylene glycol (EG) is found most commonly in automotive radiator antifreeze (Figure 20.21) but can also be found in brake fluids, aircraft deicers, condensers, heat exchangers, snow globes, home solar units, and portable basketball goal post bases.



FIGURE 20.21 Ethylene glycol antifreeze can be purchased in both full strength (95%–100%) and prediluted (50%). (*Courtesy of Tim Williams.*)

Pathophysiology

As a parent compound, EG is about as toxic as other alcohols. The metabolites are, unfortunately, quite toxic. Ethylene glycol is initially oxidized to glycolaldehyde by alcohol dehydrogenase (ADH), it is then oxidized to glycolic acid, and then to glyoxylic acid. Glyoxylic acid is primarily converted to oxalic acid. Ethylene glycol and glycolaldehyde are mainly responsible for the initial CNS signs. The accumulation of glycolic acid and glyoxylic acid cause metabolic acidosis. Acidosis will alter consciousness and increase cerebral damage. Glycolic acid accumulates because the lactic dehydrogenase enzyme that metabolizes glycolic to glyoxylic acid becomes saturated. Renal tubular injury is from the direct nephrotoxic action of glycolaldehyde and glyoxylate on the renal tubules as well as mechanical injury and obstruction by calcium oxalate crystals.

Clinical Presentation

Due to the metabolism of EG, the clinical signs will change as time progresses. The initial signs of ataxia, lethargy, and polyuria/polydipsia (PU/PD) are from the alcohol effects in the CNS and are seen around 30 minutes post exposure. The pet may appear to recover or worsen. The cardiopulmonary stage generally occurs from 12 to 24 hours following exposure. Tachypnea, tachycardia, depression, and pulmonary edema may occur as this is due to the severe acidosis and electrolyte disturbances that are from the metabolites. The renal stage can be seen as early as 12 hours, especially in cats, but is generally seen within 24–72 hours following exposure. Clinical signs include azotemia, depression, anorexia, vomiting, abdominal pain, oral ulcers, oliguria/anuria, and seizures. This is due to renal tubular injury from EG metabolites and calcium oxalate crystals. Urinalysis shows low urine SG, glucosuria, and possibly calcium oxalate crystals (only 40% of animals develop these). BUN and creatinine become elevated but usually not before 12 hours post exposure; therefore, BUN and creatinine are of minimal benefit in diagnosing early exposures. Death can occur at any stage.

Diagnosis

Diagnosis is based on history, clinical signs, and confirmatory laboratory testing. There are some cage side tests available for in clinic use. Make sure to read the insert about potential false-positive results. EG levels may be able to be run at a human hospital. Greater than 50 mg/dL in dogs is significant. In cats, any level above zero should be treated. Other supportive tests include measuring anion gap (>25 mEq/L) or serum osmolal gap (>20 mOsm/kg). Observation, via Wood lamp, of fluorescence in urine, stomach contents, or on paws/muzzle may suggest exposure (fluorescein dye is added to automotive antifreeze to help in detecting radiator leaks).

Management

Treatment of EG toxicosis must be timely and aggressive. For recent (within 45 minutes) exposures and asymptomatic animals, induce vomiting or perform gastric lavage. Activated charcoal does not bind well to EG. Based on exposure history and/or diagnostic test results, the use of either fomepizole or ethanol infusion is indicated. IV ethanol and fomepizole (4-MP, 4-methylpyrazole) are used to delay the breakdown of EG to its more toxic metabolites. Best results with either of these treatments require initiation of treatment as soon as possible following ingestion. The dose for 20% ethanol in the dog: 5.5 mL/kg q4hr for 5 treatments; then every 6 hrs for 4 treatments. Cats: 5.0 mL/kg q6hrs for 5 treatments; then q8hrs for 4 treatments. Ethanol has the advantages of being inexpensive and readily available, but it has some serious drawbacks, including worsening of metabolic acidosis and CNS depression. These side effects are lessened if using a CRI instead of bolus dosing. Fomepizole is administered every 12 hours for 36 hours. The main drawback with fomepizole is the cost and the need to have it compounded. Symptomatic animals should be stabilized as needed. IV diuresis is important, high infusion rates of crystalloids are necessary to correct dehydration and hypoperfusion. Treat acidosis and renal failure as needed. Oliguric or anuric animals may require hemodialysis. Treatment should be continued until animals are clinically normal and have had at least 24 hours with normal renal function and acid–base parameters.

Prognosis

Prognosis is good to grave depending on the degree of exposure, length of time between exposure and treatment, and aggressiveness of treatment. The presence of oliguria/anuria indicates a grave prognosis.

LILIUM spp. AND *HEMEROCALLIS* spp. (LILIES)

Definition/Overview

Members of the *Lilium* (Figure 20.22) and *Hemerocallis* genera (Easter lilies, tiger lilies, day lilies, etc.) have been incriminated in causing acute kidney injury in cats.



FIGURE 20.22 White Oriental lily – *Lilium.* (*Courtesy of Laura Stern.*)

Pathophysiology

The toxin is unknown, but even minor exposures (bite on a leaf, ingestion of pollen) may result in toxicosis. On histopathology, there is proximal convoluted tubule degeneration and necrosis with denudation of basement membrane and filling of tubular lumen with cellular debris.

Clinical Presentation

Vomiting begins within a few hours after exposure. Elevations in BUN, creatinine, phosphorus, and potassium are detectable as early as 12 hours post ingestion. Within 24–72 hours of ingestion, oliguric to anuric renal failure develops accompanied by depression, anorexia, and dehydration. Abundant casts, proteinuria, glucosuria, and isosthenuria are found on urinalysis within 24 hours of ingestion, reflecting lily-induced damage to renal tubular cells. In severe cases, death or euthanasia due to acute renal failure generally occurs within 3–6 days of ingestion.

Diagnosis

History and clinical signs.

Management

Intravenous fluid therapy is the most important part of treatment. A diuretic rate should be administered for 48 hours, and urine output monitored. Baseline renal values should be obtained upon presentation and then repeated at 24 and 48 hours. In severe cases, hemodialysis may aid in managing renal failure until tubular regeneration occurs (10–14 days or longer).

Prognosis

When fluids are initiated within 18 hours of ingestion, prognosis is good. Conversely, delaying treatment beyond 18 hours frequently results in death or euthanasia.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Definition/Overview

Nonsteroidal anti-inflammatory drugs (NSAIDs) are marketed for both human and veterinary use. Common NSAIDs include ibuprofen (Figure 20.23), naproxen, celecoxib, flurbiprofen, piroxicam, diclofenac, ketoprofen, carprofen (Figure 20.24), etodolac, meloxicam, and deracoxib.

Pathophysiology

NSAIDs decrease pain and inflammation by blocking the conversion of arachidonic acid to prostaglandins through cyclooxygenase inhibition. This decreases pain but also stops the beneficial effects of prostaglandins, leading to increased production of gastric acid and pepsin, decreased secretion of the protective mucous layer in the stomach and small intestine, and decreased blood flow to the gastric mucosa and kidneys. These changes put the animal at risk of GI ulcers and acute kidney injury (AKI). Hepatotoxicity can be seen with any NSAID and is thought to be an idiosyncratic process.



FIGURE 20.23 Ibuprofen is one of the most common toxicants in dogs. (*Courtesy of Tim Williams.*)



FIGURE 20.24 Chewable carprofen is very palatable, and pets will eat multiple tablets if available.

Clinical Presentation

Vomiting is usually the first clinical sign. The onset of GI upset is generally within the first 2–6 hours after ingestion, with GI hemorrhage and ulceration occurring 12 hours to 4 days post exposure. Renal failure often occurs within the first 12–48 hours after exposure. Some NSAIDs (ibuprofen) can cause neurologic signs (ataxia, seizures, coma) at high doses. This occurs within a few hours after exposure, and the mechanism is unknown.

Diagnosis

History and clinical signs; laboratory confirmation is usually not timely.

Management

If the exposure was <1 hour and the animal is asymptomatic, emesis can be induced. Activated charcoal can be given if the dose is of renal concern or higher. Intravenous fluids and gastroprotectants are the mainstays of therapy. Assisted ventilation and supplemental oxygen may be required if the animal is comatose. Seizures should be treated with diazepam. Both naloxone and lipids have been used to reverse the coma seen in ibuprofen toxicosis with mixed results. Severe cases may benefit from therapeutic plasma exchange. Most hepatotoxicity cases are reversible with discontinuation of the medication and supportive care.

Prognosis

Prognosis in most cases is good with therapy. Cats are thought to be more sensitive to NSAID toxicosis than dogs due to their limited glucuronyl-conjugating capacity. Dogs ingesting doses of >50 mg/kg can develop GI ulcers, and at >125 mg/kg, AKI will develop. At doses >400 mg/kg, CNS signs can develop. Cats who ingest ibuprofen are at risk of developing GI ulceration at >5 mg/kg and AKI at >20 mg/kg. Naproxen has a half-life of 74 hours in the dog, as it undergoes extensive enterohepatic recirculation. Ulcerative gastritis is possible in dogs at 5 mg/kg of naproxen, and doses of >10 mg/kg can cause AKI. Doses of 20 mg/kg and 40 mg/kg will induce GI ulceration and AKI, respectively. Cats will develop GI ulceration at 4 mg/kg and AKI at 8 mg/kg. COX selectivity is not protective in overdose situations. Dogs will develop GI ulceration at 15 mg/kg and AKI at 30 mg/kg.

VITIS spp. (GRAPES AND RAISINS)

Definition/Overview

Members of the *Vitis* spp. have been documented to cause vomiting and AKI in some dogs.

Pathophysiology

Unknown toxin causes proximal renal tubular necrosis in some dogs.

Clinical Presentation

Vomiting usually begins within 6 hours of ingesting the grapes/raisins, followed by elevations of BUN and creatinine in 12–18 hours.

Diagnosis

History and clinical signs.

Management

If the ingestion was in the past 8 hours and the animal is asymptomatic, emesis can be attempted. Monitor renal values for 48 hours. Intravenous fluids at a diuretic rate are the most important part of therapy. If renal values are normal at 48 hours, the patient can be discharged. Symptomatic care for vomiting, diarrhea, or other signs may be required.

Prognosis

Prognosis variable and unpredictable with some dogs being asymptomatic with ingestion, while others may develop mild GI signs and recover. Dogs developing severe oliguria or anuria are generally poorly responsive in attempts to increase urine production (mixed results with peritoneal and hemodialysis).

Cardiorespiratory

There are several risk factors for toxic effects on the cardiovascular and respiratory systems. The heart needs a steady supply of nutrients (ATP, oxygen, etc.), and it receives all of the systemic circulation. The cardiac muscle also does not have the ability to regenerate. The lungs receive almost all inhaled toxins. Refer to Table 20.1 for a list of potential cardiovascular and respiratory toxicants.

ALBUTEROL

Definition/Overview

Albuterol is a synthetic sympathomimetic amine used as a bronchodilator in the treatment of asthma. It comes as tablets, liquid, and as an inhaler.

Pathophysiology

Albuterol is normally a beta-2 receptor agonist. In overdose situations, albuterol stimulates beta-1 receptors, causing increased inotropic and chronotropic effects on the heart.

Clinical Presentation

Dogs are usually exposed by chewing on inhalers. This leads to a quick onset and prolonged duration signs. The most common signs are tachycardia, vomiting, depression, tachypnea, hyperactivity, muscle tremors, hypokalemia, and muscle weakness. Death has rarely been reported. Clinical signs generally resolve within 12 hours but may persist for up to 48 hours.

Diagnosis

History and clinical signs.

Management

Decontamination is not advised for inhaler, solution, or syrup exposure due to rapid absorption and onset of actions. Emesis and activated charcoal can be given

with tablet ingestion. Monitor heart rate and rhythm, body temperature, and serum potassium. Propranolol (0.02–0.06 mg/kg IV, titrate up as needed) or other nonselective beta-blockers should be administered if heart rates greater than 160–180 bpm are observed. Propranolol slows the heart rate, has direct myocardial depressant effects, and helps normalize serum potassium levels. Potassium should be supplemented as needed. Agitation can be treated with diazepam or low-dose acepromazine.

Prognosis

Prognosis in most cases is good. Animals with known or underlying cardiac disease may be at risk for decompensation and sudden death.

CARBON MONOXIDE (CO)

Definition/Overview

Carbon monoxide is a colorless, odorless, and tasteless gas produced by incomplete combustion of hydrocarbon fuels. Pets are most commonly exposed to malfunctioning gas water heaters, space heaters, or furnaces in tight or poorly ventilated spaces.

Pathophysiology

CO is rapidly absorbed through the lungs. The affinity of hemoglobin for CO is 250 times greater than for oxygen (O_2). This forms carboxyhemoglobin, which has a decreased ability to release oxygen, resulting in systemic tissue hypoxia.

Clinical Presentation

Animals will present with cherry-red mucous membranes and skin; however, they are demonstrating signs of hypoxia (lethargy, weakness, dyspnea, coma, seizures, and death).

Diagnosis

History and clinical signs; confirmation can be made by measuring carboxyhemoglobin levels in whole blood (stable for several days, keep refrigerated).

Management

Therapy consists of oxygen; a hyperbaric chamber can decrease treatment time.

Prognosis

Good to grave depending on degree of hypoxia.

PHENYLPROPANOLAMINE

Definition/Overview

Phenylpropanolamine (PPA) is a sympathomimetic agent used in veterinary medicine for controlling urinary incontinence in dogs.

Pathophysiology

PPA indirectly stimulates both alpha and beta receptors by causing the release of norepinephrine. It also acts on peripheral alpha receptors, with a weak effect on beta receptors. This results in vasoconstriction and severe hypertension.

Clinical Presentation

Initially animals are agitated and tachycardic. As the blood pressure begins to rise, the animals will become lethargic, hypertensive, and bradycardic (reflex bradycardia). The pet may develop erythema and piloerection. Signs start within 30–90 minutes and may continue up to 48 hours, depending on dose.

Diagnosis

History and clinical signs.

Management

Emesis may be induced if the ingestion was within 10–15 minutes. Activated charcoal can be given if the patient is asymptomatic. Heart rate and blood pressure should be closely monitored. Mild agitation and mild hypertension may respond to acepromazine. Nitroprusside or other pressor agents can be used to manage more severe hypertension. Animals should be put on IV fluids to protect renal function and help with thermoregulation.

Prognosis

Severe signs appear at doses above 20 mg/kg. If the blood pressure can be controlled, prognosis is good.

Hematopoietic

A variety of toxicants can affect the formation or function of red blood cells. The site of action may be in the circulation, the clotting cascade, or in the bone marrow.

ALLIUM spp. (ONIONS, GARLIC)

Definition/Overview

Allium spp. are commonly used in cooking (garlic, onions, shallots, leeks, chives [Figure 20.25]). The volatile oils that give these products their distinctive smell are also pharmaceutically active.

Pathophysiology

The *Allium* genus contains propyl disulfide compounds that cause oxidative damage to the red blood cells (RBCs). This leads to anemia.

Clinical Presentation

Vomiting can occur right after ingestion, but the hematological changes do not occur until 3–7 days post



FIGURE 20.25 Members of the *Allium* genus include (L to R) yellow onions, garlic, red onions, and shallots. (*Courtesy of Tim Williams*.)

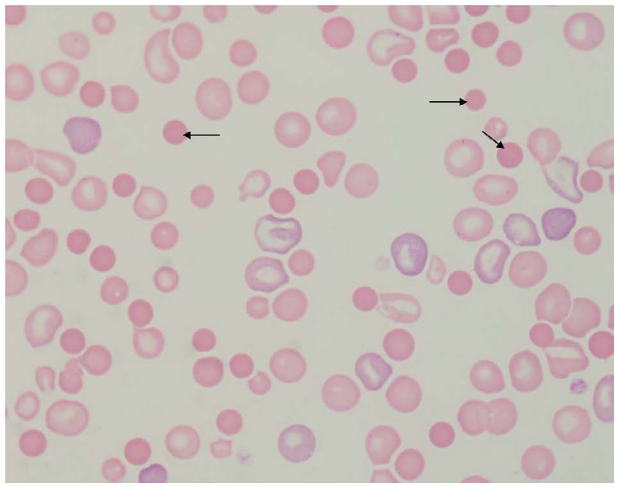


FIGURE 20.26 Spherocytes, indicated by black arrows. Canine blood, 100x, Wright-Giemsa stain. (*Courtesy of Amy Schnelle, University of Illinois Urbana-Champaign*.)

ingestion. Heinz bodies, eccentrocytes, spherocytes (see Figure 20.26), hemolysis, and anemia occur secondary to oxidative damage. Patients may present weak, tachypneic, and tachycardic.

Diagnosis

History and clinical signs.

Management

Emesis and charcoal can be given if the amount is over a dose of concern. Decontaminate dogs that have ingested >10 g/kg of garlic or 15 g/kg of onion. Decontaminate cats that have ingested >1 g/kg of garlic or 5 g/kg of onion. Mild gastrointestinal signs can be managed with antiemetics. Blood work should be monitored, and if anemia develops, a blood transfusion may be needed.

Prognosis

Good. Cat hemoglobin is more sensitive to oxidative damage due to having more sulfhydryl groups on their RBCs.

ANTICOAGULANT RODENTICIDES

Definition/Overview

Anticoagulant rodenticides are toxic to the consumer and potentially cause relay toxicosis (poisonous to pet that ate the poisoned rodents).

Pathophysiology

Anticoagulant rodenticides inhibit the activity of vitamin K1 epoxide reductase. This stops the activation of clotting factors II, VII, IX, and X, and a coagulopathy develops.

Clinical Presentation

Initial clinical signs are vague and then the subsequent signs will depend on where the bleeding is occurring. Because the body has several days' worth of active vitamin K stored in the liver (the site of the reactivation activity), there is a delayed onset of effect on blood clotting after ingestion of an anticoagulant. Hemothorax is the most common presentation (dyspnea, pale gums, weakness), but bleeding can occur anywhere. Petechiae and ecchymoses are seen later in the course of illness after the platelet numbers have been depleted in smaller bleeds.

Diagnosis

History, clinical signs, prothrombin time (patient) testing; specific rodenticides can be identified by veterinary laboratories. (Note that if point-of-care diagnostic tests are unavailable, the clinician can easily determine the Whole Blood Clotting Time. If >20 minutes, treatment can proceed while awaiting outside laboratory test results. It is understood that this test is not as accurate as the prothrombin time, but it can save lives while awaiting delayed lab results.)

Management

Emesis can be induced if ingestion has occurred within the last 4 hours. One dose of activated charcoal may be given. Depending on the dose ingested, PT testing could be performed (48–72 hours after ingestion), or the pet could be started on vitamin K_1 therapy (2.5–5 mg/kg per day divided subcutaneously for the first day and orally subsequently). If the animal is actively bleeding, start vitamin K_1 and give clotting factors via a whole blood transfusion, fresh frozen plasma, or fresh plasma. Minimize physical activity throughout therapy.

Prognosis

Prognosis depends upon where the bleeding occurs (bleeding into the brain or spinal cord carries a grave prognosis).



FIGURE 20.27 Serum with gross hemolysis. (*Courtesy of Amy Schnelle, University of Illinois Urbana-Champaign.*)

ZINC

Definition/Overview

Zinc can be found in U.S. pennies (minted after 1983), screws, bolts, nuts, game pieces, and any galvanized metals.

Pathophysiology

The stomach acid ionizes the zinc, which is then absorbed into the circulation. Zinc causes oxidative damage to the RBC leading to hemolysis (see Figure 20.27), hemoglobinuria, and secondary renal injury.

Clinical Presentation

Vomiting, lethargy, anorexia, hemoglobinuria, weakness, and pale gums are common. Hemolysis and anemia are seen on the complete blood count (CBC). Radiography may reveal the presence of metal objects within the stomach.

Diagnosis

Serum zinc levels (need special blue topped tube), abdominal radiographs.

Management

The zinc must be removed from the GI tract (emesis, endoscopy, surgery). Activated charcoal does not bind to heavy metals. Treatment for symptomatic animals should include blood transfusion as needed, intravenous fluids, and other supportive care. The use of chelators is not necessary.

Prognosis

Good to guarded depending on how long the zinc has been in the stomach.

Gastrointestinal

A wide range of toxins can affect the GI tract from mild vomiting and diarrhea to severe loss of fluids and blood (hypovolemic shock). Refer to Table 20.1 for selected gastrointestinal toxicants.

ASPIRIN

Definition/Overview

Aspirin (acetylsalicylic acid, ASA) is a salicylate ester of acetic acid and a weak acid It is used to decrease pain and treat fevers.

Pathophysiology

Aspirin reduces pain and inflammation by inhibiting cyclooxygenase, which reduces prostaglandin and thromboxane synthesis. At very high doses, aspirin and other salicylates uncouple oxidative phosphorylation leading to decreased ATP production. Salicylates also affect platelet aggregation and can cause increased bleeding times.

Clinical Presentation

Vomiting is the most common sign and can be seen at any dose. In dogs, GI ulcers can be seen at doses >150 mg/kg, and >400 mg/kg can cause liver injury, fever, and seizures. Respiratory alkalosis can occur acutely followed by metabolic acidosis.

Diagnosis

History and clinical signs.

Management

Emesis can be performed in the asymptomatic animal. Activated charcoal can be given if over a hepatotoxic dose. Maintain hydration and start GI protectants. Liver values, glucose, acid–base status, and electrolytes should be monitored. Assisted ventilation and supplemental oxygen may be required if the animal is comatose. Seizures should be treated with diazepam. Fluids and whole blood may be needed to control hypotension and hemorrhage.

Prognosis

Prognosis is good if the animal is treated promptly. Cats are more sensitive as they are deficient in glucuronyl transferase and have prolonged excretion due to decreased metabolism.

CORROSIVE, CAUSTICS, AND DETERGENTS

Definition/Overview

Acids are corrosive with a low pH. They are found in toilet bowl cleaners, drain openers, metal cleaners, antirust compounds, automobile battery fluid, and pool sanitizers (Figures 20.28 and 20.29). Alkalis (sodium



FIGURE 20.28 Acid-based bathroom cleaner. Keep pets away until rinsed and dried. (*Courtesy of Tim Williams*.)



FIGURE 20.29 Reading labels is important, even products with similar names can be different. The center product is an acid (oxalic acid), while the left and right are a combination of alkaline (sodium carbonate, sodium hydrosulfite) and acid (citric acid). (*Courtesy of Tim Williams*.)



FIGURE 20.30 Alkaline automatic dishwasher pacs. (*Courtesy of Tim Williams*.)



FIGURE 20.31 Anionic and nonionic detergents. Can see mild GI signs if ingested. (*Courtesy of Tim Williams*.)

or potassium hydroxide, ammonium hydroxide, sodium or potassium hydroxide, potassium permanganate) are caustics with a high pH (>11). They are found in drain openers, oven cleaners, industrial cleaners, bathroom and household sanitizers, hair relaxers, alkaline batteries, electric dishwasher detergents, low-phosphate detergents, and cement (Figure 20.30). Detergents are classified according to their charge in solution: Nonionic, anionic, cationic. Anionic and nonionic detergents are found in shampoos, hand dishwashing detergents, and laundry detergents (Figure 20.31). Cationic detergents are found in fabric softeners, germicides, disinfectants, and sanitizers (Figure 20.32).

Pathophysiology

Acids produce coagulative necrosis, and the severity of tissue damage is directly related to the concentration. Coagulative necrosis is painful. Alkalis produce



FIGURE 20.32 Cationic detergent. Concentration determines whether it is an irritant (ready-to-use product) or corrosive (concentrate). (*Courtesy of Tim Williams*.)

liquefactive necrosis. Liquefactive necrosis kills the nerve endings, so animals will continue to chew, and more extensive damage can occur. Anionic and nonionic detergents are just mucosal irritants, while cationic detergents can dissolve superficial layers of epithelial tissue.

Clinical Presentation

Nonionic, anionic, and dilute solutions of acids, alkalis, and cationic detergents can cause mild oral or dermal irritation. Vomiting is expected to be self-limiting. Signs due to concentrated acids, alkalis, or cationic detergents are often indistinguishable from each other. Hypersalivation, gagging, pawing at the mouth, vomiting +/- blood, and oral ulcers. Hyperthermia (>104°F) can be seen with alkalis and cationic detergents. There can potentially be esophageal and gastric ulcers. Esophageal and gastric damage is more likely with alkalis. Dermal exposure can cause pain, erythema, and full-thickness burns. It may take up to 12 hours for the full extent of the damage to be seen with alkalis and cationic detergents.

Diagnosis

History and clinical signs.

Management

Do not induce emesis or give activated charcoal. Dilution with milk or water as soon as possible after exposure is recommended. Opioids should be used for pain control. Sucralfate slurries and GI protectants should be started. If the burns are severe, antibiotics, nutritional support (blenderized food or gastrostomy tube), and fluids may be needed.

Prognosis

Good for exposures to nonionic, anionic detergents or dilute acids, alkalis, and cationic detergents. Prognosis is good to guarded with concentrated acids, alkalis and cationic detergents. Most recover without any long-term problems, but the prognosis worsens for animals with esophageal burns (stricture formation).

INSOLUBLE CALCIUM OXALATE-CONTAINING PLANTS

Definition/Overview

Many of the most common houseplants are in the Araceae family and contain insoluble calcium oxalate crystals. Refer to Table 20.7 for a list of plants.

Pathophysiology

Insoluble calcium oxalate crystals are needle shaped. These raphides are packing into idioblasts within the plant. When the leaf is damaged, the broken idioblast allows sap/saliva to enter, and the swelling ejects the raphides. These needles penetrate oral mucosa and cause pain. In severe cases, swelling of oral tissues can occur.

TABLE 20.7 Insoluble calcium oxalate plants

Genus	Common name
Aglaonema spp.	Chinese evergreen
Alocasia spp. or *Colocasia* spp.	Elephant's ear
Anthurium spp.	Flamingo plant
Arisaema triphyllum	Jack-in-the-pulpit
Arum maculatum	Arum, cuckoo pint
Caladium spp.	Caladium, elephant's ear
Dieffenbachia spp. (Figure 20.33)	Dieffenbachia, dumb cane
Epipremnum spp.	Pothos, Devil's ivy
Monstera spp.	Cutleaf philodendron, Swiss cheese plant
Philodendron spp. (Figure 20.34)	Philodendron
Schefflera spp.	Umbrella tree
Spathiphyllum spp.	Peace lily
Syngonium podophyllum	Nephthytis
Zantedeschia aethiopica	Calla lily, Arum lily

Clinical Presentation

There is a quick onset of hypersalivation, gagging, and potentially vomiting. In rare cases, there can be swelling of the oral cavity and pharynx (obstruction is extremely rare).



FIGURE 20.33 *Dieffenbachia* spp.—Dieffenbachia, Dumbcane.



FIGURE 20.34 *Philodendron* spp.—Philodendron.

Diagnosis

History and clinical signs.

Management

Oral milk or water should be given. Calcium-containing products are thought to precipitate soluble oxalates in the oral cavity and reduce pain.

Prognosis

Good. Clinical signs usually resolve within a few hours with no lasting effects.

RECOMMENDED FURTHER READINGS

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CHAPTER 21

Infectious Diseases
CHAPTER 21.1 Dogs

Stuart Walton

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The discussion on infectious diseases that follows is not intended to be comprehensive. Instead, the diseases presented in this chapter represent the most common infections encountered in dogs seen in clinical practice. Updates on practical, accessible, diagnostic testing protocols, treatment recommendations, and prevention/vaccination are included.

INTRODUCTION

Successful management of infectious disease requires a combination of early, reliable, definitive diagnostic tests, and aggressive interventional therapy. Advanced diagnostic technology has not only increased our awareness of the spectrum of infectious agents capable of causing clinical illness in companion animals, it has also made it quite clear that coinfection (i.e., simultaneous infection with two or more pathogens in the same patient) is prevalent in veterinary medicine and can be a major influence in the outcome. To better provide early, aggressive, successful medical therapy, it is important for clinicians to assimilate historical and clinical information, as well as accurately and critically evaluate performed diagnostic tests so that an accurate diagnosis can be made.

The following chapter on infectious diseases is not intended to be comprehensive. Instead, the diseases presented in this chapter represent the most common infections encountered in dogs and cats seen in clinical practice. Updates on practical, accessible, diagnostic testing protocols, treatment recommendations, and prevention/vaccination are included.

BACTERIAL INFECTIONS

CANINE INFECTIOUS RESPIRATORY DISEASE

Definition/Overview

Canine infectious respiratory disease (CIRD) complex, also known as "kennel cough," is an endemic, highly contagious upper respiratory tract infection that occurs acutely in dogs. Disease is multifactorial, manifesting as a cough. It is caused by a number of pathogens occurring individually or as coinfections. Occasionally, lower respiratory disease (bronchopneumonia) will result and may become life-threatening, particularly in young dogs. CIRD can occur at any age with illness occurring when large numbers of dogs are in close contact (i.e., animal shelters, boarding facilities, day-care facilities, or dog parks).

Etiopathogenesis

The bacterial and viral pathogenic agents implicated in CIRD are summarized in Tables 21.1.1. and 21.1.2. Incubation period can be up to 10 days depending on the pathogen. Pathophysiology varies with all CIRD pathogens that cause upper respiratory tract pathology. Traditional CIRD involves both viral and bacterial agents (i.e., canine parainfluenza virus (CPIV), canine adenovirus (CAV), canine distemper virus (CDV), canine herpesvirus (CHV), and *Bordetella bronchiseptica*). New, emerging, and novel pathogens associated with CIRD include canine influenza virus (CIV), canine

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TABLE 21.1.1 Common bacterial respiratory pathogens implicated in canine infectious respiratory disease

Pathogen	Incubation period	Preclinical shedding	Duration of shedding	Persistent infection
Bordetella bronchiseptica	3–10 days	Yes	Several weeks	Recovered up to 14 weeks after clinical resolution
Streptococcus equi subspecies *Zooepidemicus*	1–3 weeks	Yes	1–2 weeks	Possible
Mycoplasma spp.	1–4 weeks	Yes	Several weeks	Up to 3 weeks in lung tissue
Chlamydophila	Unknown	Yes	Unknown	Possible

TABLE 21.1.2 Common viral respiratory pathogens implicated in canine infectious respiratory disease

Pathogen	Incubation period	Preclinical shedding	Duration of shedding	Persistent infection
Canine parainfluenza virus (CPIV)	< 1 week	Yes	1 week	No
Canine adenovirus (CAV-2)	< 1 week	Yes	1 week	No
Canine distemper virus (CDV)	1–3 weeks	Yes	< 1 month	No
Canine herpesvirus (CHV)	< 1 week	Yes	2 weeks	Yes
Canine influenza virus (CIV)	2–4 days	Yes	7–21+ days	No
Canine respiratory coronavirus (CRCov)	< 1 week	Yes	2 weeks	No

respiratory coronavirus (CRCoV), canine pneumovirus, canine bocavirus, canine hepacivirus, canine picornavirus, *Mycoplasma cynos*, and *Streptococcus equi* subsp. *zooepidemicus* (*S. zooepidemicus*).

Bordetella is a Gram-negative coccobacilli bacterium capable of causing disease in a variety of species, including cats, pigs, rabbits, and people. Transmission is airborne through both direct and indirect contact (i.e., contaminated bedding, food bowls, water bowls). Upon entering the body, the organism expresses virulence factors linked to a gene complex (Bvg), which aid in adherence of the organism and damage to ciliated respiratory epithelial cells. This causes ciliostasis and excessive mucus secretion due to failure of mucociliary clearance, predisposing affected patients to secondary opportunistic infections.

Streptococcus equi subspecies *zooepidemicus*, a β-hemolytic Lancefield group C *Streptococcus* is responsible for severe, acute to peracute upper respiratory tract infections and acute, severe hemorrhagic bronchopneumonia in dogs. Pathogenesis of disease is not fully understood but is thought to involve exotoxins which act as superantigens significantly augmenting the patient's immune response comparable with human streptococcal toxic shock syndrome. Coinfection with other pathogens is possible, which may worsen severity of infection after exposure to *S. zooepidemicus*.

Mycoplasma spp. are normal commensals that colonize mucous membranes of the upper respiratory tract. Their exact role in CIRD is still debatable. *Mycoplasma cynos* has been associated with pneumonia in dogs, although it is still unclear whether it is a primary or secondary opportunistic pathogen, as it has also been cultured from the lungs of healthy dogs. Younger dogs are more likely to be infected.

Canine adenovirus type 2 (CAV-2) and canine parainfluenza virus (CPIV) are the best recognized viruses for causing CIRD. They cause inflammation of the laryngeal, tracheal, and bronchial epithelium. Both diseases cause mild-to-moderate, self-limiting disease as solo pathogens; however, when there is coinfection with other pathogens, more serious illness can ensue.

Canine influenza virus (CIV) is an H3N8 virus that is known to have been derived from the equine influenza virus. Virus shedding is generally limited to less than 14 days post infection. Experimentally infected dogs demonstrate fever and mild inflammation involving tracheal epithelium. Viral pneumonitis is uncommon. Clinical infection is generally considered to be mild unless the dog is coinfected. Bacterial pathogens (discussed previously) in combination with CIV can result severe respiratory disease and death.

Canine distemper virus (CDV) is not commonly implicated as a primary agent of CIRD because respiratory disease is just one of the many severe systemic manifestations that occur in unvaccinated dogs. Canine respiratory coronavirus (CRCoV), and canine pneumovirus (CPnV) infections appear to occur less commonly and may actually be most important as cofactors in CIRD.

Clinical Presentation

Clinical signs are variable. Typically, cases are mild and self-limiting consisting of a paroxysmal "goose honk" cough, sneezing, oculonasal discharge, and increased

tracheal sensitivity. Some patients can develop more severe clinical signs depending on age, immune status, and the presence of coinfections. Clinical signs in these patients may include fever, lethargy, anorexia, and dyspnea. The occurrence of coinfection explains, at least in part, why predicting clinical outcomes of CIRD in individual dogs can be difficult, and it also explains why well-vaccinated dogs still develop kennel cough.

Viral pathogens tend to be associated with acute-onset productive cough that lasts 1–2 weeks. Some patients will only develop mild or no clinical signs (seroconversion only). Coughing may persist for several weeks, even though the virus is usually cleared within 2 weeks following the development of clinical signs.

Patients with bacterial infection are systemically unwell. The characteristic "goose honk" cough is usually accompanied with fever, anorexia, mucopurulent nasal and ocular discharge, orthopnea, and dyspnea. Life-threatening pneumonia has been reported in young animals.

Differential Diagnosis

Understanding, and more importantly, distinguishing causes of acute coughing in patients is key for selection of diagnostics, initiating empiric medical therapy, and the institution of proper preventative/control measures to prevent further infection to other animals. Nine organisms play a role in CIRD (Tables 21.1.1 and 21.1.2).

Diagnosis

Diagnosis is often made based on a thorough history and physical examination. History should include recent boarding, dog park visits, or day-care stays. Dogs are usually systemically well and will typically exhibit mild clinical signs such as paroxysmal breathing, harsh "goose honk" cough, serous ocular or nasal discharge, and/or sneezing. Ancillary diagnostics (complete blood count [CBC], serum biochemistry, urinalysis, and thoracic radiographs) are usually unremarkable. Further diagnostics are indicated in dogs with a persistent cough (> 7–10 days) who have severe rapidly progressing clinical signs. In these unwell dogs, a neutrophilia with left shift and changes on thoracic radiographs may be present (i.e., bronchointerstitial to alveolar pulmonary pattern). Upper respiratory tract bacterial cultures (conjunctival, nasal, oropharyngeal, tracheal) should be interpreted with caution, as normal microbial flora and many CIRD pathogens may be isolated, especially in otherwise healthy animals. *Bordetella bronchiseptica* or *M. cynos* isolation in animals with consistent clinical signs supports infection; however, coinfection with other CIRD pathogens should also be considered. Commercial canine respiratory disease panel polymerase chain reaction (PCR) assays (conjunctival, nasal, and pharyngeal swabs) are available from most diagnostic laboratories, which has led to increased detection of CIRD pathogens and provided information regarding the presence of coinfections. Samples should be collected in patients with clinical signs of < 4 days.

Management

Treatment/Prognosis

Under the current guidelines, no specific therapy is indicated in patients that are systemically well with a good appetite as most cases are self-limiting and will resolve in spite of treatment. Minimizing cough precipitating situations (i.e., avoidance of excitement, avoidance of neck leashes, etc.) is advised. Cough suppressants can be used to reduce cough frequency and severity; however, caution is advised in prescribing these if the cough is productive due to reduced bacterial clearance and the possibility of a secondary bacterial pneumonia developing. In otherwise healthy patients, short-term treatment (≤ 5 days) with anti-inflammatory corticosteroids (e.g., prednisolone at 0.5 mg/kg p.o. once or twice daily) reduces not only inflammation but also reduces the intensity of cough. Antimicrobial therapy is indicated in patients that are systemically unwell or who have a persistent cough for > 1 week. Empiric antimicrobial therapy should be based on the most likely agent to be present. Considerations for antibiotic selection should also include the ability of antimicrobials to achieve good airway concentration and penetrate airway secretions as well as safety margins for their use. Doxycycline (2.5–5.0 mg/kg p.o. q.12 h. for 5–7 days), azithromycin, and fluoroquinolones achieve good airway concentrations, while beta-lactam drugs (e.g., amoxicillin/clavulanate) achieve lung tissue concentrations but do not penetrate airway secretions well. Fluoroquinolones should be reserved for more severe infections. Fluoroquinolones and tetracyclines may cause cartilaginous defects in young animals and dental staining in puppies.

Severely affected animals may require hospitalization, parenteral fluids, oxygen therapy, nebulization/coupage, and nutritional support.

Prognosis for simple uncomplicated disease is good to excellent. Clinical signs may persist beyond the time of viral shedding. Infected puppies appear to be at greater risk for developing complications associated with CIRD (e.g., bronchopneumonia). Outcomes are directly related to the severity of disease and any coinfection present.

Prevention

Vaccines are available for the most common CIRD pathogens (Table 21.1.3). In general, these vaccines do not produce immunity. Rather, they are effective in reducing severity of cough in challenged dogs. Several types of vaccine (Tables 21.1.4 and 21.1.5) are available

TABLE 21.1.3 Vaccines (available in the United States) for prevention against known CIRD pathogens

– *Bordetella bronchiseptica*
– Canine parainfluenza virus
– Canine adenovirus-2
– Canine distemper virus
– Canine influenza virus

TABLE 21.1.4 Initial vaccination recommendations for dogs based on the 2017 American Animal Hospital Association (AAHA) vaccination guidelines

Core vaccines	Administration	First booster
MLV or recombinant Canine distemper virus + MLV parvovirus + MLV adenovirus-2 ± MLV parainfluenza virus*	3 doses recommended between 6 and 16 weeks of age (e.g., 8, 12, and 16 weeks of age) Dogs ≥ 16 weeks should receive 2 doses 2–4 weeks apart**	Administer a single dose (of a combination product) at 1 year following the last dose in the initial series
Rabies (killed) 1-year and 3-year labeled vaccines available	Administer single dose not earlier than 12 weeks of age (state/local/provincial laws apply)	Administer a single dose of vaccine no later than 1 year following administration of the first dose regardless of age (state/local/provincial laws apply)
Noncore vaccines	Administration	First booster
Bordetella bronchiseptica + canine parainfluenza virus (IN only) (Some IN products may also contain CAV-2 antigen)	Single IN dose generally administered between 8 and 16 weeks of age Intranasal vaccine may be administered as early as 3–4 weeks of age	Where sustained risk of exposure, administer a single dose 1 year following the last dose administered No known value administering IN vaccine every 6 months
Bordetella bronchiseptica only (monovalent) Three options available – Parenteral (killed bacterium) – IN (avirulent live) – Intraoral (avirulent live)	Two parenteral SQ doses initially administered 2–4 weeks apart beginning ≥ 8 weeks of age Single IN dose beginning ≥ 3 weeks of age Single oral dose into the buccal pouch ≥ 8 weeks of age	Where sustained risk of exposure, administer a single dose 1 year following the last dose administered
Leptospira (killed) 4-serovar SQ – Serovar *L. canicola* – Serovar *L. icterohaemorrhagiae* – Serovar *L. grippotyphosa* – Serovar *L. pomona* (2-way leptospirosis vaccines not recommended by either AAHA or the American College of Veterinary Internal Medicine)	Two initial doses, 2–4 weeks apart, administered at ≥ 8 weeks of age	Where sustained risk of exposure, administer a single dose at 1 year following completion of last dose
Borrelia burgdorferi (canine Lyme disease) SQ Four vaccine types currently available – Killed (whole cell bacterin [OspA] or whole cell bacterin [OspA + C]) – Recombinant (OspA or chimeric-recombinant OspA + OspC)	Two initial doses, 2–4 weeks apart, administered at ≥ 8 weeks of age	Where sustained risk of exposure, administer a single dose at 1 year following completion of last dose Option – Dogs traveling into Lyme-disease endemic areas from nonendemic areas may be at increased risk for exposure and infection – Vaccination may be indicated for these dogs – Administer 2 vaccine doses 2–4 weeks apart – Last dose should be administered 2–4 weeks prior to travel
Canine influenza virus-H3N8 SQ (killed)	Two initial doses, 2–4 weeks apart, administered at ≥ 6 weeks of age Any at risk dog for exposure to influenza virus vaccination against both H3N2 and H3N8 strains recommended	Where sustained risk of exposure, administer is sustained, administer a single dose at 1 year following completion of last dose
Canine influenza virus-H3N2 SQ (killed)	Two initial doses, 2–4 weeks apart, administered at ≥ 6 weeks of age Any at risk dog for exposure to influenza virus vaccination against both H3N2 and H3N8 strains recommended	Where sustained risk of exposure, administer is sustained, administer a single dose at 1 year following completion of last dose

* Parainfluenza administered as combination as DA2PPi.

** A minimum interval of 2 weeks between any 2 doses of vaccine is recommended.

Canine coronavirus vaccination is not recommended.

Crotalus atrox (western diamondback rattlesnake) vaccine should only be used in dogs with a defined risk for exposure. Follow the manufacturer's recommendations for dosing.

IN, intranasal; MLV, modified live virus.

TABLE 21.1.5 Booster recommendations for adult dogs

- After completing the initial series of core vaccines (distemper + parvovirus + adenovirus–2), it is recommended to administer a single dose (combination vaccine) at intervals of every 3 years (or longer)
  - Note: Substantial data exists demonstrating protective immunity for dogs at least 5 years following MLV vaccine administration in the absence of maternally derived antibody
- In the United States, all states currently recognize and accept the use of "3 year" rabies vaccines in dogs
  - Note: Some local municipalities may mandate stricter booster requirements (i.e., annually)
- *Noncore vaccines:* Administer annually where risk of exposure is sustained

for administration to dogs by the intranasal, oral, and parenteral (subcutaneous) route. The constituents and the routes of administration of commercially available vaccines vary. The route of vaccine administration indicated by the manufacturer must be strictly adhered to.

Quarantining new shelter arrivals for 1 week and isolating all dogs showing clinical signs of respiratory infection may help reduce the risk of exposure to CIRD pathogens. Likewise, ensuring animals are appropriately vaccinated upon intake will help reduce risk of exposure. Strict hygiene protocols with hand sanitation, cleaning contaminated clothing, hands, equipment, and surfaces should be mandatory as this will limit disease spread.

LYME BORRELIOSIS (BORRELIOSIS; CANINE LYME DISEASE)

See Tick-Borne Disease.

CANINE BOTULISM

Definition/Overview

Botulism is a rare neuroparalytic disorder of dogs and humans caused by intoxication of botulinum neurotoxin produced by *Clostridium botulinum* (most common), *Clostridium baratii*, and *Clostridium butyricum*.

Etiopathogenesis

Clostridium botulinum is a Gram-positive, spore-forming, anaerobic bacterium that indirectly causes clinical signs from the production of neurotoxins. Seven botulinal neurotoxins have been identified (A–G), which result in flaccid lower motor neuron paralysis. This bacterium, normally found in organic-rich environments, produces vegetative cells and spores that are highly conserved in the environment. The most common source of toxin is raw and spoiled food or carrion. In dogs, botulinum neurotoxin type C is most commonly associated with clinical illness in dogs. Following ingestion of rotten food, lysis of vegetative cells and spores occurs, resulting in botulinum toxin being released as a preformed toxin. The toxin, which is stable at low pH, passages through the stomach into the small intestine where it dissociates and releases botulinum neurotoxin. Botulinum neurotoxin is then rapidly absorbed across the small intestine by endocytosis. It then enters the lymphatic system followed by the bloodstream. From there, the toxin leaves the circulation and enters tissue fluids, binding rapidly and irreversibly to presynaptic membrane receptors at cholinergic nerve terminals. This interrupts acetylcholine release, resulting in lower motor neuron and autonomic nervous system dysfunction (sympathetic and parasympathetic).

Clinical Presentation

Clinical signs can take up to 6 days after ingestion of contaminated food to develop. Severity of disease is associated with amount of toxin ingested, individual susceptibility, and speed of onset of clinical sign development. Initially, affected dogs develop progressive ascending symmetric weakness, followed by progressive ascending flaccid paralysis beginning with the pelvic limbs (Figure 21.1.1). On neurological examination, patients are often tetraparetic or tetraplegic with severely decreased to absent spinal reflexes. Patients have a normal mental status while maintaining a tail wag and pain perception. Cranial nerve abnormalities include mydriasis with a reduced pupillary light response, decreased jaw tone, ptyalism, diminished palpebral reflexes, constipation, urine retention, and weak vocalization. Severely affected dogs may have trouble breathing, associated with decreased muscular tone. Affected patients appear to have decreased swallowing reflexes which may predispose them to aspiration pneumonia. Death may result in a small number of patients due to respiratory paralysis or secondary respiratory/urinary tract infections.



FIGURE 21.1.1 The toxin of *Clostridium botulinum* can cause a severe bulbar and lower motor neuron paralysis, causing impaired respiration and requiring life-preserving ventilatory support. (*Courtesy of M. Schaer.*)

Differential Diagnosis

Rabies is an important differential among dogs with overt signs of botulism toxicity. In addition, dysautonomia, myasthenia gravis, polyradiculoneuritis, and intoxications like organophosphate and carbamate intoxications should be considered.

Diagnosis

Botulism is usually suspected from a history of access to spoiled, rotten, or raw food and progressive symmetric hindlimb lower muscle neuron paresis accompanied by cranial nerve abnormalities and disruption of the parasympathetic system. Because the toxin is dietary in origin, animals in the same household may be affected. However, isolated cases are also possible. Routine laboratory tests (CBC, serum biochemistry, urinalysis [UA]) are usually unremarkable. Thoracic radiographs should be performed in any case suspected of having botulism, as megaesophagus and subsequent aspiration pneumonia are usually present. Definitive diagnosis is made based on finding botulinum toxin in serum (10 mL), feces, vomitus/stomach contents, or in samples of spoiled ingested food (50 g). It should be noted that identification of the *C. botulinum* organism from feces is not necessarily diagnostic. In clinical practice, clinicians should contact laboratories prior to sample collection and submission to verify the volume required and sample preparation for each specimen type.

Samples should be:

1. Collected early during disease when clinical signs are maximal to be diagnostic as circulating toxin levels are rapidly degraded, often low, or may be absent in source material.
2. Refrigerated (not frozen) and examined as soon as possible.
3. Labeled as biological hazards because people are much more susceptible to botulism toxin than dogs or cats.

Electromyogram (EMG), if available, may show spontaneous electrical activity (fibrillations, positive sharp waves) in any affected muscles after 2 weeks of paralysis but may also be normal.

Management

Treatment/Prognosis

Botulinum toxin causes degeneration of the affected synapse rather than death of the affected neuron. Recovery from toxicity occurs with new endplate formation. Therefore, the mainstay of treatment of botulism is supportive care once clinical signs are present, as antitoxin is not effective once botulinum toxin is already bound to membrane receptors. Antitoxin type C can be administered to asymptomatic dogs suspected of recent (within 1 hour) ingestion of contaminated food and ongoing intestinal absorption of botulinal toxin. Always have epinephrine ready to administer at a dose of 0.01 mg/kg IM if anaphylaxis occurs. The cornerstones of supportive care are nutritional support and physical therapy. Patients are often hospitalized initially until stable (1–3 weeks).

Patients should:

1. Be maintained on well-padded, soft, clean bedding and repositioned every 4–6 hours to avoid the development of pressure sores/ulcers.
2. Be maintained in sternal recumbency to facilitate easier eating and interaction with their environment.
3. Have their urinary bladder frequently emptied (every 6–8 hours) to prevent urinary retention and secondary urinary tract infection. This is performed either by manual expression or via intermittent or permanent placement of a urinary catheter.
4. Have both eyes lubricated with artificial tears frequently (every 4 hours) to protect corneas from desiccation and ulcer development.
5. Have a balanced nutritional plan formulated and be monitored while eating and drinking. Enteral or parenteral nutrition should be considered in animals with either a poor gag reflex or megaesophagus as they are at risk of aspiration pneumonia.
6. Have physical therapy in the form of passive range of motion and massage every 6 hours to avoid muscle contracture and atrophy as well as to help maintain joint movement.

Antibiotics should not be routinely prescribed in affected patients unless a secondary bacterial infection is diagnosed (e.g., aspiration pneumonia, urinary tract infection).

Prevention

Thorough cooking of food (i.e., 80°C [176°F] for 30 minutes or to 100°C [212°F] for 10 minutes) and preventing access of dogs to raw meat, contaminated food, and carrion is best to prevent disease.

Public Health Implications

Botulism is not transmitted from dogs to humans.

CANINE BRUCELLOSIS

Definition/Overview

Clinical disease of canine brucellosis is attributed to infection with *Brucella canis*, a Gram-negative intracellular aerobic coccobacillus. Disease manifests as infertility, epididymitis, and late-term abortion. Other *Brucella* species, including *B. melitensis*, *B. abortus*, and *B. suis*, can infect dogs. Infection follows after the ingestion of contaminated placentas or aborted fetuses of livestock. Dogs do not play a significant role in the transmission of infection. *Brucella canis* predominantly affects domestic dogs, with the organism primarily being shed reproductive fluids (e.g., vaginal discharge, semen).

Etiopathogenesis

Clinical disease is caused by *Brucella canis* as well as other *Brucella* species (e.g., *B. melitensis*, *B. abortus*, and *B. suis*). Disease transmission occurs through oronasal, genital, or conjunctival mucosal inoculation during normal reproductive, social, and grooming activities in dogs. After attachment to and penetration of the mucosal barrier, bacteria are transported as free bacteria or within phagocytic cells to regional lymph nodes (e.g., retropharyngeal, inguinal, superficial iliac), the liver, spleen, and possibly bone marrow. After infection and replication (1 week to 1 month), bacteria move into the blood stream causing an intermittent bacteremia. Bacteria target "steroid-dependent" reproductive tissues (e.g., prostate, testicles, epididymides, gravid uterus, and placenta). Once bacteria accumulate within this tissue among others (i.e., mammary tissue, spleen, lymph nodes, intervertebral disc, eyes, kidneys, and meninges), affected animals become infertile and experience cyclical fevers. Shedding of the organism occurs in females (vulvar secretions after abortion [≤ 6 weeks], during estrus) and males (semen for up to 2 years after infection). Minor transmission routes include in utero, broken skin surfaces, blood transfusions, feces, milk, and fomites (e.g., contaminated syringes, food bowls, clothing, vaginoscopes).

Clinical Presentation

The most common clinical sign associated with *B. canis* infection is infertility. However, a wide range of nonreproductive signs can occur, with dogs being systemically well at presentation.

Female dogs infected venereally experience either early embryonic death (i.e., up to 3 weeks after transmission), which is consistent with infertility, or experience late-term spontaneous abortion (i.e., 45–55 days' gestation). Females will develop vaginal discharge (mucoid, serosanguinous, or gray green) that may persist for up to 6 weeks post abortion. Puppies surviving to term will either be weak and die within several weeks of birth, be clinically normal initially but then develop clinical signs associated with infection, or test positive for the disease later in life.

Male dogs may have more obvious clinical signs manifest initially as epididymitis, scrotal swelling, pain, and edema. As disease becomes more chronic, the testicles may become atrophied with epididymal swelling resolving. *Brucella canis* can also localize within the prostate, leading to prostatitis clinically manifesting as difficulty urinating/defecating and an enlarged, painful prostate on rectal examination. Ultimately males develop infertility due to spermatogenic arrest (antisperm agglutinating antibodies and delayed-type hypersensitivity reactions against spermatozoa).

Nonreproductive clinical manifestations of *B. canis* infection include chronic uveitis, endophthalmitis, and discospondylitis (Figure 21.1.2 and Table 21.1.6).

Differential Diagnosis

In male dogs, clinical disease may be silent. Among females, vaginitis and/or open pyometra should be considered. Occasionally, dogs will present with acute neurologic signs consistent with intervertebral disc disease or discospondylitis.

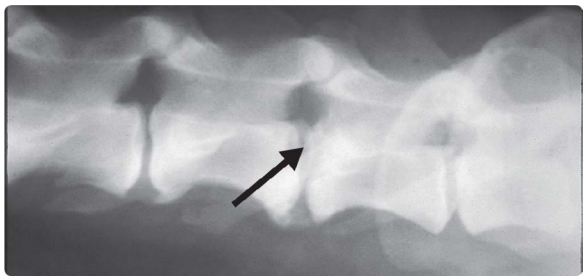


FIGURE 21.1.2 Radiograph depicting discospondylitis in a dog, which can be caused by *Brucella canis*.

TABLE 21.1.6 Nonreproductive clinical signs associated with *B. canis* infection

Clinical signs
– Ocular   – Blepharospasm, aqueous flare, constricted pupils, synechiae, hypopyon, hyphema
– Discospondylitis   – Stiffness, back pain, lameness, exercise intolerance, paresis, paralysis due to spinal compression
– Lymphadenitis (common)
– Pyogranulomatous dermatitis (rare)
– Endocarditis (rare)
– Appendicular osteomyelitis (rare)
– Meningoencephalitis (unknown frequency)
– Decreased appetite
– Weight loss
– Lethargy
– Fever (rare)

Diagnosis

A thorough history, including the reproductivity activity, meticulous physical examination paying specific attention to male/female genitalia and peripheral lymph nodes should be performed. The presence of back pain and uveitis should warrant additional diagnostics in sexually mature dogs. Routine diagnostics (e.g., CBC, serum biochemistry, and urinalysis) are often unremarkable. Blood culture is considered the "gold standard" for diagnosis of early infection as > 50% of dogs will be bacteremic up to a year following infection. Culture of other fluids (e.g., urine, semen, post-abortion vaginal discharge) or tissue (e.g., aborted placenta and aborted fetal tissue) may be positive during the first 3 months of infection; however, this testing is not widely available.

Definitive diagnosis is usually based on serologic testing. Testing relies upon an agglutination reaction between canine *B. canis* antibodies and bacterial cytoplasmic protein antigens. Seroconversion producing a positive test can take up to 12 weeks after exposure for

TABLE 21.1.7 Available serologic tests for *B. canis* infection

Test	Advantages	Disadvantages
Agar gel immunodiffusion (AGID)	– Confirmation tests for suspected *B. canis* cases detected initially by RSAT or ME-RSAT – Serum Ab test – Identifies chronically infected	– Not used as screening test – Lag time to develop Ab (up to 4 weeks) – Variable turnaround time (up to 48 hours) – Variable rates of false-negative results
Rapid slide agglutination test (RSAT)	– Serum Ab test – Short turnaround time (RSAT 2 minutes) – Highly sensitive	– Lag time to develop Ab (up to 4 weeks) – May take up to 8–12+ weeks for positive test results – Variable rates of false-positive results – Decreased sensitivity for chronically infected due to intermittent bacteremia
Modified rapid slide agglutination test (ME-RSAT)	– Serum Ab test – 2-mercaptoethanol incorporated into RSAT test to inactivate IgM preventing misidentification of positive sera	
Tube agglutination test (TAT)	– Serum Ab test – 1:200 titer is positive for infection – Identifies chronically infected	– Erratic availability of testing – Cross reaction with other infectious agents – No commercial tests for TAT

anti–*B canis* antibodies. The most common serologic tests include agar gel immunodiffusion (AGID), rapid slide agglutination test (RSAT), tube agglutination test (TAT), microagglutination test (MAT), complement fixation test (CFT), and several enzyme-linked immunosorbent assay (ELISA) protocols with different antigens (Table 21.1.7). Indirect immunofluorescent antibody (IFA) testing and ELISA assays are not in widespread use and may not be available to clinicians.

Limitations of serologic testing include nonspecific reactions (occurs with hemolyzed sera, samples with high lipid content, or because of cross-reaction with other pathogens [e.g., *Pseudomonas* spp., *Streptococcus* spp., *Staphylococcus* spp., etc.]). Mercaptoethanol rapid slide agglutination (ME-RSAT) point-of-care (POC) test is performed initially as a screening test. This is followed by the agar gel immunodiffusion test, which is used to confirm infection in dogs that are positive with POC testing. PCR testing of whole blood (not serum) is more sensitive than blood culture or serologic testing. Additionally, PCR testing of vaginal swab samples may be used to confirm positive test results.

Management

Treatment/Prognosis

Treatment is generally discouraged in infected animals due to organism persistence within cells. Euthanasia is generally recommended for these animals. In breeding facilities, voluntary quarantining is mandated to ensure no animals are being introduced or sold/relocated. There should be no breeding, and isolation of positive dogs is advised. Recommended guidelines include:

1. Do not allow infected and uninfected dogs to share common areas as bacteria can have prolonged survival in the environment (days to weeks).
2. Use separate feeding and watering dishes.
3. Care for the negative dogs first, then suspected positive dogs, followed by positive dogs.

Serum positive patients with no clinical signs should be isolated and allowed to self-eliminate the organism if possible. These patients may take up to 2–3 years to spontaneously recover.

Treatment, when attempted, should involve spaying/neutering the patient followed by antibiotic therapy. Combination antibiotic therapy is recommended (Table 21.1.8), with multiple protocols being recommended. Some success has been reported using enrofloxacin (5 mg/kg p.o. q.24 h.) for 4 weeks alone. Once the antibiotic treatment cycle is completed, AGID testing is repeated with testing performed every 3 months until results are negative on at least two consecutive occasions. For animals that return positive results, repeat treatment is necessary. Relapses are common once antimicrobials

TABLE 21.1.8 Antimicrobial therapy for *B. canis* infection

Therapy	Length of therapy
Dihydrostreptomycin*, ** + tetracycline/minocycline**	4 weeks
Streptomycin*** + tetracycline/minocycline**	4 weeks
Gentamicin† + tetracycline/minocycline**	4 weeks
Gentamicin†† + doxycycline††† + rifampin‡	3 months
Enrofloxacin‡‡	4 weeks

* 20 mg/kg IM, SC q.24 h. for 7 days, weeks 1 and week 4; however, its availability is limited.

** 12.5 mg/kg p.o. q.12 h. or 25 mg/kg p.o. q.24 h. for 4 weeks.

*** 20 mg/kg IM, SC q.24 h. for 7 days, weeks 1 and 4.

† 2.5 mg/kg IM or SC q.12 h. on treatment, weeks 1 and 4.

†† 5 mg/kg SC q.24 h. for 7 days and repeated every 3 weeks.

††† 10 mg/kg p.o. q.12 h.

‡ 5 mg mg/kg p.o. q.24 h.

‡‡ 5–10 mg/kg p.o. q.24 h.

are discontinued, necessitating repetitive courses of antibiotics. Post therapy, patients are retested. Persistently positive patients are retreated and tested again until the patient has a negative test. Once negative, patients are retested every 4–6 months with treatment repeated as necessary. It is important to note that the therapy is not curative, and the dog may be a risk to other dogs and humans, especially young children, older persons, and immunocompromised individuals.

Brucella ocular infections are difficult to treat, and enucleation is generally recommended as the eye can act as a persistent nidus of infection.

Prevention

Risk of infection is greatest among dogs utilized in breeding programs or maintained in breeding kennels. Prevention strategies in breeding facilities include:

1. Quarantining and testing all new additions to kennels. Due to the lag time with many of the diagnostic tests, dogs should test negative on serial screening tests (ME-RSAT or TAT) performed 8 weeks apart prior to coming out of quarantine.
2. Artificial insemination to decrease male dog's exposure to disease. Unfortunately, this does not protect females from disease.
3. Periodic testing of all of the dogs twice a year in kennels. Kennel screening can help decrease exposure in the event a positive dog is introduced to the kennel.
4. Routine disinfection using 2.5% sodium hypochlorite, quaternary ammonium compounds, or 70% ethanol with a minimum of 10-minute contact time to clean facilities and equipment.

Public Health Implications

Canine brucellosis is regarded as a zoonotic infection. Both natural and laboratory-acquired infections have been reported. Caution should be taken when handling aborted tissues and discharges from dogs suspected of having brucellosis.

LEPTOSPIROSIS

See also Chapter 13.

Definition/Overview

Leptospirosis is caused by a Gram-negative, motile spirochete bacterium with worldwide distribution known to cause disease in dogs, humans, and many other animal species. Disease in canines is primarily caused by *L. interrogans* and *L. kirschneri*. Species are further classified into serovars based on surface O antigen serology. Closely related serovars are further divided into serogroups, with at least 10 being potentially important for dogs. Serogroups implicated in causing infection include *L. canicola*, *L. icterohaemorrhagiae*, *L. grippotyphosa*, *L. pomona*, and *L. bratislava*.

Etiopathogenesis

Ten serogroups are known to infect and cause disease in dogs. Serogroups implicated in causing infection include *L. canicola*, *L. icterohaemorrhagiae*, *L. grippotyphosa*, *L. pomona*, and *L. bratislava*. Persistence in the environment is through a reservoir host, most commonly rodents, with the organism being shed in the urine. Pathogenic serovars can remain viable in water or soil for weeks to months.

Clinically affected dogs are more likely to be living in close proximity to water and have indirect exposure to wildlife. Infection is seasonal, with outbreaks being linked to heavy rainfall or flooding. Transmission is via either direct contact of mucous membranes or broken skin with the urine from infected animals or by indirect contact with contaminated soil or surface water. Infection can also occur through bite wounds, ingestion of infected tissues/fluids, and by venereal and placental transfer. Initially, leptospires bind inhibitors of complement activation evading the host immune response and a bacteremic phase, lasting for 10 days, establishes via hematogenous spread. Bacteria then invade the kidney and liver, among other organs, with bacteria then being shed in the urine. Once there is an effective host immune response, the organism is cleared from the bloodstream. Following clearance, Leptospira persist in "immune-privileged sites" such as the eye and renal tubules.

Clinical Presentation

Clinical manifestation of disease is highly variable and dependent on patient age, geographical location, host immune response, and strain of pathogen. Common presenting clinical signs are related to various combinations of vasculitis, acute kidney injury (AKI), and liver impairment (**Figure 21.1.3**). Other clinical signs can include fever, pulmonary hemorrhage, uveitis, myositis, and reproductive failure. Acute infection is characterized by fever (39.4°C–40.0°C [103°F–104°F]), a reluctance to move due to pain, and myositis. Clinical signs associated with AKI include polyuria, polydipsia, dehydration, vomiting, diarrhea, inappetence, lethargy, or abdominal pain.

Differential Diagnosis

Acute-onset signs associated with leptospirosis may manifest as any one of several serious systemic illnesses, including acute kidney injury/chronic kidney disease, acute hepatitis, neoplasia, adverse drug reaction, polyarthritis, myositis (e.g., canine toxoplasmosis), pneumonia, and spinal cord injury.

Diagnosis

The diagnosis of leptospirosis is typically based on presenting clinical signs and clinician intuition. Clinicians should suspect leptospirosis in dogs with signs of renal or hepatic failure, uveitis, pulmonary hemorrhage, or abortion. Findings on CBC may include neutrophilia



FIGURE 21.1.3 Bilirubinuria in an icteric dog with leptospirosis-induced hepatitis. The urine of dogs infected with leptospirosis can remain infectious for several weeks or months following clinical recovery.

with/without a left shift and a nonregenerative anemia. Up to 60% of patients will present with thrombocytopenia. This is accompanied by varying degrees of an azotemia (up to 80% of cases) or hepatic injury (30%–50% of patients) as evidenced by increased serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and hyperbilirubinemia. Increases in ALP and bilirubin are more common than increases in serum ALT. The former changes are often found with concurrent electrolyte abnormalities (e.g., hyponatremia, hypokalemia, hypochloremia, and/or hyperphosphatemia). Patients are commonly isosthenuric, with glucosuria, proteinuria, and hematuria being common. Often there is an active urine sediment (i.e., low numbers of white blood cells, red blood cells, and granular casts). Urine should always be submitted for quantitative culture and sensitivity to rule out other causes of acute kidney injury such as pyelonephritis.

Definitive diagnostic tests for leptospirosis are divided into 2 broad categories (Table 21.1.9):

1. Direct bacterial visualization detection tests (e.g., culture, dark field microscopy, or PCR). These diagnostics are best used early in the course of disease in patients naïve to antimicrobial therapy. These tests may detect disease earlier compared to the microscopic agglutination test (MAT) (i.e., peracute/acute phase). For PCR, both urine and blood should be collected and tested separately to increase the test sensitivity. Commencement of antibiotics prior to performance of a PCR may result in false negative test results.
2. Antibody detection tests (e.g., point-of-care [POC] and MAT). Currently, there are two rapid, simple to perform, commercial POC antibody tests: The Zoetis WITNESS test and the IDEXX SNAP test. The WITNESS POC test is recommended for the initial screening of acutely ill dogs suspected to have leptospirosis as it can detect *Leptospira*-specific antibodies earlier compared to both the MAT and SNAP. A positive test is highly supportive for a diagnosis of leptospirosis. A negative test should be viewed with caution and retesting performed in 7–10 days.

TABLE 21.1.9 Diagnostic tests for leptospirosis

Test	Results	Sample submission
Point of care – WITNESS – SNAP Lepto test	– Initial screening test – Ab detection 7–10 days post infection	– Serum
Microscopic agglutination test (MAT)	– Collect acute and convalescent specimens 7–14 days apart – A fourfold rise in Ab titer is consistent with active infection – False-negative MAT during first week of infection	– Serum
Polymerase chain reaction (PCR)	– Detects leptospiral DNA before development of Ab – Perform within 7–10 days of illness (i.e., bacteriuric and bacteremic phase of disease, respectively)	– Whole blood or urine – Can submit on kidney or lung tissue

The "gold standard" serologic test for leptospirosis is the MAT. The test reports titers to common serogroups. Seroconversion can take over a week to occur (i.e., negative MAT test with early disease). A titer to any serovar of > 1:800 with compatible clinical signs is consistent with infection. Submission of two samples, representing acute and convalescent titers, collected 7–14 days apart is advised. A 4-fold increase in titer supports infection. Medical therapy may blunt antibody production and prevent this expected rise. Vaccination results in positive MAT (1:6400) with titers of > 1:1600 persisting for up to a year after vaccination.

Management

Treatment/Prognosis

Individualized therapeutic plans consisting of antimicrobials and supportive care is based upon a thorough clinical and clinicopathologic evaluation as well as the severity of organ system dysfunction. Therapies should

be based on both American College of Veterinary Internal Medicine (ACVIM) and European College of Veterinary Internal Medicine (ECVIM) guidelines. Dogs with clinical signs associated with leptospirosis require hospitalization and intensive supportive therapy. Aggressive fluid replacement with a balanced and buffered crystalloid (e.g., lactated Ringer solution [LRS] or Norm-R) is indicated initially to replace fluid losses and maintain renal perfusion. Hydration status should be monitored every 6 hours (i.e., changes in body weight, respiratory rate, blood pressure). An indwelling urinary catheter is recommended to monitor urine output and reduce environmental contamination and exposure of staff to infectious urine. Urinary catheters are left in place until patients are polyuric. In euhydrated, oliguric (urine output < 2 mL/kg/h) or anuric patients initial use of osmotic diuretics (e.g., 20% mannitol) at 0.5 g/kg IV over 30–60 minutes followed by furosemide 2 mg/kg IV q.6–8 h. or 2 mg/kg followed by a constant rate infusion of 0.25–1 mg/kg/h IV may be required. Hemodialysis is recommended in patients that do not respond to therapy. Urinary catheter care should be performed every 6 hours to reduce the risk of nosocomial infection, and once removed (within 12 hours), urine should be collected via cystocentesis and cultured. In systemically unwell patients, supportive care correcting electrolyte and acid–base derangements, administering antiemetics, antihypertensives, pain control medications, and nutritional support are important. Parenteral antibiotic therapy is initiated in systemically unwell patients (ampicillin at 20 mg/kg IV q.6 h. or ampicillin/sulbactam (Unasyn; Pfizer; New York (NY) at 30 mg/kg IV). Dose intervals should be increased in severely azotemic animals. Patients should be transitioned to oral doxycycline (5 mg/kg p.o. q.12 h. or 10 mg/kg q.24 h. for 2 weeks) once stable, as penicillins do not clear leptospires from the renal tubules or eliminate the patient's carrier state.

Prognosis is highly variable and dependent upon clinical signs at presentation and aggressiveness of medical therapy. The reported survival rate to hospital discharge is approximately 80%. Dogs with acute onset of clinical signs associated with icterus and disseminated intravascular coagulation (DIC), or dogs requiring but not receiving hemodialysis, have a poor prognosis. Dogs with subacute leptospirosis, with evidence of mild renal disease have a fair prognosis for recovery if treatment is instituted early and maintained for a minimum of 2 weeks. Recovered patients may have lasting chronic renal changes requiring long-term management and monitoring for chronic kidney disease.

Prevention

Vaccination is recommended for any dog in an endemic area and is advised for dogs with access to outdoors (yard, dog park, etc.). Vaccines are annual with a bacterin against the four most common *Leptospira* serovars currently diagnosed in dogs: *L. icterohaemorrhagiae*, *L. canicola*, *L. grippotyphosa*, and *L. pomona* being available in North America (see Table 21.1.4). Available vaccines are serovar specific and do not provide any cross-protection against other serovars. Initial immunization involves 2–3 injections at 2- to 3-week intervals beginning at 12 weeks of age.

Public Health Implications

Leptospirosis is zoonotic. Contaminated dog urine is infectious and poses a risk for both humans and other susceptible animals. Those working directly with animals are at increased risk of exposure as are immunocompromised people and children. Any hospitalized dog that is either suspected of having or confirmed to have leptospirosis should be handled appropriately (i.e., limit movement of patient while hospitalized, place warning signs on patient's cage, wear personal protective equipment (gloves, disposable gown, eyewear/facemask) when handling the patient, clean cages with disinfectant solutions that will inactivate leptospires (e.g., bleach, iodine-based products, accelerated hydrogen peroxide, quaternary ammonium, etc.). In patients receiving appropriate antimicrobial therapy, risk of infection decreases significantly after 72 hours of treatment. It is recommended that any other dogs living in the same household should receive oral doxycycline therapy for 2 weeks as exposure histories are probably similar.

TETANUS

Definition/Overview

Tetanus is a rare, noncommunicable, neurologic disease characterized by spastic paralysis of dogs and humans. It is caused by tetanus neurotoxin (TeNT), a potent neurotoxin produced by *Clostridium tetani*, an environmental soilborne, Gram-positive, sporulating, anaerobic bacterium. Infection and clinical disease often result from wound contamination with *C. tetani* spores.

Etiopathogenesis

Clostridium tetani is a ubiquitous organism found in the soil from all parts of the world. There is a higher incidence of infection in warm humid regions (i.e., West and Central Africa, Southeast Asia, India, the Pacific Islands, and the southern United States). Tetanus occurs after *C. tetani* spores contaminate a wound and secrete TeNT (i.e., tetanospasmin and tetanolysin). These toxins diffuse locally from the site of infection and bind with demyelinated nerve endings. Bound TeNT is internalized, routed to endocytic vesicles, and then undergoes retrograde axonal transport to neuronal cell bodies in the central nervous system (CNS). Within the CNS, TeNT binds irreversibly to inhibitory neurons preventing the regulated release of glycine and gamma-aminobutyric acid (GABA), allowing excessive firing of motor neurons producing rigidity and tetanic spasms of voluntary muscles. Recovery is dependent on the development of new axon terminals.



FIGURE 21.1.4 Generalized tetanus in this 5-month-old Airedale is characterized by profound limb and neck rigidity and erect ears.

Clinical Presentation

Clinical signs vary depending on severity of disease and are usually seen 5–10 days after exposure. Clinical disease appears as either a systemic (generalized) or localized disease process. These signs may last for several weeks. Generalized disease is characterized initially by ocular and facial abnormalities (contracted facial musculature, trismus, retracted lips, wrinkled forehead, rictus grin, miosis, enophthalmos, prolapse of the third eyelid). The ears are typically held close together and erect. Hypertonus of masticatory muscles is responsible for trismus, also known as "lockjaw." As the disease progresses, spastic paralysis accompanied by opisthotonos and tetanic spasming of the muscles of the trunk and upper and lower limbs develops (Figure 21.1.4). Hyperthermia can result from excessive muscular activity. The patellar reflex may be accentuated but may be difficult to assess because of muscle stiffness.

In localized tetanus, the muscles of the infected region become painful and stiff. Gradually, the opposite extremity becomes involved. With time, localized tetanus can become generalized. Affected patients can develop spasms when stimulated by touch, light, or noise.

Patients may also be affected by episodes of tachycardia (supraventricular or less commonly ventricular), systemic hypertension, alternating with bradycardia and hypotension. Death results from respiratory failure as a result of laryngeal, diaphragmatic, and respiratory muscle paralysis.

Differential Diagnosis

Muscle rigor and conformational changes associated with localized and generalized tetanus are characteristic of the disease. Differential diagnoses that should be considered include rabies, encephalitis, meningitis, toxins (e.g., strychnine), and trauma, particularly trauma involving the CNS.

Diagnosis

Diagnosis is based upon recognition of characteristic spastic paralysis accompanied by a history of a recent wound. Physical evidence of a wound or skin penetration may not be apparent on physical examination. Complete blood count often reveals a neutrophilic leukocytosis with a left shift. Creatinine kinase and aspartate aminotransferase may be elevated due to sustained recumbency and tetanic muscle spasming.

Identification of TeNT in biological samples is not indicated, as animals that develop signs of tetanus usually have low levels of TeNT. Likewise, there is limited utility of serological testing for antibodies to TeNT and isolation of *C. tetani* from contaminated wounds, as both procedures are laborious and have a low diagnostic yield.

Management

Treatment/Prognosis

Dogs with clinical signs require intensive supportive care. Severely affected animals with respiratory compromise due to excessive tetanic muscle spasms may need to be anaesthetized, intubated, and placed on positive-pressure ventilation. Those with mild clinical signs often respond well with minimal hospitalization time. In cases of generalized tetanus, intensive treatment may be as long as 3–4 weeks.

Therapy consists of:

1. *Antitoxin:* Immunization with either equine antitetanus serum (IV or IM) or human immunoglobulin-VF (IM). Tetanus antitoxin neutralizes unbound toxin or toxin that has yet to be formed. It does not bind to the toxin within the axon. Slow intravenous administration (5–10 minutes) is recommended in patients with acute disease (i.e., early stages), with therapeutic concentrations being reached faster compared with IM or SC administration. A test dose (0.1 mL) of antitoxin is recommended either SC or intradermally 15–30 minutes prior to IV administration, as IV administration is commonly associated with anaphylaxis. Development of a wheal at the site of injection may indicate antitoxin hypersensitivity; however, false-positive tests are known to occur. Affected patients should be pretreated with a glucocorticoid or an antihistamine prior to administration of the IV dose. Circumferential intralesional therapy and injections of small dose of antitoxin proximal to the wound may be performed (Table 21.1.10).
2. *Surgery:* Wound exploration and debridement may be indicated to remove foreign material and devitalized tissue for wounds as this may be a continued source of toxin. Prior to surgery, antitoxin should be administered, as further toxin may be released into the circulation with tissue manipulation.
3. *Antimicrobial therapy:* The goal of antimicrobial therapy is to eliminate *C. tetani* organisms and prevent further toxin production. Chosen antibiotics have good tissue penetration and have good efficacy against anaerobic organisms. Intravenous routes are preferred in critical dogs/cats with tetanus. Once eating, patients are transitioned to oral antibiotics (Table 21.1.10).

TABLE 21.1.10 Recommended therapeutics for tetanus

Drug	Dose	Route
Antitoxin		
– Equine antitoxin	100–1,000 U/kg	IV, IM, SC
– Human tetanus immunoglobulin	500–1,000 U per site 500–2,000 U near wound	Intralesional IM
Antimicrobials		
– Penicillin G*	20–100,000 units/kg q.6–12h.	IV, IM or SC
– Metronidazole (preferred)**	10–15 mg/kg q.8–12h.	IV p.o.
– Amoxicillin-clavulanate	13 mg/kg q.12h. 30 mg/kg q.8h.	IV IV
– Ampicillin-sulbactam	3–10 q.8–12h. 11–33 mg/kg q.8–12h.	IV p.o.
– Clindamycin		
Sedative and muscle relaxants		
– Phenothiazine		
– Chlorpromazine	0.5–2 mg/kg***	IV, IM, SC
– Acepromazine	0.01–0.07 mg/kg***	IV
– Barbiturates		
– Phenobarbital	2 mg/kg†	IV
– Benzodiazepines		
– Diazepam††	0.2–0.5 mg/kg	IV
– Midazolam†††	0.1–0.2 mg/kg	IV, IM
– Skeletal muscle relaxant		
– Methocarbamol	44 mg/kg‡	IV
– Anesthetic agents		
– Propofol‡‡	1–2 mg/kg	IV
Autonomic agents		
– Atropine	0.02–0.04 mg/kg	IV, IM, SC
– Glycopyrrolate	0.005–0.01 mg/kg	IV, IM, SC
Others		
– Magnesium	100 mg/kg	IV

* Potassium (aqueous), sodium salt, procaine salt.
Procaine salt given IM administered close to wound site.
Penicillin G 1440–1680 U = 1 mg.

** Bactericidal and able to penetrate anaerobic tissue.

*** Maximum dose IV of 3 mg in any dog.

† Every 20–30 minutes to effect and a maximum 24-hour dose of 24 mg/kg. If given at constant-rate infusion, use 1 mg/kg per hour.

†† Initial diazepam bolus dose may be as high as 0.95 mg/kg IV, followed by constant rate infusion of 0.2–0.4 mg/kg per hour.

††† If given at constant rate infusion, use 0.6–1.8 mg/kg per hour.

‡ Administer rapidly half of the estimated dose. Pause until animal starts to relax, then administer to affect. Do not exceed total cumulative dose of 330 mg/kg.

‡‡ If given at constant-rate infusion, use 0.5–2 mg/kg per hour for severe muscle rigidity and CNS excitability.

IM, intramuscular; IV, intravenous; p.o., by mouth; SC, subcutaneous.

4. *Sedative and muscle relaxants:* Muscle rigidity and spasming is controlled using mono or combination therapy drugs. These drugs indirectly control the hyperthermia resulting from uncontrolled muscle contractions. A combination of phenothiazines with barbiturates are effective in controlling convulsions, muscle stiffness, and opisthotonos. Benzodiazepines can be used in lieu of barbiturates. Methocarbamol, a skeletal muscle relaxant, may be used initially in severely affected animals to control muscle rigidity. After the patient is stabilized, this is replaced by either a phenothiazine/barbiturate or a phenothiazine/benzodiazepine combination. Adjunctive use of magnesium sulfate to help reduce tetanic muscle spasms has been utilized in veterinary patients. Muscle relaxation is facilitated by reducing calcium entry into presynaptic terminals at the neuromuscular junction and by decreasing the sensitivity of the motor endplates to acetylcholine.
5. *Autonomic agents:* Occasionally autonomic agents are required to control the cardiac rhythm as bradyarrhythmia (i.e., HR < 60 beats per minute) may occur. This type of arrhythmia is often self-limiting.
6. *Supportive care:* Patients should:
   i. Be hospitalized in a quiet, dark, well-padded environment with minimal stimulus.
   ii. Be repositioned every 4–6 hours to avoid the development of pressure sores/ulcers.
   iii. Have their urinary bladder frequently emptied (every 6–8 hours) via manual expression or catheterization to prevent urinary retention and secondary urinary tract infection.
   iv. Have a balanced nutritional plan formulated and be monitored while eating and drinking. Enteral (nasogastric/nasoesophageal tube, percutaneous endoscopic gastrostomy [PEG]/esophagostomy tubes) or parenteral nutrition should be considered as animals have problems prehending and swallowing food. Animals being tube fed are at risk of developing aspiration pneumonia.
   v. Antiemetics, prokinetics, and gastrointestinal protectants are also commonly utilized in patients with tetanus.

Complications associated with tetanus include the development of aspiration pneumonia secondary to either feeding a patient that is unable to prehend/swallow or due to the development of a hiatal hernia or megaesophagus. Other reported complications include respiratory failure, laryngeal paralysis, systemic hypertension, hyperthermia, rhabdomyolysis-induced acute kidney injury, and disseminated intravascular coagulopathy.

Prognosis

Prognosis is directly related to the degree of systemic involvement, with survival rates of 50%–92% being reported. Patients with localized tetanus (i.e., peripheral limb) have a better prognosis compared to patients with generalized tetanus.

Prevention

Tetanus toxoid is only administered to patients with acute-onset signs.

Public Health Implications

Tetanus is not a zoonotic disease.

VIRAL INFECTIONS

ADENOVIRUS-1 INFECTIONS (INFECTIOUS CANINE HEPATITIS)

Definition/Overview

Infectious canine hepatitis (ICH) is a systemic disease of dogs caused by canine adenovirus type 1 (CAV-1). Canine adenovirus type 1 also causes disease in wolves, coyotes, skunks, and bears, as well as encephalitis in foxes. The virus is a nonenveloped, icosahedral, double-stranded DNA virus that is genetically and antigenically related to canine adenovirus type 2 (CAV-2). Found globally, it commonly causes disease in dogs less than a year of age. It can survive in the environment for months at room temperature. Recently, CAV-1 has reemerged, sporadically causing a severe, often fatal disease.

Etiopathogenesis

Active infection results in the virus being shed in many bodily fluids (i.e., saliva, feces, and urine). Viral shedding in urine is long-lasting (up to 6–9 months post infection). Although the virus may persist in the kidney for several months post infection, urine contamination is not an important source of infection for susceptible dogs. Viral transmission is through close contact or indirectly through exposure to contaminated fomites (i.e., hands, utensils, and clothing). After oronasal exposure, CAV-1 rapidly replicates within the tonsils before disseminating to regional lymph nodes and the bloodstream via lymphatics. Viremia develops 4–6 days post exposure. The virus principally targets the liver and vascular endothelial cells within a variety of tissue (e.g., lungs, liver, kidneys, spleen, and eye). The virus replicates within the nucleus of these cells, forming virions, causing cell death that results in hemorrhage, inflammation, and necrosis. Clinical signs develop after an initial incubation period (i.e., 4–9 days), with an antibody response appearing after 7 days, which limits further tissue damage. There is good correlation between antibody titer and protection from infection. Pyelonephritis, anterior uveitis, and corneal edema may be observed in dogs recovering from acute illness. This is most likely due to viral persistence within the renal glomeruli, uveal structures of the eye (the iris and ciliary body), and the cornea, which triggers immune complex formation leading to inflammation.

Clinical Presentation

Infection is common in dogs < 1 year of age, with the most severe infections occurring in dogs from birth to 3 weeks of age. Three overlapping disease syndromes are recognized.

1. Peracute disease characterized by a brief illness (< 24–48 hours) followed by circulatory collapse, coma, and death.
2. Acute disease (most common) is associated with high mortality rates (approximately 10%–30%). Dogs with acute disease either recover or die within a 2-week period. Variable clinical signs include a transient or biphasic fever (> 40°C), tachycardia, enlarged tonsils, tachypnea, coughing associated with bronchopneumonia, inappetence, lethargy, weakness, vomiting, hematemesis, and diarrhea with or without blood. Bleeding diathesis due to vascular endothelial damage may be seen (e.g., petechial/ecchymotic hemorrhages and epistaxis). Neurological signs (e.g., seizures, ataxia, circling, apparent blindness, head pressing, and nystagmus) are rare in dogs. Corneal edema ("hepatitis blue eye") occurs in the first week of illness.
3. Chronic disease results from partial immunity. Death occurs weeks to months after initial infection.

Differential Diagnosis

Differentials for this disease should include poisoning, canine distemper virus, canine herpesvirus, canine parvovirus, fading puppy syndrome, leptospirosis, lymphoma, sepsis, and acute hepatitis.

Diagnosis

Although considered rare, infection should be suspected in any dog less than a year of age that is either unvaccinated or has a questionable vaccination history, who has concurrent fever, respiratory or gastrointestinal signs, or has evidence of hepatic disease. Likewise, any dog that develops corneal edema should have infectious canine hepatitis as a possible differential. Antemortem laboratory abnormalities are variable and may include a leukopenia (initially lymphopenia followed by neutropenia), anemia, and thrombocytopenia. During the acute viremic stage, there are variable changes to both direct/indirect liver function tests (bilirubin, albumin, glucose, ammonia) and liver enzymes (ALT, AST, and serum ALP). Coagulation defects consistent with DIC are possible.

Antemortem diagnosis is made based on virus isolation. In dogs surviving acute disease, CAV-1 may be able to be isolated from the urine, as the virus localizes and persists within the kidney for at least 6 months following initial infection. Alternatively, inclusion bodies may be discovered following cytologic examination of hepatic aspirates or impressions of hepatic biopsies.

Definitive diagnosis is achieved on postmortem examination. Dogs dying from acute disease will typically have findings of edema and hemorrhage of superficial lymph nodes and subcutaneous tissue, particularly in the area of the neck. Petechial and ecchymotic hemorrhage is commonly found throughout the abdomen. The gallbladder is characteristically thickened and edematous. Ocular lesions are characterized by anterior uveitis and corneal edema.

Management

Treatment/Prognosis

There is no specific antiviral therapy, with treatment being symptomatic and supportive until hepatocellular

repair can occur. Clinical management encompasses aggressive fluid therapy with isotonic fluids (e.g., lactated Ringer's solution), electrolyte and glucose supplementation where indicated, antiemetics, antacids, whole blood or plasma transfusions, and enteral nutrition. Monitoring the patient's hydration status is crucial, as patients are susceptible to fluid overload due to increased vascular permeability and hypoalbuminemia. Patients with severe hepatic necrosis may develop acute liver failure and subsequent hepatic encephalopathy. These patients should be managed with cleansing acidifying lactulose enemas, oral lactulose (in the absence of vomiting), and empiric antimicrobials (i.e., metronidazole, neomycin, ampicillin). Dogs with corneal edema without corneal ulceration can be treated with topical ophthalmic preparations of glucocorticoids and atropine to prevent glaucoma.

Prognosis is dependent on the immune status of the affected dog, severity of disease, and possibly the virus strain. Dogs recovering from the acute form of disease may develop chronic hepatitis and fibrosis or glomerulonephritis.

Prevention

Infection caused by CAV-1 has been controlled in domestic dog populations because of vaccination. Parenteral modified live CAV-2 vaccines (see Tables 21.1.4 and 21.1.5) are now used in vaccination programs due to the strong antigenic relationship between CAV-1 and CAV-2 and because modified live CAV-1 vaccines have historically caused adverse reactions. Maternal antibodies may interfere with immunization until puppies are 12 weeks of age. Vaccines are administered every 3–4 weeks from 6 weeks of age, with the last vaccine given no earlier than 16 weeks of age. Readers should be aware that a CAV-2 vaccine is currently offered in combination with *B. bronchiseptica* and canine parainfluenza for intranasal (mucosal) administration (see Table 21.1.4).

Public Health Implications

Canine adenoviruses do not pose a risk to human health.

CANINE INFLUENZA

See also Canine Infectious Respiratory Disease.

Definition/Overview

Canine influenza is a term used to describe disease induced by any influenza virus infection in dogs. These enveloped single-stranded RNA viruses belong to the family Orthomyxoviridae and have a complex natural history. Influenza A viruses, which are naturally found in the gastrointestinal tract of bird populations, can occasionally "spill over" into nonavian populations. Subtypes of influenza A viruses, which are specified by their antigenic surface glycoproteins, hemagglutinin (HA) and neuraminidase (N), are responsible for infection in dogs. H3N8 and H3N2 CIV are responsible for disease in dogs. H3N8, which originated from cross-species transmission of an equine influenza A virus, was first discovered in early 2004 in a racing greyhound kennel in Florida. H3N2 CIV, which originated in avian species, initially emerged from China and Korea in 2004–2005. Transfer of the CIV subtypes to dogs from birds and horses is thought to have been facilitated by the presence of hemagglutinin binding receptors on the bronchial/bronchioalveolar epithelial and tracheal/bronchial epithelial cells, respectively. Both diseases are associated with mild upper respiratory tract disease.

Etiopathogenesis

Transmission of the virus is via direct (i.e., oronasal contact or inhalation of aerosolized droplets) or indirect contact via fomites (e.g., clothing, footwear, food, and water bowls, etc.). Dogs housed in communal facilities (e.g., kennels, shelters, etc.) are at a higher risk of exposure to circulating CIV.

The virus enters and replicates in the mucosal epithelium cells lining the airways from the nose to the terminal airways. Viral replication leads to epithelial cell necrosis and destruction of the respiratory epithelial barrier, predisposing patients to secondary bacterial infection (e.g., *Bordetella bronchiseptica, E. coli, Klebsiella* spp., etc.). When affected, alveoli walls in the lower respiratory tract become thickened with inflammatory cells, which may lead to bronchopneumonia (< 20% of cases). The virus may also cause lymphocytic or neutrophilic rhinitis. Clinical signs usually develop within 2–5 days with viral shedding limited to 7–10 days post infection.

Clinical Presentation

There is no breed predilection. Immunocompromised dogs, puppies, and elderly dogs are at higher risk for infection. Approximately 80% of infected dogs will demonstrate clinical signs with two clinical syndromes being described. The first is a mild upper respiratory tract infection, which is usually self-limiting and manifests as a nonproductive dry cough, nasal discharge, fever, ocular discharge, lethargy, and anorexia. Up to 5% of dogs will develop more severe lower respiratory tract disease (i.e., pneumonia). Clinical signs associated with this form of disease include a productive cough, fever (104°F–106°F), increased respiratory rate and effort, purulent nasal discharge, lethargy, and anorexia. Hemorrhagic pneumonia and subsequent death has been reported in greyhounds with H3N8 infections.

Differential Diagnosis

Many dogs with H3N8 infection are subclinical. Those that do develop clinical disease are most likely to present with signs consistent with canine infectious respiratory disease (CIRD) complex. Viral pathogens associated with this disease complex include parainfluenza, adenovirus-2, respiratory coronavirus and herpesvirus-1 as well as others. Bacterial infections implicated in CIRD

include *Bordetella bronchiseptica*, *Mycoplasma* spp., and *Streptococcus zooepidemicus*. Additionally, in more severely affected animals, canine distemper virus, fungal or bacterial pneumonia are all considerations.

Diagnosis

No point-of-care rapid assay is available for the diagnosis of canine influenza. PCR is the preferred clinical diagnostic test. Samples for PCR should be collected early within the course of infection (i.e., within 4–5 days of clinical signs developing). Beyond that period, viral shedding declines and may have even ended. Pooled swab samples from multiple sites, including nose, conjunctiva, and pharynx, with a plastic handled swab is recommended.

In patients with clinical signs greater than 5 days, serology can be performed using acute and convalescent titers. Clinical diagnosis of recent infection in these patients is predicated on documenting a ≥ 4-fold rise in antibody titer over a 2- to 4-week period. A single, positive titer only denotes prior exposure or vaccination.

Management

Treatment/Prognosis

Treatment consists of symptomatic and supportive care based on the presenting clinical signs and laboratory tests. Most CIV infections are self-limiting resolving over several weeks. Dogs with a cough +/- nasal discharge should be isolated from other dogs for at least 7–10 days and have restricted exercise. Patients developing clinical signs (inappetence, fever with mucopurulent discharge) or radiographic evidence of pneumonia require more aggressive therapy. This will include intravenous fluids to maintain hydration, antimicrobial therapy for systemically unwell patients, supplemental oxygen, and nebulization/coupage. Ideally, antibiotic choices should be guided by tracheal wash or bronchoalveolar lavage diagnostics. In patients not undergoing this diagnostic testing, empiric broad-spectrum antibiotic therapy is recommended. Commonly used antibiotics include amoxicillin-clavulanate, azithromycin, doxycycline, and enrofloxacin. Cough suppressants should not be used in patients with a productive cough or evidence of pneumonia.

Prevention

Inactivated (killed) CIV vaccines against H3N2 and H3N8 CIV are currently available (see Table 21.1.4). These vaccines are noncore with at-risk dogs (frequently boarded dogs, dogs competing in sporting events, dogs frequenting dog parks or dog shows, or shelter animals) being recommended for vaccination. Vaccination does not prevent infection nor shedding of virus following exposure. However, vaccination will mitigate the severity of disease and decreases the period of virus shedding among exposed/infected dogs. Also recommended is isolation of infected dogs from other household animals for 28 days, restricting access into and out of kennels for up to 1–2 weeks following an outbreak, and regular cleaning and disinfection of both equipment and facilities with a 1:30 dilution of bleach or quaternary ammonium compounds.

Public Health Implications

Although human influenza viruses have been recovered from dogs and cats, CIV is not considered to represent a threat to human health.

CANINE ENTERIC CORONAVIRUS

Definition/Overview

Canine enteric coronavirus (CECoV) is a large, spherical, enveloped, single-stranded, positive-sense RNA virus that is named for the ultrastructural "crown-like" (corona) appearance of the spike proteins on the virion surface. It is a common infection in dogs and has a worldwide distribution. Although dogs of all ages can be affected, CECoV is considered to be a common cause of mild, self-limiting diarrhea in young puppies. More severe disease has been reported in combination with other pathogens, including canine parvovirus-2 and canine adenovirus-1. Although CECoV is highly contagious and capable of spreading rapidly among susceptible dogs, the overall incidence of disease is considered to be low.

Etiopathogenesis

Canine coronavirus is transmitted via the fecal–oral route. Disease is more prevalent in dogs housed in more densely populated (e.g., kennels or shelters) contaminated environments. Following ingestion, the virus infects and replicates within the cytoplasm of mature enterocytes (i.e., apical and lateral enterocytes of the intestinal villi). Incubation is 1–4 days. These cells then die and slough into the intestinal lumen. Loss of mature villi causes villus atrophy, leading to loss of normal digestive and absorptive functions of the small intestine. Small bowel diarrhea and dehydration are observed clinically. Concurrent coinfection with other viral pathogens (e.g., canine parvovirus) can lead to complications such as intussusceptions or more severe forms of disease (e.g., hemorrhagic enteritis).

Clinical Presentation

Canine coronavirus is a highly contagious disease. Disease most commonly effects dogs under 12 weeks of age. Clinical signs are usually mild and self-limiting with small intestinal diarrhea predominating (Figure 21.1.5). Feces are described as malodorous, orange in color, and may contain blood. In severe cases, dehydration, electrolyte imbalances, and vomiting may ensue. These clinical signs are difficult to distinguish from other causes of infectious enteritis (e.g., canine parvovirus).



FIGURE 21.1.5 Diarrhea is a common sign of canine coronavirus infection. (*Courtesy of Pfizer Ltd.*)

Differential Diagnosis

Infection can mimic several causes of mild enteritis of puppies (e.g., intestinal parasites, dietary indiscretion, and food intolerance). Other reasonable infectious disease differentials include viral disease (e.g., canine rotavirus, canine distemper virus, and canine parvovirus), bacterial enteritis (e.g., clostridial enteritis, *E. coli*, salmonellosis), and protozoal enteritis (e.g., coccidiosis, giardiasis, cryptosporidiosis). Affected puppies should also be evaluated for the presence of intussusception.

Diagnosis

Several commercial veterinary diagnostic laboratories offer real-time PCR assays for the detection of CECoV and other enteric infectious pathogens based on isolation of the virus in fresh feces. Assays may detect as few as 1,000 copies of viral DNA per milligram of stool.

Management

Treatment/Prognosis

Supportive therapy is the mainstay of treatment with CECoV infection inconsistently causing clinical disease. Disease is typically mild and self-limiting, with most cases not requiring therapeutic intervention. In severe cases, electrolyte and fluid replacement is indicated to counter the effects of fluid loss, acidosis, and rarely shock.

Prevention

Both killed and modified live CECoV vaccines are currently available. With disease commonly being mild and self-limiting and the fact that these vaccines provide only incomplete protection against CECoV infection, vaccination is not currently recommended. Furthermore, the value of vaccinating adult animals is limited by the fact that natural resistance to the disease occurs with age.

Public Health Implications

CCV is not zoonotic.

CANINE ORAL PAPILLOMA INFECTION (PAPILLOMATOSIS)

See also Chapter 18.

Definition/Overview

Canine oral papillomavirus 1 (CPV-1) is a small, nonenveloped, double-stranded DNA virus belonging to the Papillomaviridae family. It is host specific, spread by direct contact or contact with the virus in the environment, targeting keratinizing and mucous membrane tissue. The virus predominantly affects young dogs (≤ 2 years) causing cauliflower-like warts of the lips and mucocutaneous junctions. There is no sex or breed predilection. Malignant transformation of papillomavirus-induced tumors is extremely rare.

Etiopathogenesis

The virus infects basal cells of the skin through microabrasions. During this asymptomatic phase (4 weeks), the virus replicates within these cells. Clinical presentation is determined by the degree of cell proliferation induced by CPV-1, with most dogs (> 50%) having no clinical symptoms. Lesions develop when CPV-1 replication is amplified, resulting in hyperplasia development in the stratum spinosum and the generation of cauliflower-like wart growths of the lips and oral cavity with acanthosis and hyperkeratosis. Many dogs remain clinically well. Age and immune status of affected dogs may determine the outcome of infection, with spontaneous wart regression being reported young healthy dogs (i.e., 2–12 months), while older and/or immunosuppressed dogs have a higher risk of developing not only persistent clinical disease but also neoplastic transformation of lesions.

Clinical Presentation

Disease commonly occurs in young dogs (≤ 2 years), with the oral mucosa, lips, and mucocutaneous junctions being the most common tissue affected (**Figure 21.1.6**).

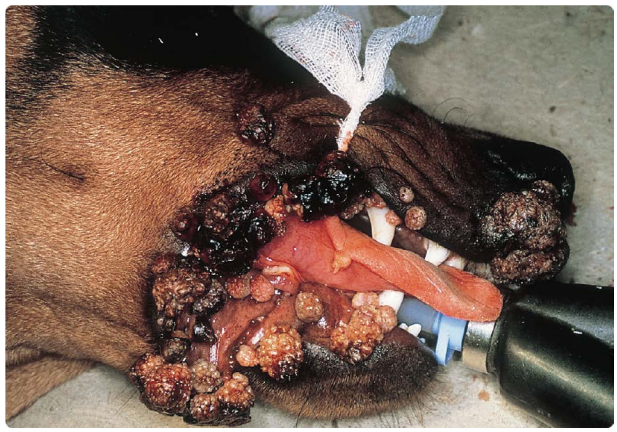


FIGURE 21.1.6 Advanced viral oral papillomatosis in a young Dobermann.

Other affected tissue includes the eyelids, palate, tongue, pharynx, epiglottis, and esophagus. Papillomas most frequently occur in small clusters with occasional severe manifestation being noted (Figure 21.1.6). Associated signs include secondary oral ulcerations/infection, halitosis, hypersalivation, minor bleeding of affected tissue, and discomfort. Dogs with severe disease may find it difficult or painful to eat or have problems breathing.

Differential Diagnosis

Benign and malignant oral neoplasms (e.g., epulides, fibroma, hemangioma, hemangiopericytoma, and histiocytoma).

Diagnosis

Diagnosis is based on characteristic physical examination findings and the clinical history, which may negate further laboratory testing. In questionable cases, full-thickness excisional biopsies with adjacent normal tissue should be obtained to perform histologic examination. PCR assays to detect CPV-1 DNA can be performed on Cytobrush or biopsy samples.

Management

Treatment/Prognosis

Most papillomas will spontaneously regress over time (2–12 months) following their initial appearance. In papillomas that do not regress or cause problems due to their size or location, surgical excision, cryosurgery, or electrosurgery is indicated. This has been associated with increased recurrence. Anecdotally, it has been reported that simply crushing 5–15 of the tumors may provoke spontaneous regression and, thereby, shorten the course of disease. Prognosis of this disease is excellent.

Prevention

Most papillomas are self-resolving. Preventing close contact between an affected dog and a dog that has never had papillomas is advisable. Currently a commercial vaccine does not exist.

CANINE DISTEMPER VIRUS (DISTEMPER, "HARD-PAD DISEASE")

Definition/Overview

Canine distemper virus (CDV) is a single-stranded RNA virus belonging to the genus *Morbillivirus*, family Paramyxoviridae. It is highly contagious, causing severe multisystemic disease characterized by fever, respiratory disease, enteric signs, and neurologic disorders. Viral transmission is via direct animal contact with infected animals shedding viral secretions up to 2 weeks after acute systemic illness. The virus is quickly inactivated in the environment, being especially susceptible to disinfectants, UV light, drying, and temperatures > 50°C–60°C (122°F–140°F). At freezing temperatures, the virus is reported to survive for several weeks.

Etiopathogenesis

Canine distemper virus has a broad host range, primarily infecting carnivores as well as the giant panda and certain primates. Dogs are the primary host and the likely reservoir for infection. Infection can sometimes occur concurrently with canine infectious respiratory disease complex infections. In unvaccinated animals, CDV poses a significant health threat. In unvaccinated dogs, infection can occur at any age, with unvaccinated puppies between 3 and 6 months of age being most commonly affected once they have lost their maternally derived antibody.

Disease transmission from infected animals is via aerosol or microdroplet contact with the epithelium of the nose or oral cavity of naive animals. Transplacental infection can occur from infected dams. Once attached, the virus invades and multiplies within tissue macrophages spreading to local lymphatics, tonsils, and bronchial lymph nodes, which results in severe immunosuppression. The virus then disseminates throughout the body via the lymphatics, infecting the spleen, liver, and gastrointestinal tract (4–6 days post infection [PI]), followed by hematogenous spread to epithelial tissue and CNS tissue (8–9 days PI). Viral shedding into the environment initiates with epithelial colonization. Clinical signs and viral clearance are related to the virus strain and animal's immune response. Animals with an adequate immune system are able to eliminate the virus within 2 weeks of infection. Animals with a poor immune status have global dissemination of the virus to epithelial tissue of the skin, gastrointestinal, respiratory, and genitourinary tract among others, which ultimately results in death. Those animals mounting a poor immune response may develop secondary bacterial infections resulting in more severe clinical illness. Viral spread and persistence in the uveal tissue, neurons, and integument such as the footpads occurs in animals mounting an intermediate response.

Clinical Presentation

Clinical signs are variable and depend on strain virulence and animal's immune status. Greater than 50% of CDV infections may be subclinical because of an adequate immune response, resulting in clearance of the virus within 2 weeks. In animals demonstrating clinical signs, respiratory signs predominate. Initially in mild cases, there is a transient fever, lethargy, anorexia, and leukopenia corresponding to immunosuppression at 3–6 days PI. This is usually accompanied by coughing, dyspnea, and discharge from the eyes and nose.

In dogs mounting a poor immune response, clinical signs are more severe with gastrointestinal signs of vomiting, diarrhea, and tenesmus accompanying the aforementioned clinical signs. Dehydration may develop due to persistent anorexia, vomiting, and diarrhea.

Central nervous system (CNS) signs may coincide with or can occur 1–3 weeks following recovery from systemic disease. Neurological signs, whether acute or chronic, are progressive and typically affect both recovery from infection and prognosis. Signs vary according to the area of CNS involved. Seizures, cerebellar, and vestibular signs accompanied by ataxia and myoclonus (i.e., involuntary rhythmic muscle twitching) are common. Focal facial seizures (i.e., "chewing gums") often occur in dogs developing polioencephalomalacia of the temporal lobes (Figure 21.1.7).

Other clinical findings may include enamel hypoplasia prior (Figure 21.1.8) to the eruption of permanent teeth and ocular signs of keratoconjunctivitis sicca, anterior uveitis, optic neuritis (associated with sudden-onset blindness), as well as retinal degeneration and necrosis involving both the tapetal and nontapetal fundus. On funduscopic examination, chronic inactive retinal lesions are seen as hyperreflective areas in the tapetum, often called "gold medallion lesions" (Figure 21.1.9). Young, growing, large-breed dogs between 3 and 6 months of age can develop metaphyseal osteosclerosis and hypertrophic osteodystrophy of the long bones.



FIGURE 21.1.7 A 3-year-old unvaccinated Pointer presented with acute-onset seizures followed by progressive neurologic signs and eventual coma.



FIGURE 21.1.8 Enamel hypoplasia in a 1-year-old dog that recovered from CDV infection at 3–4 months of age.



FIGURE 21.1.9 Hyperreflective tapetum in a dog that recovered from CDV infection.

Differential Diagnosis

Canine distemper, although rare, is associated with a complex array of clinical signs, depending on the individual animal. Alternative diseases to consider include rabies, pneumonia (a common secondary event), *B. bronchiseptica* infection, idiopathic epilepsy, hypoglycemia, CNS trauma, and renal failure.

Diagnosis

Canine distemper virus infection should be considered in any febrile puppy with multisystemic symptoms. Antemortem diagnosis is challenging when presented with a patient having only respiratory, gastrointestinal, or neurological signs due to insensitive laboratory diagnostic assays. Often a combination of laboratory tests is required, testing multiple specimens (blood, urine, conjunctival smears, and CSF) from different anatomic locations is required to establish a diagnosis. Conversely, distemper virus should be suspected in a young unvaccinated dog presenting with severe gastrointestinal, respiratory, and neurological signs, especially when myoclonus is present.

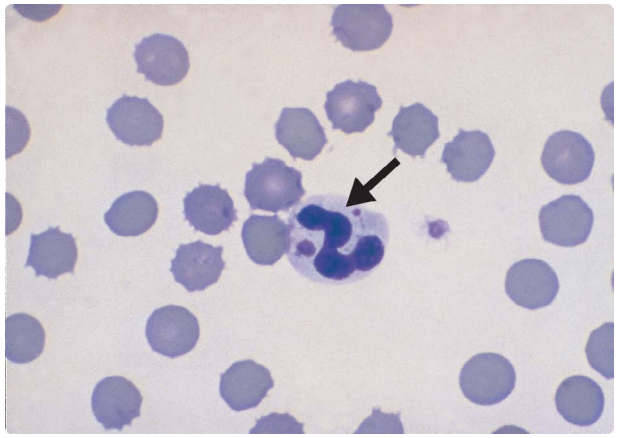


FIGURE 21.1.10 Distemper inclusion body (arrow) in a peripheral blood neutrophil collected from a dog with acute CDV infection.

Hematologic changes may include lymphopenia, thrombocytopenia, and regenerative anemia. Occasionally, CDV cytoplasmic and intranuclear inclusion bodies (Figure 21.1.10) may be found in peripheral blood smears, especially in early infection, or conjunctival swabs/scrapings of white blood cell (WBC) lines (mainly lymphocytes) and epithelial cells, respectively. Inclusion bodies are best elucidated in blood films stained with a quick Romanowski-type stain [e.g., Diff-Quik]. Examination of buffy coat smears and bone marrow aspirates may increase the chances of detecting inclusions.

Cerebrospinal fluid analysis may be normal in cases of acute, noninflammatory encephalomyelitis. Chronic infection may reveal an increased intracranial pressure causing a rapid flow rate of CSF, increased protein concentration (> 0.25 g/L [25 mg/dL]), and a mononuclear pleocytosis (> 10 cells/μL, primarily lymphocytes). Increased distemper-specific IgG in the CSF is definitive for infection, as it is locally produced, with vaccine-induced CDV antibody not usually being present in CSF.

Other diagnostic tests for CDV infection include immunocytology, immunohistochemistry, serum antibody testing, and virus isolation. These require special sample preparation and equipment and are not available in all diagnostic laboratories. PCR is not only sensitive and specific for diagnosing CDV but is also useful for differentiating a virulent from viral vaccine strain. Samples for collection and analysis include whole blood, serum, CSF, conjunctival swabs, buffy coat smears, respiratory lavage specimens, impression smears of tissue specimens, and urine sediment.

Immunofluorescent testing can be performed on conjunctival, tonsillar, respiratory, and genital epithelium. It should be noted that immunofluorescence is typically positive for only the first 3 weeks post infection in the conjunctival and urinary epithelium due to increasing antibody titers and virus neutralization. In dogs mounting an intermediate response, CDV may persist for ≥ 60 days in the skin, uveal tissue, CNS tissue, and footpads.

Management

Treatment/Prognosis

There is no specific anti-CDV therapy with treatment consisting of supportive care. Dogs with mild respiratory or gastrointestinal distemper may recover spontaneously without treatment. Supportive care consists of parenteral fluids, antiemetics, electrolyte supplementation, maintaining adequate nutrition, artificial tears, and managing secondary bacterial infections. Ideally, treatment for secondary bacterial pneumonia should be guided by tracheal wash or bronchoalveolar lavage diagnostics. Alternatively, empiric broad-spectrum antibiotic therapy using amoxicillin-clavulanate, azithromycin, and doxycycline as monotherapies or initiating combination parenteral therapy in patients with severe pneumonia using ampicillin and enrofloxacin is recommended. In those patients that do develop severe, progressive CNS signs, euthanasia should be recommended. For patients that develop seizures, myoclonus, and optic neuritis, anticonvulsant therapy and muscle relaxants should be considered along with anti-inflammatory therapy (i.e., corticosteroids) to reduce edema.

Prevention

Vaccination with either an attenuated live or recombinant vaccine is recommended (see Table 21.1.4). These vaccines are safe and are highly efficacious. While most manufacturers recommend three doses of vaccine between 6 and 16 weeks of age, the duration of immunity (DOI) following the initial booster vaccination (1 year following the last of the initial series inoculations) has been documented to persist for at least 5 years. Current guidelines recommend triennial administration of booster vaccine in adult dogs. Furthermore, dogs recovering from natural infection are expected to have lifelong immunity. Rarely, dogs vaccinated with the Rockborn strain of CDV have been reported to develop postvaccinal encephalitis. Postvaccinal encephalitis has been reported in neonatal puppies subsequent to the vaccination of pregnant dogs at or near parturition. Vaccination of pregnant dogs is not recommended.

In high-risk environments such as animal shelters, administration of a single dose of recombinant CDV vaccine to puppies given hours before shelter entry can provide protective immunity from severe disease despite the presence of maternal antibody.

Public Health Implications

CDV infection is not considered to be zoonotic.

CANINE PARVOVIRUS INFECTION

See also Chapter 9.

Definition/Overview

Canine parvovirus type 2 (CPV-2) is a common cause of acute canine enteritis with high morbidity and mortality

rates in untreated dogs worldwide. First recognized in the mid-to-late 1970s, this small, nonenveloped, single-stranded DNA virus has three variants (CPV-2a, CPV-2b, and CPV-2c), all with similar pathogenicity leading to indistinguishable clinical disease. Disease is common in dogs younger than 6 months of age and adults with insufficient immunity. It principally infects rapidly dividing cells of the gastrointestinal tract, bone marrow, lymphoid tissue, and cardiac myocytes. The virus, which is ubiquitous, can survive up to for more than a year in the environment. Exposure of naïve dogs to the virus occurs through contact with infected feces, vomitus, or fomites (e.g., clothing, floors, and utensils). Seasonal prevalence and breed predisposition are geographically variable. Vaccination along with good hygiene practice has been demonstrated to be crucial in prevention of infection.

Etiopathogenesis

All three variants (CPV-2 a, b, c) are able to cause clinical disease. There are a number of factors may precipitate or exacerbate parvoviral infection. These include a lack of protective immunity, comorbid conditions (e.g., intestinal parasites), and stressful environments (e.g., overcrowding, unsanitary living conditions). Breeds at risk for severe CPV infection include Rottweilers, Dobermann Pinschers, American Pit Bulls, Terriers, Labrador Retrievers, and German Shepherd Dogs. The reasons for this are unclear. Males are more prone to infection, with most dogs succumbing to infection during the summer. Transmission to susceptible dogs occurs directly (fecal–oral route) or indirectly (oronasal exposure) through either contact with infected feces, vomitus, or fomites (e.g., clothing, floors, and utensils). The incubation period is 7–14 days. Post exposure, the virus localizes and replicates within the lymph nodes (i.e., oropharyngeal and mesenteric) and thymus before disseminating and localizing into rapidly dividing cells of the gastrointestinal tract (i.e., tongue, oral cavity, esophagus, small intestine), bone marrow, cardiac myocytes, and lymphoid tissue. Viral shedding starts several days prior to the development of clinical signs and progressively declines over 3–4 weeks postexposure. Clinical signs are related to virus-induced destruction of rapidly dividing cells (i.e., intestinal crypt epithelial cells, thymus, lymph nodes, and bone marrow precursor cells) resulting in vomiting, diarrhea, dehydration, bacterial translocation from the gastrointestinal tract, profound leukopenia (mainly neutropenia and/or lymphopenia), metabolic acidosis (or alkalosis), systemic inflammatory response syndrome (SIRS), multiorgan dysfunction, and finally death.

Clinical Presentation

Clinical signs associated with CPV infection are highly variable, ranging from inapparent infection to acute fatal disease. Historically, affected dogs developed clinical signs associated with enteritis and myocarditis. Today, clinical signs associated with myocarditis are rare (Figure 21.1.11). Common clinical signs associated with acute enteritis include lethargy, inappetence, vomiting, and small bowel mucoid to hemorrhagic diarrhea with disease mostly seen in puppies (i.e., < 6 months of age). Affected animals may become dehydrated and hypovolemic due to excessive gastrointestinal fluid losses. Viral destruction of rapidly dividing cells may result in malabsorption of nutrients, loss of electrolytes, and gastrointestinal bacterial translocation with subsequent development of systemic bacteremia. Signs associated with this include pallor, prolonged capillary refill time, fever or hypothermia, abdominal discomfort, and neuroglycopenia. Small intestinal intussusception can occur, manifesting as a painful, firm, tubular soft tissue mass effect found on abdominal palpation.

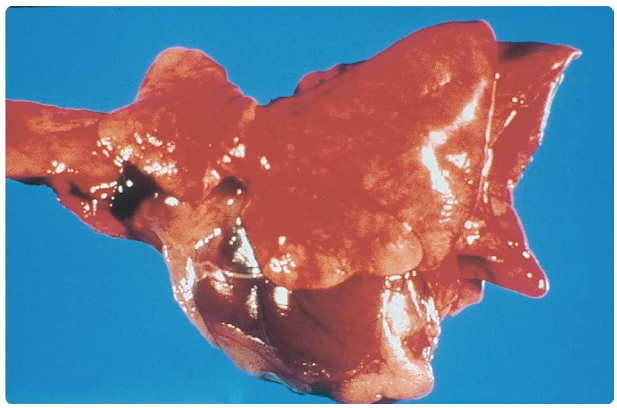


FIGURE 21.1.11 Viral myocarditis in conjunction with CPV in dogs is associated with ventricular arrhythmias, congestive heart failure, pulmonary edema, and death.

Differential Diagnosis

Differentials include bacterial, viral, parasitic, and protozoal enteritis, gastrointestinal foreign body, intussusception, pancreatitis, hypoadrenocorticism (Addison's disease), and poisoning or toxicity.

Diagnosis

Diagnosis is based upon a combination of clinical signs, physical exam findings, hematology, and point-of-care testing. All young dogs presenting with acute-onset diarrhea should be evaluated using an ELISA fecal antigen test. In acute disease, profound leukopenia and lymphopenia will develop within 7–10 days following exposure. The most common screening and detection test is a point of care immunochromatographic ELISA test. These tests are highly specific (few false-positive results); however, the period during which parvovirus can be detected in feces appears limited. Recent vaccination (< 10 days) with modified live virus can result in false-positive results. As such, any recently vaccinated puppy with clinical signs of vomiting and diarrhea should be viewed as a true infection or have further testing performed (i.e., PCR). Polymerase chain reaction tests are definitive, differentiating the recently

vaccinated from the truly infected by detecting virus particles in the feces. False-negative fecal ELISA tests can occur due to testing prior to viral shedding, low fecal viral loads, and higher serum antibody titers.

Management

Treatment/Prognosis

Outpatient treatment may be instituted for patients with mild clinical signs or when owners have financial constraints. This protocol recommends initial stabilization with parenteral fluids (15–45 mL/kg IV), electrolyte replacement, and glucose supplementation (2.5% dextrose at 1–2 mL/kg). Patients are then discharged and have subcutaneous crystalloid fluid therapy (40 mL/kg) divided q.8 h., cefovecin, once at 8 mg/kg SC once, buprenorphine 0.02 mg/kg SC q.6 h., and maropitant at 1 mg/kg SC q.24 h. Syringe feeding of Hill's a/d every 6 hours (1 mL/kg p.o.) is also performed. See Table 21.1.11 for drug therapy.

The mainstay of treatment is supportive, consisting of parenteral fluids to restore intravascular volume and maintain hydration and enteral nutrition (i.e., nasogastric tube feeding) to help prevent enterocyte atrophy and provide nutrients required for healing. Other treatments such as antiemetics (e.g., maropitant and ondansetron) decrease nausea and the frequency of vomiting events. Because patients are at risk for developing a bacteremia, broad-spectrum antimicrobials are recommended in all patients. Patients with abdominal discomfort secondary to vomiting, ileus, and possible intussusception are treated with a multifaceted, individualized approach based on the patient's level of pain. The initial choice of analgesic agent is an opioid (full or partial μ agonist). Then, depending on the severity of pain, an NMDA (N-methyl-D-aspartate) antagonist (e.g., ketamine) and/or a local anesthetic agent (e.g., lidocaine) may be added adjunctively as intravenous constant-rate infusions.

To restore the fecal microbiota, fecal transplantation from a healthy host has been found to resolve diarrhea earlier, decrease the length of hospitalization, and improve survival (10 g of feces diluted in 10 mL of sterile 0.9% saline).

Survival rate ranges from 60%–90% with prognosis being dependent upon the severity of clinical signs at presentation. Patients that are severely dehydrated, hypovolemic, lymphopenic, and hypoalbuminemic have a poorer prognosis. Likewise, concurrent comorbidities are associated with a poorer prognosis.

TABLE 21.1.11 Drug therapy for parvovirus infection

Drug	Dosage
Antibiotic	
– Ampicillin	20–40 mg/kg IV q.8 h.
– Ampicillin-sulbactam	30–50 mg/kg IV q.6–8 h.
– Cefovecin	8 mg/kg SC once
– Cefoxitin	20–30 mg/kg IV q.8 h.
– Enrofloxacin	10 mg/kg IV q.24 h.
– Metronidazole	10 mg/kg IV q.8 h.
Antiemetics	
– Ondansetron	0.5 mg/kg IV q.8 h.
– Maropitant	1 mg/kg IV, SC q.24 h.
Analgesia	
– Butorphanol	0.1–0.2 mg/kg/h
– Buprenorphine	0.01–0.02 mg/kg IV q.8 h.
– Methadone	0.1–0.2 mg/kg IV q.6 h.
– Morphine	0.1–0.2 mg/kg IV, IM, SC q.8 h.
– Hydromorphone	0.1 mg/kg IV, IM q.8 h.
– Fentanyl	1–5 μg/kg/h IV CRI
– Ketamine	5–20 μg/kg/min IV CRI
– Lidocaine	25–50 μg/kg/min IV CRI
Antiparasitic drugs	
– Pyrantel pamoate*	5–10 mg/kg p.o. q.24 h. (repeat in 7–10 days)
– Fenbendazole**	50 mg/kg p.o. q.24 h. for 3–5 days
– Sulfadimethoxine†	50–60 mg/kg p.o. q.24 h. for 5–20 days
– Metronidazole††	10–30 mg/kg p.o. q.12 h. for 5–7 days

* Efficacy against *Toxocara canis* and *Ancylostoma* spp.

** Efficacy against *Giardia duodenalis, Ancylostoma* spp., *Trichuris vulpis*, and *T. canis.*

Repeat fenbendazole dose for *T. vulpis* in 3 weeks then again in 3 months.

† Efficacy against *Isospora* spp.

†† Efficacy against *G. duodenalis*.

Prevention

Effective immunization programs provide effective protection of individual pet patients and decrease the susceptible population of animals (i.e., provide "herd immunity"). Today, all CVP vaccines are attenuated (modified live) virus (see Table 21.1.4). These vaccines provide prolonged (7 years or longer) immunity. Three doses of vaccine are recommended between 6 and 16 weeks of age. A booster dose is administered 1 year later, then every 3 years thereafter. In dogs that are 16 weeks or older, two doses 2–4 weeks apart are generally recommended. Isolation of new puppies is essential to prevent exposure to CPV. Puppies should not be exposed to other dogs until the puppy has received its full series of vaccinations.

There are several potential reasons for vaccinated dogs to remain susceptible to infection. Maternally derived antibody interference with vaccination in young dogs and genetically predisposed non- and low responders (to vaccination) are among the most important. Subsequent to vaccination, transient lymphopenia (4–6 days) and shedding of vaccine virus are possible. Dogs tested with the ELISA fecal antigen test may actually have a transiently positive test result during the time of vaccine virus shedding. Immunity derived from natural infection and recovery is a minimum of 20 months and may last for life.

Public Health Implications

CPV is not zoonotic and poses no threat to human health.

CANINE RABIES

Definition/Overview

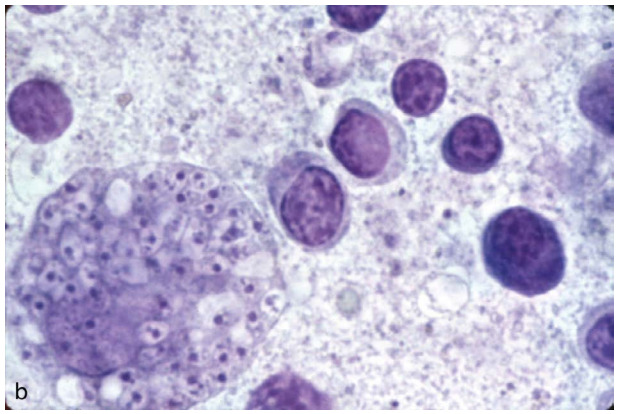
Rabies is regarded as a fatal viral zoonotic acute disease infecting both humans and animals. Disease is caused by an enveloped, bullet-shaped, single-stranded RNA virus of the *Lyssavirus* genus, family Rhabdoviridae. Infection leads to development of a fatal encephalitis in mammals, characterized by CNS signs resulting in an initial paralysis followed by death soon after. The virus is unstable in the environment, being readily inactivated by conventional disinfectants, ultraviolet light, and heat.

Etiopathogenesis

Rabies can infect all mammalian groups. Currently, wild animals, including raccoons, foxes, coyotes, and skunks, account for greater than 92% of rabies caused by animals. The incidence of wildlife rabies correlates with the incidence of rabies in dogs and cats. The virus enters the body through infected saliva via a bite from an infected animal. Transmission via other routes (e.g., scratch, mucosal exposure) is possible but rare. Once deposited in the subcutaneous tissues or muscles, rabies virus glycoprotein binds to postsynaptic nicotinic acetylcholine receptor of peripheral nerves travelling retrograde within axons towards the CNS. Once in the spinal cord, the virus disseminates throughout and radiates from the CNS, spreading along neuroanatomical pathways and to multiple organs (i.e., heart, gastrointestinal tract, skin, and salivary glands) via the parasympathetic nervous system. Within the salivary gland, there are high concentrations of rabies virus, which allows transmission to additional animals when bitten. The virus is excreted in saliva for a brief period of time, typically 1–5 days before onset of clinical signs and continues until death. Typically, the incubation period lasts 20–90 days.

There are two clinical forms: An encephalitic or "furious" form (80% of cases) and a paralytic or "dumb" form (Figure 21.1.12a). The underlying pathogenetic mechanisms of these are poorly defined; however, it is thought that the paralytic form reflects a greater burden of disease in the spinal cord, nerve roots, and peripheral nerves, whereas encephalitic form reflects greater involvement in the brain.





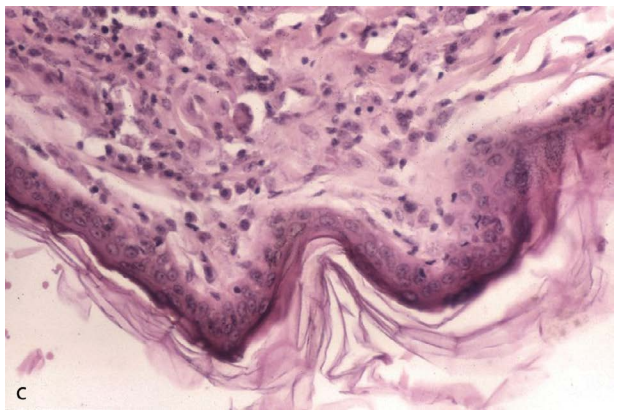


FIGURE 21.1.12 (a) Progressive lower motor neuron paralysis with cranial nerve deficits similar to those shown here can be early signs of "dumb" rabies in the dog. **(b)** Cytology showing Leishmania amastigotes within macrophage. **(c)** Histopathology of dog skin showing promastigotes in the epidermal region. (a, *Courtesy of M. Schaer.*)

Clinical Presentation

Due to the variation in clinical signs and disease progression, affected animals do not necessarily fit into one classification. The course of disease typically lasts 3–8 days. Recognized clinical stages of disease include the prodromal, furious, and paralytic stages. During the prodromal period, clinical signs are nonspecific and can include minor behavioral changes. These signs, if recognized, usually last 2–3 days in dogs. As dogs enter the excitatory phase ("furious" phase: 1–7 days), they may suddenly become vicious and behave erratically. These dogs will become restless and irritable, developing heightened sensitivities to visual and auditory stimuli. Some dogs may bypass this phase and progress directly from the prodromal to the paralytic stage. The paralytic stage is the final stage and is characterized by weakness and eventually paralysis. The area where the bite wound occurred is initially affected, followed by a progressive ascending paralysis affecting the neck and head. This phase lasts 2–4 days, ending in death from respiratory failure. The course of rabies typically lasts 3–8 days in dogs.

Differential Diagnosis

Rabies should be strongly suspected in any dog with acute onset of neurological signs associated with behavior change, especially in dogs that do not have a vaccination history. Other differentials include canine distemper, intracranial neoplasms, other causes of encephalitis and seizures, pseudorabies, toxins that cause CNS signs, sepsis, tetanus, and botulism.

Diagnosis

Definitive antemortem diagnosis is not possible with rabies being suspected in patients presenting with acute onset of behavioral changes and flaccid paralysis. Postmortem definitive diagnosis is made by demonstrating rabies virus antigen by direct fluorescent antibody (DFA) test in nervous tissue (brain and spinal cord). The entire head or spinal cord should be submitted as soon as possible after humane euthanasia to ensure an accurate diagnosis. Tissue should be chilled or refrigerated and not frozen. Other diagnostic assays available include PCR testing of nervous system tissue (e.g., brain, spinal cord, and CSF), histologic identification of Negri bodies (intracytoplasmic eosinophilic inclusions), and mouse/cell culture inoculation.

TABLE 21.1.12 Algorithm for dogs sustaining a bite from an unknown or unvaccinated animal

Scenario	Action
Vaccinated dog exposed to a confirmed or suspected rabid animal	Assessment, wound cleansing, and booster vaccination Quarantine and observance by owner for 45 days
Vaccinated dog overdue for a booster vaccine exposed to a confirmed or suspected rabid animal	If overdue for a rabies booster vaccine with past rabies vaccine documentation, quarantine and observance by owner for 45 days If overdue for a rabies booster vaccine without appropriate documentation, consult local public health authorities to determine quarantine period and utility of serologic testing to provide proof of an anamnestic response
Unvaccinated dog that has never been vaccinated exposed to a confirmed or suspected rabid animal	Euthanasia recommended

Note: If during quarantine, signs suggestive of rabies develop (e.g., paralysis or seizures), the animal should be euthanized and submitted for rabies testing.

Management

Treatment/Prognosis

No premortem tests or effective treatments are available for rabies. Dogs sustaining a bite from an unknown or unvaccinated animal should be immediately vaccinated and quarantined or euthanized as recommended (Table 21.1.12).

Eliminating feral animals or wildlife populations that harbor rabies is not economically feasible, nor is it socially or ecologically acceptable. As such, immunization is paramount to protect dogs.

Prevention

Inactivated (killed) vaccines are available for use in dogs (see Table 21.1.4). Rabies vaccination is a core vaccine in dogs and is the only companion animal vaccine required by law in most states. After vaccination, a rabies vaccination certificate verifying the vaccinate, the health of the vaccinate, the product used, the booster interval, and the administering veterinarian is issued to identify vaccinated dogs.

The first dose is given at a minimum of 3 months of age because of the potential interference by maternally derived antibodies. Regardless of the age at first vaccination, a single booster vaccine is repeated 1 year after the initial vaccine. Subsequent boosters are performed either annually or triennially depending on the labeled duration of immunity of the vaccine used. Where required, veterinarians are expected to follow state, provincial, or local law. Serologic testing can be done to establish an individual dog's response to vaccination but cannot be utilized to forgo revaccination where legally required. Some states may allow a medical exemption from a rabies booster vaccination. Testing may be required prior to shipment of dogs to rabies-free countries or regions of the world.

Public Health Implications

Any human that is exposed to rabies-infected saliva is at risk of developing rabies. Any wounds that are sustained should be washed with soap and water, and then professional healthcare should be sought. Healthcare professionals will decide if you need postexposure prophylaxis (PEP). These decisions are based upon the type of exposure, the animal you were exposed to, whether the animal is available for testing, and knowledge of rabies prevalence in the geographic area.

Postexposure prophylaxis consists of immune globulin and four doses of rabies vaccine over a 14-day period. The first rabies vaccine is administered immediately after exposure. For further information, refer to the CDC rabies website.

VECTOR-BORNE DISEASE

Definition/Overview

Canine leishmaniasis, caused by *Leishmania infantum*, is a zoonotic vector-borne disease caused by *Leishmania infantum*. Female phlebotomine sand flies act as vectors spreading disease primarily between animals and

secondarily to humans. It is endemic in more than 70 countries and is a common disease in the Mediterranean region and Central and South America. Clinical presentation is highly variable, with most dogs not developing clinical disease and remaining asymptomatic. Of the dogs that become clinical, disease ranges from self-healing cutaneous wounds (i.e., cutaneous leishmaniasis) to fatal disseminated visceral disease (i.e., visceral leishmaniasis). Cure is rare, and relapses are frequent, especially in endemic areas.

Etiopathogenesis

Leishmaniasis caused by protozoal *Leishmania* spp. is a disease affecting the mononuclear phagocyte system of mammals, with the dog being not only a major reservoir for infection but also playing a key role in transmission. Disease in dogs and cats is caused by *Leishmania infantum*, also known as *Leishmania chagasi*. Disease transmission occurs during female sandfly feeding. Leishmania parasites have a digenetic life cycle. The first is a promastigote flagellate form which resides within the midgut of sandflies. Here, these protozoa reproduce then migrate to the foregut and mouthparts of sandflies. Upon feeding, these promastigotes are inoculated into the dermis and are then phagocytized by macrophages. Within the macrophage, they then evolve into the amastigote form, replicating continuously within the phagolysosome until the macrophage ruptures. Liberated amastigotes then are free to disseminate via the lymphatics and blood and infect other macrophages rich tissue (i.e., spleen, liver, bone marrow, lymph node, etc.). Amastigotes are ingested by female sandflies during feeding and then revert back into the promastigote flagellate form over a week. Other modes of disease transmission include vertical transmission from bitches to puppies, venereal transmission, and transmission through blood transfusions.

Clinical Presentation

Clinical signs may develop months to years after initial inoculation. Clinical manifestation of disease is highly variable with parasite strain, genetics, and the host immune status all affecting the clinical course of disease. Cutaneous lesions are common and often noted prior to signs associated with systemic infection. Dogs generally present with peripheral lymphadenopathy and either localized or disseminated nonpruritic exfoliative dermatitis with or without alopecia, pustular dermatitis, nasal hyperkeratosis, nasal depigmentation, and onychogryphosis (abnormally long or brittle claws). Systemic signs of disease include anorexia, lethargy, weight loss, pallor, splenomegaly, and hepatomegaly. Other clinical manifestations of disease characterized by anemia, thrombocytopenia with subsequent bleeding/melena, lameness, joint swelling, uveitis, vasculitis, and glomerulonephritis culminating in nephrotic syndrome are thought to be the result of the development of autoantibodies and circulating immune complexes. Keratoconjunctivitis may result from the direct infection of the lacrimal gland by *Leishmania*.

Differential Diagnosis

Initial cutaneous disease differentials include demodicosis, bacterial dermatitis, dermatophytosis, discoid lupus erythematosus, follicular dysplasia, cutaneous lymphoma, nasal parakeratosis, pemphigus erythematosus, pemphigus foliaceus, sebaceous adenitis, seborrhea, sterile granuloma/pyogranuloma syndrome, systemic lupus erythematosus, and zinc-responsive dermatosis. Differentials for visceral leishmaniasis include babesiosis, canine distemper virus, ehrlichiosis, hepatozoonosis, and systemic lupus erythematosus.

Diagnosis

Successful diagnosis is dependent upon both the presenting clinical signs and epidemiological origin of disease. Common laboratory abnormalities found on complete blood count, serum chemistry, and urinalysis include a normocytic, normochromic, nonregenerative anemia; hyperglobulinemia; and renal azotemia with proteinuria. Confirmational diagnostic tests include both direct testing to confirm the presence of the parasite and indirect testing to detect the host's response to the parasite. Diagnostic assays include cytologic or histopathologic examination of affected tissues, organism culture, PCR assays of infected tissue, and serology. In endemic areas, results from these tests may need to be interpreted critically in association with presenting clinical signs.

Fine-needle aspiration and skin scrapes should be performed on peripheral lymph nodes, papules, nodules, and ulcerative cutaneous lesions, respectively, to look for amastigotes within lesions (**Figure 21.1.12b**). Likewise, bone marrow, splenic, and hepatic aspirates may be performed to confirm a diagnosis of leishmaniasis. A simple skin biopsy of what appears to be normal-appearing skin can histopathologically demonstrate the promastigote stage of *Leishmania* (**Figure 21.1.12c**).

Biopsy and histopathology can be used to demonstrate the presence of *Leishmania* when cytology is negative. Besides conventional H&E staining, presence of amastigotes can be confirmed using immunohistochemistry, in situ hybridization, or PCR on formalin-fixed and paraffin-embedded specimens.

PCR may be performed on any sampled tissue or biologic fluid. PCR is a sensitive technique for the diagnosis of leishmaniasis when organisms are not routinely identified on cytology or histopathology. Conjunctival, oral, and nasal swabs are very sensitive for the detection of *Leishmania* spp. DNA, providing positive results earlier when compared to the sampling or other tissue or biologic fluid.

The most common serological tests to detect anti-leishmanial antibodies are immunofluorescent antibody test (IFAT), enzyme-linked immunosorbent assay (SNAP canine *Leishmania* antibody test kit, IDEXX Laboratories), and immunochromatographic POC testing. Sensitivity and specificity varies depending on the test chosen, with IFA and the SNAP antibody tests both being highly sensitive and specific for leishmaniasis.

Diagnosis using serology alone may prove difficult as the time for seroconversion can be long (i.e., approximately 5 months) and because the *Leishmania* vaccine elicits a long-standing low-to-medium antileishmanial antibody titer.

Management

Treatment/Prognosis

Cures are rarely achieved, and disease can recur after successful therapy. Treatment is ultimately aimed at eliminating disease and a cure; however, even if treatment does not provide a cure, it may increase life expectancy and improve quality of life in addition to reducing parasite load (Table 21.1.13). For reasons of public health and to prevent re-infection, ectoparasiticides that contain permethrin are recommended.

Drugs that either inhibit protozoal enzymes, interfere with protein synthesis, or damage protozoal DNA have been used with varying degrees of success. Clinical improvement, if observed, generally occurs within 1–2 months of initiating therapy. Clinical remission of disease is variable and has been reported in 65%–100% of patients using combination therapies, with recurrence rates of up to 10% being reported.

Prevention

Prevention should focus on preventing contact with sandflies either through physical barriers (fine-mesh nets in windows and kennels) or chemical barriers (repellents); the use of domperidone (Leisguard, available in Europe), a dopamine D2 receptor antagonist that activates phagocytic cells and enhances killing of the parasite; and through vaccination. Several commercial vaccines are currently available in other countries; however, they have low protective efficacy.

Public Health Implications

Leishmaniasis is a zoonotic disease. Dogs and cats serve as reservoirs for human disease. Each year it is estimated that there are 700,000–1.2 million new cases of cutaneous leishmaniasis and < 100,000 new cases of visceral leishmaniasis. People of all ages are at risk for infection, with the immunocompromised, people that are poverty stricken, and the malnourished being at a higher risk for infection. The World Health Organization currently recommends that people who are diagnosed receive effective, prompt treatment to reduce both the prevalence and the transmission of disease and that vector control, disease surveillance, and control of reservoir hosts should be utilized to reduce and interrupt disease transmission.

TICK-BORNE DISEASE

Tick-borne diseases are caused by etiologic agents that are transmitted from ticks to dogs. Such agents include *Ehrlichia, Anaplasma, Babesia, Rickettsia,* hemotropic

TABLE 21.1.13 Treatment recommendations for canine leishmaniosis

Drug	Dose protocol	Duration	Potential adverse effects
Allopurinol*	10 mg/kg p.o. b.i.d.	At least 6–12 months or until clinical and serological resolution of disease	Xanthine urolithiasis**
Amphotericin B deoxycholate	0.5 mg/kg IV twice per week	2 months	Nephrotoxicity
Lipid-complexed amphotericin B	3 mg/kg IV	Monday, Wednesday, Friday (optimal treatment length unknown)	Nephrotoxicity
Meglumine antimoniate†	75–100 mg/kg SQ s.i.d. or 40–75 mg/kg SQ s.i.d.	4 weeks	Nephrotoxicity Possibly myocardiotoxic in dogs
Sodium stibogluconate	50 mg/kg IV, SQ s.i.d.	3–4 weeks	Nephrotoxicity
Miltefosine	2 mg/kg p.o. s.i.d.	28 days	Gastrointestinal upset
Allopurinol + Meglumine antimoniate†,‡	10 mg/kg p.o. b.i.d. 100 mg/kg SQ s.i.d.	12 months 4 weeks	Urolithiasis and nephrotoxicity
Allopurinol + Miltefosine††	10 mg/kg p.o. b.i.d. 2 mg/kg p.o. s.i.d.	12 months 28 days	Urolithiasis and gastrointestinal upset
Marbofloxacin‡‡	2 mg/kg p.o. s.i.d.	28 days	–

* Most effective for the dermatologic form.

** Rare.

† Currently unavailable in the United States without federal and state permits.

†† Combination does not result in parasitologic cure.

‡ Treatment of choice. Treat until resolution of clinical signs and quantitative serology becomes negative.

‡‡ Reduced signs of clinical disease and parasite load.

TABLE 21.1.14 Common tick-borne diseases

Disease	Agent	Vector	Infected cell type	Geographic distribution
Ehrlichia canis	Rickettsial	*Rhipicephalus sanguineus*	Monocyte Macrophage	– Nationwide – Southern United States
Ehrlichia ewingii *Ehrlichia chaffeensis*	Rickettsial	*Amblyomma americanum*	Granulocytes	– Central – Southeast – North Atlantic coast
Anaplasma phagocytophilum	Rickettsial	*Ixodes scapularis* *Ixodes pacificus*	Granulocytes	– Northeast – Midwest – West Coast
Anaplasma platys	Rickettsial	*Rhipicephalus sanguineus*	Platelets	– Nationwide – South Central – Southwestern United States
Borrelia burgdorferi	Spirochete	*Ixodes scapularis* *Ixodes pacificus*		– Northeast – Midwest – West Coast – Southern Canada – Recent expansion in Mid-Atlantic
Large-form *Babesia*	Protozoan	*Rhipicephalus sanguineus* *Dermacentor reticulatus*	Red blood cells	– Nationwide
Small-form *Babesia*	Protozoan	*Haemaphysalis* spp. *Ixodes*	Red blood cells	– Nationwide
Rocky Mountain spotted fever	Rickettsial	*Dermacentor variabilis* *Dermacentor andersoni* *Amblyomma americanum* *Rhipicephalus sanguineus*	Endothelial cells	– South Atlantic region – Pacific region – West South-Central region

Mycoplasma, *Hepatozoon americanum*, and *Borrelia* species. Discussed in this section are the more common diseases transmitted to dogs (Table 21.1.14).

Etiopathogenesis

Most ticks that cause disease in dogs are a three-host hard tick (i.e., each stage feeds on a different host after molting) belonging to the Ixodidae family (Figure 21.1.13). After hatching, larval ticks and then nymphs feed on hosts for several days, dropping off and molting with each successful meal. After becoming an adult and feeding, adults are able to reproduce. Once they attach to the skin through biting mouth parts, ticks cement themselves into the skin. Blood feeding occurs usually within 24–36 hours after attachment. While feeding, ticks secrete anticoagulant and anti-inflammatory agents from their salivary glands to ensure their survival and avoidance of the host's immune response.



FIGURE 21.1.13 The nymphal and adult life stages of the brown dog tick *Rhipicephalus sanguineus*. (*Courtesy of D.J. Meyer.*)

For ticks to become vectors of disease, ticks must first become infected. This usually occurs when they ingest a blood meal from an infected reservoir host. At the time of feeding, the host's infection must be blood-borne. Once ingested, these microbes are phagocytosed by gut cells whereby they multiply and disseminate to other organs. Infection persists within ticks due to transstadial (i.e., molting) or transovarial (i.e., infected ova) transmission. Persistence varies depending on the microorganism involved.

When a naïve host is parasitized by a tick, microbes within the tick multiply and disseminate within the tick. Transmission of infection occurs via saliva, coxal fluid, regurgitation, contamination, or a combination of routes. Feeding disease transmission time is highly variable between ticks and microorganisms, ranging from 3–48 hours.

Clinical Presentation

Infection is usually seasonal, with disease prevalence dependent on environmental temperature, humidity, the activity of ticks, tick geographic distribution, and the presence of adequate hosts. Over the recent years, disease has spread due to environmental change (e.g., global warming) and urbanization. All dogs are susceptible to tick-borne disease with infection commonly producing both hematologic changes and single/multiorgan dysfunction (Table 21.1.15). Common clinical signs include fever, lethargy, anorexia, lymphadenopathy, chronic cyclic anemia, thrombocytopenia, polyarthropathy, uveitis, and vasculitis. Animals with an incomplete protective immune response may develop chronic subclinical disease, which can recrudesce with stress or concurrent disease. Infection with multiple microorganisms is possible through heavy exposure to ticks. These coinfections may explain variations in clinical presentation, pathogenicity, and variable response to medical therapy.

Diagnosis

Unfortunately, there is no diagnostic test that is 100% sensitive or specific. Diagnosis should be made based on geographical location, lifestyle, history, presenting clinical signs, hematologic abnormalities, and serology. Complete blood count, serum chemistry, and urinalysis have variable nonspecific changes. Sampling of peripheral blood is most often used to detect exposure to or infection with tick-borne disease agents. Commonly used tests include cytological examination (i.e., blood smear or buffy coat evaluation), serological testing, and PCR (Table 21.1.16).

Routine cytological evaluation of blood smears should be included for any patients suspected of having tick-borne disease. Although not considered a sensitive

TABLE 21.1.15 Clinical overview of tick-borne disease

Disease	Agent	Transmission	Incubation period	Clinical signs
Borreliosis	Spirochete	≥ 50-hour attachment	2–5 months	Fever, shifting-leg lameness, joint swelling, joint pain, malaise, and decreased appetite
Ehrlichiosis	Rickettsial	24- to 48-hour attachment	1–3 weeks	Fever, thrombocytopenia, hemorrhage, lymphadenopathy, splenomegaly, pancytopenia, peripheral edema, and uveitis
Anaplasmosis	Rickettsial	36- to 48-hour attachment	1–3 weeks	Lethargy, fever, lameness, vomiting, diarrhea, lymphadenopathy, splenomegaly, and bleeding tendencies
Rickettsia rickettsii	Rickettsial	≤ 48-hour attachment	2 days to 2 weeks	Fever, ocular signs (i.e., mucopurulent discharge scleral/conjunctival injection, scleral/conjunctival/retinal hemorrhage, conjunctivitis, uveitis, retinitis), generalized lymphadenopathy, splenomegaly, nasal discharge, tachypnea, peripheral edema, bleeding tendencies, and neurological signs (paresis, ataxia, hyperesthesia, vestibular signs, stupor, seizures, coma)
Babesiosis	Protozoal	2- to 3-day attachment	10 days to 3 weeks	Fever, hemolytic anemia, splenomegaly, lymphadenopathy, and thrombocytopenia

TABLE 21.1.16 Comparisons of testing for tick-borne disease

Diagnostic method	Benefits	Limitations
Blood smear evaluation	– Rapid in-clinic assay – Visualization of organisms confirms presence of *Anaplasma* species, *Ehrlichia* species, and protozoal organisms	– Low sensitivity – Unable to differentiate between *Anaplasma* and *Ehrlichia* species
Serologic testing	– Point-of-care (POC) tests detect antibodies to several different organisms in one assay – Follow-up panel from diagnostic laboratories to provide quantitative results – Paired (acute and convalescent) samples identify rising or falling titers (i.e., recent infection)	– Usefulness in acute infection – Antibodies test (confirms exposure but not active infection) – Cross-reactivity common especially IFA (includes nonpathogenic organisms)
Whole blood PCR	– Widely available – Sensitive for acute infections before antibiotics – Sensitive for identifying *Babesia* and *Hepatozoon* – More specific than serologic testing	– Lag time for results to come back – Less reliable when very low circulating organisms/chronic infection/antibiotic treatment – False-positive results due to presence of closely related agents

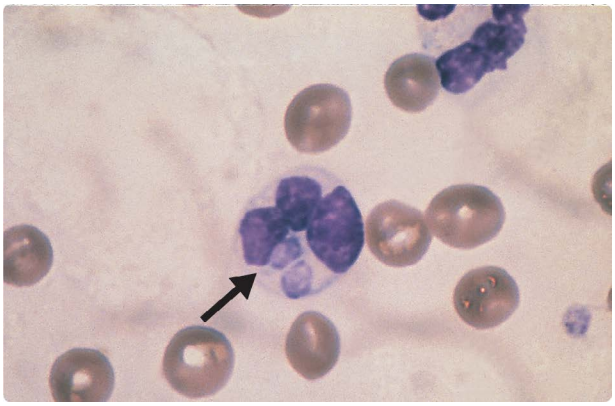


FIGURE 21.1.14 This blood smear, taken from a dog with ehrlichiosis, shows an *Ehrlichia* spp. morula (arrow) within the cytoplasm of a neutrophil. (*Courtesy of D.J. Meyer.*)

test, the ability to detect organisms is dependent on the phase of infection and skill of clinical pathologist, with organisms being abundant in the acute phase of infection. Cytology may demonstrate circulating organisms within red blood cells (e.g., *Babesia*), neutrophils (e.g., *Ehrlichia* and *Anaplasma*), monocytes (e.g., *Ehrlichia*), and platelets (e.g., *Anaplasma*) (Figures 21.1.14 and 21.1.15).

Polymerase chain reaction detects the presence of either DNA or RNA of infectious organisms. This testing is now widely available, easy to perform, and is both highly sensitive and specific. It is important to remember, however, that the organism must be present in the peripheral circulation to be detected. It is generally performed during the acute phase of infection, as organisms are usually present in their highest numbers. Although sensitive, a negative result does not rule out active infection.

Historically, antibody testing was used to diagnose tick-borne disease. Today, even though PCR is used more frequently in the definitive diagnosis of tick-borne disease, antibody testing is still used as both a screening test to detect the presence of organisms or to determine exposure of patients to tickborne organisms. Serological testing is via indirect immunofluorescence antibody (IFA) tests and commercially available

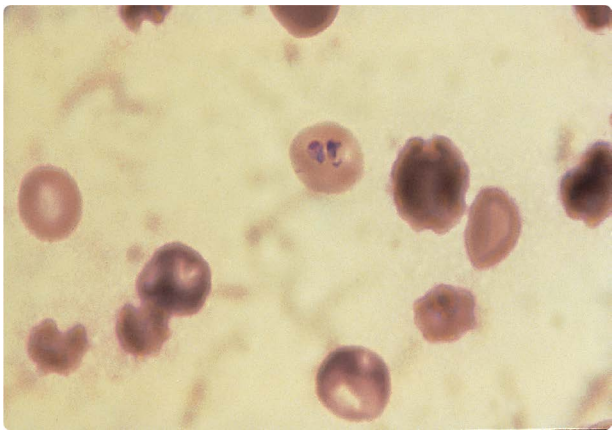


FIGURE 21.1.15 Canine *Babesia* organisms shown as intraerythrocytic protozoal organisms.

immunochromatography based point-of-care (POC) tests. These are used as part of routine annual vector-borne disease screening and as a diagnostic tool when dogs present with clinical signs. Initial POC screening rapidly detects antibodies against 5 tick-borne pathogens (*Ehrlichia canis*, *Ehrlichia ewingii*, *Anaplasma platys*, *Anaplasma phagocytophilum*, *and B. burgdorferi*) in a single sample of canine serum, plasma, or whole blood. Tests are sensitive only after seroconversion has occurred, meaning that it is of more value in diagnosing chronic infection, when PCR may be negative. Antibody detection against a tick-borne pathogen also indicates that dogs have mounted an immune response against the organism and does not necessarily translate to active infection. Active infection determined by IFA is denoted by a fourfold increase in antibody titer within 2–4 weeks with accompanying clinical signs. In clinic, POC ELISAs have similar performance to other commercial assays. Sensitivity may be increased by combining PCR and serology or demonstrating seroconversion using increasing convalescent titers. When considering positive results on a single sample, it is important to consider both the causative organism along with the pathophysiology of disease, geographic location, and presenting clinical signs. Cross reactivity is also possible between organisms of the same genus and genera. Following exposure, antibody titers decline slowly and may persist for long periods of time (i.e., months to years). To confirm whether disease/illness is being caused by one of these pathogens, in addition to the serologic evidence, a complete medical history, physical examination, and appropriate hematologic, biochemical, and PCR-based diagnostic tests may be needed.

Ehrlichiosis/Anaplasmosis

Cytology for microscopic identification of morulae in circulating neutrophils, monocytes, or platelets may be used to diagnose active infection. The sensitivity of this test is highly variable and dependent upon the stage of disease (i.e., associated with acute parasitemia). Positive point-of-care testing, with a history of tick exposure and concurrent clinical signs is usually supportive of a diagnosis; however, point-of-care assays are not able to distinguish *E. ewingii* from *E. canis* or *A. phagocytophilum* from *A. platys*. A negative point-of-care test in a symptomatic dog warrants further diagnostic testing (i.e., PCR or acute and convalescent titers) to confirm infection. For chronic ehrlichiosis, diagnosis may be difficult due to waxing and waning clinical signs and laboratory abnormalities. If clinicians are suspicious of chronic disease, it is important to realize that diagnosis is reliant upon a combination of diagnostic tests (POC test, IFA, PCR), accompanied by concurrent laboratory abnormalities (CBC, serum chemistry, and urinalysis) and clinical signs associated with disease. Treatment is often prolonged (i.e., 6–8 weeks). Successful treatment should not target seronegativity as antibody titers can remain positive or gradually decline (over 6–9 months) post treatment.

Babesiosis

Definitive diagnosis is usually made via cytology, serology, or PCR alone or in combination with each other. Whole blood examination or buffy coat smears are used to identify organisms within red blood cells. To maximize chances of parasite recovery, evaluation of either ear or toenail blood is recommended. Variable seroreactivity occurs with babesiosis. A fourfold IFA titer change (acute and convalescent) over time (2–4 weeks) indicates infection. Some dogs will not develop detectable antibody titers despite chronic infection. Polymerase chain reaction will confirm active infection and is able to identify which species of *Babesia* is causing disease. Serial sampling (≥ 2 samples obtained 2–4 weeks apart) will increase the sensitivity of PCR to approximately 100%. Successful treatment is reliant upon either two consecutive negative PCRs at 60 and 90 days post treatment.

Lyme Disease/Borreliosis

In endemic areas, ≥ 75% seropositivity can occur. This does not translate into clinical disease, with only 5%–10% of seropositive patients developing clinical signs. There is no pathognomonic test, with diagnosis being based upon a combination of tick exposure, history, clinical signs, exclusion of other disease, and response to treatment. The C6 serology POC testing determines not only exposure but also discriminates natural exposure from vaccination. Positive serology accompanied with clinical signs associated with disease translates to active infection. IFA and ELISA serology detect antibodies to Lyme vaccine and, therefore, should be interpreted with caution in vaccinated patients (i.e., false positive). Western Blot serology can differentiate natural exposure from vaccine antibodies but is difficult to perform and requires technical expertise. Polymerase chain reaction testing is used on tissue samples (e.g., skin or joint) but is an insensitive test when whole blood samples are used. Annual screening of previously treated dogs is recommended by qualitative ELISA. Follow-up complete blood count, serum chemistry, and urinalysis are also recommended for the rest of the patient's life to monitor for the development of proteinuria, identify cytopenias, and ascertain the patient's renal status.

Rocky Mountain Spotted Fever

Accurate diagnosis is important as canine infection can occur before or coincide with household/community outbreaks (i.e., dogs are sentinels for rickettsial disease in people). In patients with acute onset of clinical signs, paired acute and convalescent titers (2–4 weeks) should be performed, with a fourfold titer change indicating infection. Likewise, a single high titer of ≥ 1:1024 is consistent with an active infection. Detection of organisms via positive immunofluorescence of skin biopsies or PCR confirms active infection. PCR may be falsely negative due to low circulating organisms.

Treatment and Prognosis

Systemically well patients can be treated as outpatients once a diagnosis is made (Table 21.1.17). Educating owners about tick control and prevention is essential in management. Avoiding tick-infested areas whenever possible, mowing open grass areas regularly, removing overgrown plant debris, and pruning shrubs and trees are basic measures that can reduce both wildlife and tick numbers. Early removal of attached ticks by owners may reduce transmission. Year-round application of topical ectoparasiticides is critical for preventing infection and disease. In recent years, a number of studies have demonstrated decreased transmission of vector-borne infections in association with their use (Table 21.1.18).

Ehrlichiosis/Anaplasmosis

Rapid clinical improvement is notable within 24–48 hours of successful medical therapy. Short courses

TABLE 21.1.17 Drug therapies for tick-borne diseases

Causative organism	Drug	Dose	Length of treatment
Ehrlichia canis *Ehrlichia ewingii* *Ehrlichia chaffeensis*	Doxycycline Minocycline Rifampicin	5 mg/kg p.o. q.12 h. 5–10 mg/kg p.o. q.12–24 h. 10–15 mg/kg p.o. q.12 h.	30 days 30 days 7–21 days
Anaplasma phagocytophilum *Anaplasma platys*	Doxycycline	5 mg/kg p.o. q.12 h. or 10 mg/kg p.o. q.24 h.	14–28 days*
Lyme borreliosis	Doxycycline Ampicillin/amoxicillin	5–10 mg/kg p.o. q.12–24 h. 20 mg/kg p.o. q.8 h.	30 days
Rocky Mounted spotted fever	Doxycycline Chloramphenicol Enrofloxacin	5 mg/kg p.o. q.12 h. 30 mg/kg p.o. q.8 h. 3–5 mg/kg p.o. q.12 h.	7–14 days
Large-form *Babesia* Small-form *Babesia*	Imidocarb dipropionate Diminazene aceturate Atovaquone Azithromycin	7.5 mg/kg IM once 7 mg/kg IM 3.5 mg/kg IM once 13.3 mg/kg p.o. q.8 h. 10 mg/kg p.o. q.24 h.	Repeat in 14 days 10 days

* Optimal duration of therapy unknown.

TABLE 21.1.18 Ectoparasiticides for tick control

Product	Active ingredient	Route	Length of action
Activyl Tick Plus	Indoxacarb	Topical	1 month
Advantage Multi	Imidacloprid Moxidectin	Topical	1 month
K9 Advantix II	Permethrin Imidacloprid	Topical	1 month
Bravecto	Fluralaner	Oral Topical	3 months
Certifect	Fipronil (S)-methoprene Amitraz	Topical	1 month
Credelio	Lotilaner	Oral	1 month
Frontline Plus Frontline Tritak	Fipronil (S)-methoprene	Topical	1 month
NexGard	Afoxolaner	Oral	1 month
NexGard Spectra	Afoxolaner Milbemycin oxime	Oral	1 month
Preventic tick collar	Amitraz	Collar	3 months
Revolution	Selamectin	Topical	1 month
Seresto	Imidacloprid Flumethrin	Collar	8 months
Simparica	Sarolaner	Oral	1 month
Simparica Trio	Sarolaner Moxidectin Pyrantel	Oral	1 month
Trifexis	Spinosad Milbemycin oxime	Oral	1 month
Vectra 3D	Permethrin Dinotefuran Pyriproxyfen	Topical	1 month

of glucocorticoid therapy (prednisone/prednisolone at 1–2 mg/kg per day p.o. for 2–7 day) may be used in dogs with lameness, joint pain, uveitis, hemolytic anemia, thrombocytopenia, or vasculitis. Complete blood counts and serum chemistries are used to monitor therapy with neutrophil, monocytes, and platelet counts, typically increasing and normalizing within 24–48 hours and 14 days, respectively. Polymerase chain reaction assays can be used to monitor response to therapy, with assays being performed 2 weeks after therapy has ended.

Chronic *E. canis* infections are difficult to monitor and treat. Patients with chronic infection should be treated for 6–8 weeks with doxycycline. Success of treatment is measured by monitoring platelet counts and PCR. Serum antibody monitoring is not reliable for the assessment of successful therapy as antibody titers gradually decline over time (i.e., 6–9 months) to become negative. Organisms can also remain sequestered in the spleen after medical therapy.

Coinfection with other tick-borne organisms is possible, especially with *A. platys* and *A. phagocytophilum* infection. Because of this, some clinicians recommend treating these infections with 30 days of doxycycline.

Overall prognosis for acutely infected dogs is good. Spontaneous resolution of disease has been reported in some dogs with ehrlichiosis. If marked improvement is not seen within 24–48 hours after initiation of antimicrobial therapy, restaging for other diseases or infectious agents is recommended.

In dogs with chronic ehrlichial disease, prognosis is poorer. Negative prognostic indicators include pancytopenia, prolonged activated partial thromboplastin time, and hypokalemia.

Babesiosis

For babesiosis the mainstays of treatment are:

1. Elimination of the organism
2. Blood transfusion(s) to treat severe anemia
3. Supportive care to treat complications and metabolic derangements

A number of drugs and drug protocols have been used in the treatment of canine babesiosis (see Table 21.1.17). It is important to recognize that infectious *Babesia* spp. have dissimilar drug susceptibilities when treating patients. Treatment often reduces parasitemia and results in resolution of clinical signs. It is important to remember that organisms may not be eliminated and that dogs diagnosed with *Babesia* spp. should be considered permanent carriers of the infection.

Babesia canis, *B. rossi*, and *B. vogeli* are most successfully treated with imidocarb dipropionate (7.5 mg/kg IM once or 2 doses of 7 mg/kg IM, 2 weeks apart). This is the only FDA-approved drug for use in infected dogs in the United States. It is effective against acute infection; however, many patients continue to be carriers with subclinical disease. Side effects can include injection site pain, hypersalivation, lacrimation, gastrointestinal signs, and trembling. Diminazene aceturate may also be used against *B. canis*, *B. rossi*, and *B. vogeli*, but it is not FDA approved for treatment of canine babesiosis in the United States. In countries like South Africa where it can be used, treatment efficacy is variable, with the drug tending to be more effective against large-form *Babesia* spp.

Babesia gibsoni and small *Babesia* spp. are considered more difficult to treat than *B. canis vogeli* and large *Babesia*. Combining atovaquone (13.3 mg/kg, p.o. q.8 h. for 10 days) with azithromycin (10 mg/kg, p.o. q.24 h. for 10 days) can either reduce parasitemia or eliminate infection altogether in the majority of dogs.

Other antiprotozoal drugs that have been used with variable success include phenamidine, pentamidine, parvaquone, and artemisinin derivatives. Doxycycline, minocycline, clindamycin, enrofloxacin, and metronidazole have demonstrated variable antiprotozoal activity. Adjunctive use of glucocorticoids to counteract immune-mediated infection complications is controversial as it may worsen parasitemia. A 2- to 3-week tapering course of glucocorticoids may be used if necessary.

Lyme Disease/Borreliosis

a. Treatment of Lyme arthritis
For classical disease (i.e., fever, joint swelling, lameness, fever, and mild lymphadenopathy), doxycycline and minocycline are the preferred antimicrobials. Response is rapid, usually occurring within the first 24–48 hours. Optimum treatment length and drug dosage are unknown. However, due to the possibility of concurrent coinfection, 4 weeks of antimicrobial therapy is recommended. Amoxicillin, administered for 1 month, or cefovecin (Convenia), administered twice 2 weeks apart, are equally effective. Even with 4 weeks of antimicrobial therapy, some dogs do not clear *B. burgdorferi* organisms. Concurrent analgesia (e.g., gabapentin) should be evaluated on a case-by-case basis. Nonsteroidal anti-inflammatories should be avoided as glucocorticoids are indicated in cases of immune-mediated polyarthropathies in nonresponsive dogs. In dogs that either do not respond to therapy or that relapse, additional diagnostics (e.g., vector-borne disease diagnostic testing, orthopedic radiographs, and arthrocentesis) should be performed to exclude other potential causes such as infectious diseases, immune-mediated disease, soft tissue trauma (e.g., ligamental or meniscal tears), septic arthritis, or degenerative joint disease. All seropositive dogs with Lyme arthritis should be tested for proteinuria.

b. Treatment for Lyme-associated protein-losing nephropathy (PLN)
Proteinuria is seen in < 2% of *B. burgdorferi* seropositive dogs. When diagnosed, PLN associated with Lyme nephritis requires more aggressive therapy. Antemortem diagnosis is one of exclusion in *B. burgdorferi* seropositive dogs as there are no validated staining techniques to prove that the immune-complex glomerulonephritis (ICGN) is Lyme specific. A thorough diagnostic evaluation is warranted for both staging and to rule out other diseases causing the PLN. Besides antimicrobial therapy (see Table 21.1.17), treatment recommendations are based on standard treatment protocols for ICGN and PLN as recommended by the IRIS Canine Glomerulonephritis Study Group. This includes IV fluid therapy, a renin–angiotensin aldosterone system inhibitor (angiotensin-converting enzyme inhibitor or aldosterone receptor [RAAS] blocker), antithrombotics, protein- and phosphorus-restricted diets, omega-3 fatty acids, and antihypertensives as needed. In nonresponders with rapidly progressive disease, severe azotemia (serum creatinine concentration > 5 mg/dL) and severe hypoalbuminemia (serum albumin concentration < 2.0 g/dL), or if a renal biopsy documents immune-complex glomerulonephritis, immunosuppressive drugs (mycophenolate at 5 mg/kg p.o. q.12 h. increasing to 10 mg/kg if no gastrointestinal upset with tapering doses of prednisolone at 1 mg/kg p.o. q.12 h.) are recommended. Other immunosuppressants used to treat ICGN include azathioprine, cyclosporine, chlorambucil, and cyclophosphamide.

Efficacy of treatment is assessed by sequential monitoring of proteinuria, blood pressure, serum albumin concentration, and kidney function tests. At least 12 weeks of immunosuppressive treatment is recommended. Quantitative C6 testing can be used to monitor response to therapy. Pre- and post-treatment (6 month) C6 levels should be evaluated. Dogs experiencing ≥ 50% antibody reduction are considered to have responded to treatment.

c. Treatment of healthy nonproteinuric seropositive dogs
B. burgdorferi antibody testing is recommended annually for any dog living in endemic areas. In any dog that is seropositive, recommended screening tests include a complete blood count, serum chemistry, urinalysis, and urine protein-to-creatinine ratio. Currently, there is debate and controversy about the treatment of nonclinical, nonproteinuric, seropositive dogs. Current recommendations are that patients are not treated and that these patients are subsequently screened for proteinuria 2–3 times a year. In fact, even if dogs have been treated with antimicrobials, it is recommended that they are screened for proteinuria as clearance of microorganisms may not occur. If proteinuria is detected, screening of these patients should include urine culture, urine protein-to-creatinine ratio, blood pressure, complete blood count, serum chemistry, and diagnostic imaging (thoracic and abdominal).

Vaccination

There are several commercial vaccines available against Lyme disease (see Table 21.1.4) These vaccines stimulate the formation of antibodies against outer surface proteins normally expressed by *Borrelia* spp. when they reside within the tick. The overall outcome is halting of disease transmission through arresting of bacterial growth and the prevention of the organism invading the salivary gland of the tick. In endemic areas, vaccination is recommended for healthy seronegative dogs and healthy (nonclinical, nonproteinuric) seropositive dogs. Vaccination is not recommended for sick or proteinuric dogs. Prior to vaccination, all dogs should be tested for *B. burgdorferi*. Vaccination should not replace adequate, year-round tick control.

Rocky Mountain Spotted Fever

Antimicrobial therapy is initiated immediately based on clinical suspicion of disease. Both enrofloxacin and chloramphenicol are considered as equally effective as doxycycline, the treatment of choice. Doxycycline will eliminate *A. phagocytophilum*, *Ehrlichia* spp., and *B. burgdorferi*, which may be present as coinfections. Due to the acute nature and severity of disease, many patients are hospitalized. In order to avoid iatrogenic cerebral edema, caution should be exercised when administering parenteral fluids due to loss of vascular integrity. Prognosis is good to excellent in patients that are treated early and aggressively, with marked improvement usually noted within 24–48 hours of initiating therapy. In severely affected patients, CNS signs may persist even with successful therapy.

Public Health Implications

Canine ehrlichiosis is not a zoonotic disease; however, appropriate protective precautions (e.g., gloves) should

be taken when removing ticks or handling biological samples collected from dogs.

Human anaplasmosis, described as "influenza-like illness after a tick bite," closely resembles the disease in dogs. Disease is usually self-limiting in immunocompetent patients, typically resolving in 2 months. Severe illness tends to occur in the elderly or immunosuppressed. Dogs may act as sentinels for human exposure through mechanical carriage of ticks to humans. Appropriate protective precautions (e.g., gloves) should be taken when removing ticks or handling biological samples collected from dogs.

Babesia is not a zoonotic disease to immunocompetent people, with the majority of infections being mild or asymptomatic. Splenectomized people or people > 55 years of age are at risk of infection either through tick bites or, less commonly, through blood transfusions.

Lyme disease is the most common vector-borne disease of humans in the Northern Hemisphere; however, dogs do not pose a zoonotic risk to humans. Instead, they may act as environmental sentinels, indicating an increased risk of exposure in endemic areas.

Rocky Mountain spotted fever is a disease that can affect humans, with dogs acting as environmental sentinels for disease in endemic areas. Once a confirmed diagnosis has been made, veterinarians should inform owners that they are at risk of acquiring infection.

FUNGAL DISEASE

CANINE SINONASAL ASPERGILLOSIS

Definition/Overview

Sinonasal aspergillosis (SNA) is the second most common cause of nasal discharge in dogs and accounts for up to 34% of all chronic sinonasal nasal diseases. It is caused by *Aspergillus fumigatus*, a ubiquitous, saprophytic fungus. Organisms colonize and destroy tissue within the nasal cavity and frontal sinuses. Destruction is not directly related to fungal colonization but rather the host inflammatory responses and dermonecrolytic endotoxin produced by organisms. Mesocephalic and dolichocephalic dogs are commonly affected, with disease rarely disseminating.

Etiopathogenesis

Sinonasal aspergillosis is caused by several *Aspergillus* spp. *Aspergillus fumigatus* is most commonly associated with infection. Other fungal species capable of causing mycotic rhinosinusitis include *A. niger*, *A. nidulans*, and *A. flavus* as well as *Penicillium* spp. These organisms grow abundantly on organic debris (e.g., rotting vegetation, wood chips, compost, etc.). Pathogenesis of SNA is poorly understood. Impaired cell-mediated immunity and immunodeficiency are hypothesized as potential predisposing causes. This has not been definitively proven, with most dogs being systemically healthy. A history of facial trauma, nasal foreign bodies, and dental disease has been previously reported in some patients. Genesis of infection results from airborne conidia being inhaled, adhering to, and penetrating respiratory epithelial cells. The organism is able to evade host defense mechanisms through production of gliotoxin, which may reduce mucociliary function and impair phagocytosis.

Clinical Presentation

Dogs affected by SNA are young to middle-aged (3 months to 11 years) and have a chronic history of mucopurulent to purulent nasal discharge (unilateral/bilateral) that is refractory to empiric antibiotic therapy. Other signs reported include sneezing, epistaxis, facial pain, and depigmentation/ulceration of nasal planum, which is pathognomonic for disease (Figure 21.1.16). Other clinical signs that may develop depending on the severity of disease include severe facial deformity, epiphora, and seizures.

Differential Diagnosis

Differentials for chronic nasal disease include an extension of dental disease (i.e., oronasal fistula), neoplasia, rhinitis (lymphoplasmacytic and allergic), nasal foreign body, and cryptococcosis (rare in dogs). Bacterial rhinitis is a common secondary manifestation of intranasal disease and, regardless of the cause, should not be considered a primary diagnosis.

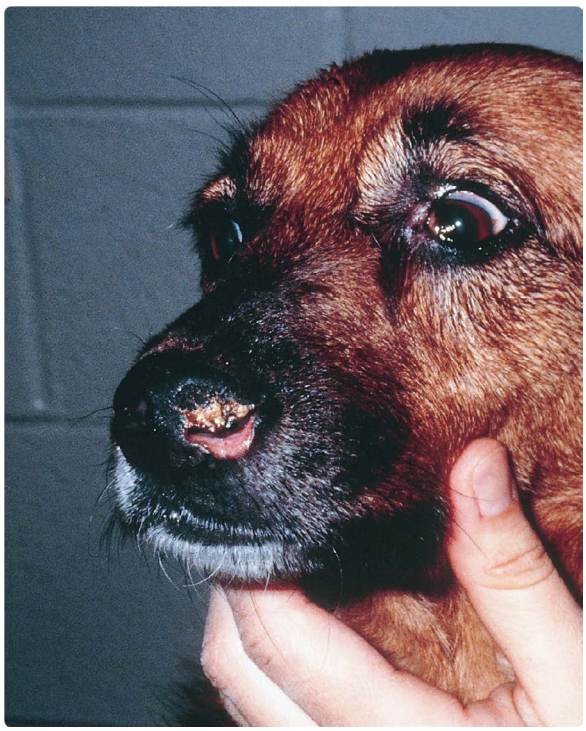


FIGURE 21.1.16 Erosion of the planum nasale in a 4-year-old mixed-breed dog with nasal aspergillosis of at least 6 months' duration.

Diagnosis

Confirmation of disease is based upon a combination of clinical signs, diagnostic imaging (computed tomography [CT] of the skull or skull radiographs), visualization of lesions with rhinoscopy/sinuscopy, histopathology, cytology, and fungal culture (Figures 21.1.17–21.1.19). Skull CT is not only a strong predictor of disease (approximately 90% accuracy), but it also allows assessment of cribriform plate integrity. Cytology and fungal culture alone are not good indicators of disease, as *Aspergillus* spp. and *Penicillium* spp. may occur as contaminants in the nasal cavity. Serological tests (*Aspergillus* antibody diffusion test, immunoglobulin G enzyme-linked immunosorbent assay) may be used in conjunction with the previous diagnostics but should not be used as the sole means for clinical diagnosis or patient management decisions. Other serological tests like the *Aspergillus* galactomannan antigen enzyme immunoassay (EIA) should not be used for screening potential cases of SNA. In the author's experience, serologic evidence of nasal mycosis is less reliable than direct visualization, culture, and cytology. Rhinoscopy/sinuscopy demonstrating turbinate destruction, mucoid nasal discharge, and fungal plaques is performed with either rigid endoscope or flexible pediatric bronchoscope. Biopsies obtained should have fungal culture performed as well as be evaluated cytologically and histologically.

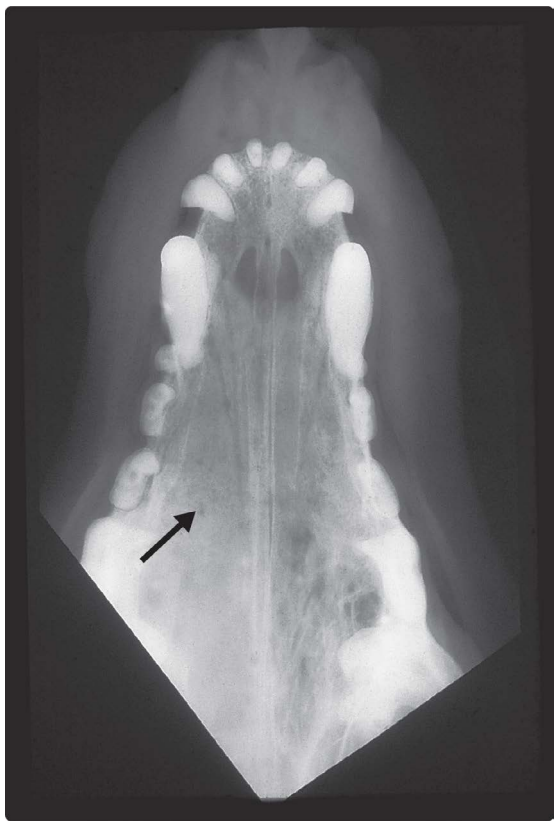


FIGURE 21.1.17 Occlusal radiographic projection of the nasal cavity of a dog with a 7-month history of nasal discharge not responsive to antibiotics. Note the loss of turbinate detail (arrow).

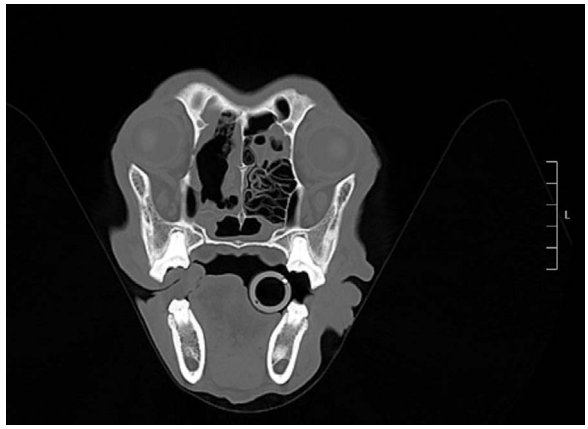


FIGURE 21.1.18 Transverse image of the nasal cavity at the level of the carnassial tooth of a 7-year-old MC mixed-breed dog with severe and near complete lysis of the ethmoid turbinates within the right nasal cavity. Minimal, multifocal osteolysis is also noted along the ventrolateral aspect (orbit) of the right frontal bone.

Management

Treatment/Prognosis

In recent years, treatment recommendations have changed for this disease. There are now multiple treatment options described. There is currently no consensus on the most effective therapy, with chosen therapies being based on personal or regional preferences. Historically, oral treatments with antifungal drugs (itraconazole 5 mg/kg p.o. q.12 h. for 10 weeks minimum or fluconazole 2.5–5.0 mg/kg p.o. q.12 h. for 10 weeks minimum) have generally poor-to-moderate efficacy. More recently, improved clinical remission rates have been observed using a combination treatment with posaconazole (5–10 mg/kg p.o. q.12–24 h.) and terbinafine (30–40 mg/kg p.o. q.24 h.) in dogs with refractory SNA disease.

Topical antifungal administration is the most widely used method and involves direct application of antifungals onto infected tissue. Various techniques have been described, ranging from surgically implanted



FIGURE 21.1.19 Rhinoscopic view of nasal aspergillosis showing fungal rhinitis. Of note are the characteristic gray–white plaques.

administration catheters in the frontal sinuses, endoscopic placement of temporary frontal sinus catheters, trephination of the frontal sinuses with instillation of depot therapy, to noninvasive techniques of rhinoscopy/frontal sinus sinuscopy with subsequent depot therapy. Today, 1% clotrimazole liquid flush followed by depot cream and 1%–2% enilconazole liquid preparations are most commonly used in both invasive and noninvasive techniques. Reported success rates are variable with 46.6%–85.7% having positive outcomes after the first treatment and 89.5%–100% of cases being cured after multiple treatments. Treatment protocols are aimed at filling the left and right nasal cavities with commercially available antifungal agent (i.e., 1% clotrimazole liquid/cream or 1%–2% enilconazole liquid) after debridement of the fungal plaques. Frontal sinus trephination may be utilized with this procedure. Sinonasal aspergillosis-associated lysis of the cribriform plate, lysis of the floor of a frontal sinus, or both is not necessarily a contraindication to topical therapy as long as potential adverse effects from the therapy are discussed with owners.

Resolution of clinical signs following treatment is considered a success. It is not uncommon for patients to have a persistent mild nasal discharge (serous to mucopurulent) due to either secondary bacterial infections or a chronic rhinitis/sinusitis from significant intranasal architectural changes. The author will usually repeat rhinoscopy/sinuscopy at 4–6 weeks post debridement and infusion to determine the success of therapy or whether a repeat treatment may be warranted. Antibody titers are not indicated to evaluate the response to treatment as they may remain positive for up to 5 years following successful treatment.

Prevention

Avoidance is impractical and unrealistic as *Aspergillus* spp. and *Penicillium* spp. are ubiquitous in the environment. There is no commercial vaccine to prevent aspergillosis or penicilliosis.

Public Health Implications

Infection is usually acquired from the environment and is not considered to be zoonotic.

Systemic Fungal Infections

Fungal pathogens are separated into primary (true) fungal pathogens and opportunistic pathogens. True fungal pathogens are able to cause disease in any animal regardless of their immune status. These fungi require a vertebrate host to complete their life cycle (i.e., provide nutrients, grow, and reproduce). Opportunistic fungi are ubiquitous in the environment, causing infection after accidental penetration of intact skin barriers or when animals are immunocompromised, have immunologic defects, or concurrent illness. Infections may be cutaneous, subcutaneous, or systemic.

True fungal pathogens are dimorphic and are converted from a nonpathogenic mold in the environment to a pathogenic yeast or spherule in the body. Typically, infections occur after inhalation of airborne conidia,



FIGURE 21.1.20 *Blastomyces dermatitidis* nasal granuloma on the nares of a young Rottweiler dog. (*Courtesy of M. Schaer.*)

although in some cases cutaneous inoculation of the fungus occurs (Figure 21.1.20). In veterinary medicine *Blastomyces dermatitidis* (blastomycosis), *Coccidioides immitis* (coccidioidomycosis), *Histoplasma capsulatum* (histoplasmosis), and *Sporothrix schenckii* are frequently encountered (Tables 21.1.19 and 21.1.20). Each of these organisms has been historically isolated from soil within specific geographic regions throughout the world. In recent years, these fungi have spread and are becoming more frequently recognized due to environmental change (i.e., global warming), rising populations in endemic areas, more travel, and with the increased use of immunosuppressants.

Opportunistic fungal pathogens are ubiquitous in the environment and have a preferred habitat independent of a living host. Virulence is inherently low, with organisms not sufficiently pathogenic to cause infection in healthy individuals. This changes when there is inhalation of spores or penetration of intact skin/mucosal barriers in immunocompromised patients or patients receiving immunosuppressive therapy. Infection can be localized, causing superficial cutaneous nonhealing wounds or can cause life-threatening systemic illness. *Aspergillus* spp. *and Cryptococcus* spp. are the most common of these fungal infections. Other opportunistic fungi of veterinary importance include phaeohyphomycosis, hyalohyphomycosis, and eumycotic mycetomas (Tables 21.1.19 and 21.1.20).

Etiopathogenesis

In susceptible animals, transition from the environment to the pathogenic form results in a change in cell shape, cell wall composition, antigenic molecules, and expression of virulence. This results in alteration and downregulation of an animal's immune response. Organisms are then able to reproduce and either locally disturb tissue structure and function, or disseminate to multiple organs through either lymphatic or hematogenous spread. Overt clinical signs are dependent on the organ system(s) infected. It is still unclear why some animals, subsequent to exposure, develop severe disseminated disease while others remain healthy. Although antibody does develop in response to infection, it is not protective. Recovery from mycotic disease is attributed to cell-mediated immunity.

TABLE 21.1.19 Systemic fungal organisms of veterinary importance

Dimorphic fungi	Infection	Transmission
Blastomyces dermatitidis	Blastomycosis	Inhalation Wound contamination
Histoplasma capsulatum	Histoplasmosis	Inhalation Ingestion
Coccidioides immitis	Coccidioidomycosis	Inhalation
Sporothrix schenckii	Sporotrichosis	Cutaneous/subcutaneous inoculation Inhalation
Opportunistic fungi	**Infection**	**Transmission**
Cryptococcus neoformans *Cryptococcus gatii*	Cryptococcosis	Inhalation
Aspergillus terreus *Aspergillus deflectus* *Aspergillus flavus* *Aspergillus niger*	Aspergillosis	Inhalation
Phaeohyphomycosis (pigmented)	Phaeohyphomycosis	Cutaneous inoculation
Hyalohyphomycosis (nonpigmented)	Hyalohyphomycosis	Cutaneous inoculation
Eumycotic mycetoma (black/white tissue grains within tissue)	Eumycotic mycetoma	Cutaneous inoculation Contaminated wounds

TABLE 21.1.20 Morphological characteristics and signalment of dogs affected by systemic fungi

Organism	Signalment		
	Breed	**Age**	**Sex**
Blastomycosis (5–20 µm)	Large breed (>15 kg) > small breed Sporting dogs & hounds (e.g., Coonhounds, Pointers, Weimaraners, etc.) Nonsporting breeds at increased risk (e.g., Dobermann)	2–4 years	Males > females (slight)
Histoplasmosis (2–4 µm)	Increased exposure in sporting/working dogs (e.g., Pointers, Weimaraners, and Brittany Spaniels)	2–4 years and 4–7 years more likely to develop disease	No sex predisposition
Coccidioidomycosis (10–200 µm)	No breed, age, or sex predilection		
Sporotrichosis (4–6 µm)	No breed predisposition	6 months to 12 years	No sex predisposition
Cryptococcosis (4–10 µm surrounded by up to 30 µm capsule)	German Shepherd Dog, Dobermann Pinschers, Great Danes, Cocker Spaniels	4 years	No sex predisposition
Systemic aspergillosis (2–3 µm)	German Shepherd Dog, Rhodesian Ridgeback	2–8 years of age (median 4.5 years)	Females > males
Phaeohyphomycosis Pigmented Hyphae (2–5 µm) Irregularly swollen up to 25 µm	No breed, age, or sex predilection		
Hyalohyphomycosis Nonpigmented Septate with acute angular branching	Most commonly affects young, large-breed dogs		
Eumycotic mycetoma	No breed, age, or sex predilection		

Clinical Presentation

Animals may present with nondescript clinical signs, including fever, anorexia, weight loss, and lethargy. Clinical signs are dependent upon the causative fungal organism and the organ system(s) affected. True fungal pathogens are more common in young dogs (1–5 years). Predominant clinical findings for each fungus are summarized in Table 21.1.21. Since the respiratory tract is the portal of entry for true fungal pathogens, coughing, dyspnea, and tachypnea predominate (Figure 21.1.21a, b).

Differential Diagnosis

Systemic mycoses can occur in dogs of any signalment, especially when they live in or have a travel history to endemic areas or have a history of immunosuppressive drug treatment. Infection should be suspected in dogs with fever; nodular, cavitary, or lobar pulmonary lesions (Figure 21.1.21a, b); osteolytic bone lesions; ocular inflammation such as uveitis or chorioretinitis; discospondylitis; enlarged lymph nodes or cutaneous nodules. Dogs refractory to empiric medical therapy should have a thorough diagnostic evaluation that includes appropriate tests for fungal disease.

Diagnosis

Table 21.1.22 represents an overview of the preferred diagnostic tests for systemic fungal infections. Cytology and histopathology are useful diagnostic tools. Cytopathology is an excellent tool for identifying disease if both the organism and concurrent granulomatous

TABLE 21.1.21 Summary of the predominant clinical findings for systemic fungal diseases

Infectious disease	Common clinical signs

Blastomycosis*	– Variable clinical signs (fever, lymphadenopathy)
	– Respiratory (common)
	  – Cough, dyspnea, exercise intolerance
	– Ocular disease (common)
	  – Anterior uveitis, endophthalmitis, optic neuritis
	– Skin disease (common)
	  – Cutaneous/subcutaneous nodules often with draining tracts

Histoplasmosis	– Fever, cough, dyspnea, diarrhea (large bowel > small, mixed), hematochezia (common) – Occasionally present with polyarthritis, peripheral lymphadenopathy, chorioretinitis, CNS disease, skin lesions
Coccidioidomycosis*	– Cough, weakness, lethargy, anorexia, weight loss, fever (103°F–106°F) (common) – Lameness with painful, swollen boney lesions – Localized lymphadenopathy, ocular lesions, and skin lesions, especially overlying bone lesions – Diarrhea
Sporotrichosis	– Variable clinical signs (anorexia, weight loss, fever, sneezing, and dyspnea) – Non painful, cutaneous, ulcerative, lesions with draining tracts (most common) – Bridge of nose, nasal planum, eyelids, and pinnae – Regional lymphadenomegaly

Cryptococcosis	– Variable clinical signs (anorexia, weight loss, and lethargy)
	– Respiratory disease (common)
	  – Sneezing, mucopurulent nasal discharge
	– CNS disease (common)
	  – Dull mentation, blindness, hypermetria, cranial nerve deficits (V, VII, and VIII)
	– Ocular disease (common)
	  – Granulomatous chorioretinitis, retinal detachment most common
	– Skin disease
	  – Nodular ulcerative draining lesions
	  – (Head, feet, nail beds, and mucous membranes)

Systemic aspergillosis	– Variable clinical signs (anorexia, weight loss, fever, lethargy, and peripheral lymphadenomegaly) – Vertebral pain, paraparesis, paraplegia, lameness with swelling, cutaneous draining tracts, AKI (most common)

Phaeohyphomycosis	– Cutaneous, ulcerative, lesions with draining tracts or visible mass (most common)
	  – Digits, pinnae, nasal planum
	– Regional lymphadenomegaly
	– Meningoencephalitis reported
	  – (Obtundation, seizures, tremors, ataxia)

Hyalohyphomycosis	– Manifests as either localized cutaneous/osseous infection or disseminated disease involving multiple organs (i.e., kidney, bone marrow, lymph nodes, liver, spleen, bone, intervertebral discs, and CNS)
Eumycotic mycetoma	– Localized granulomas forming “fungal grains” within the skin, subcutaneous tissue, or muscle with draining tracts

* Respiratory and nonspecific clinical signs common.

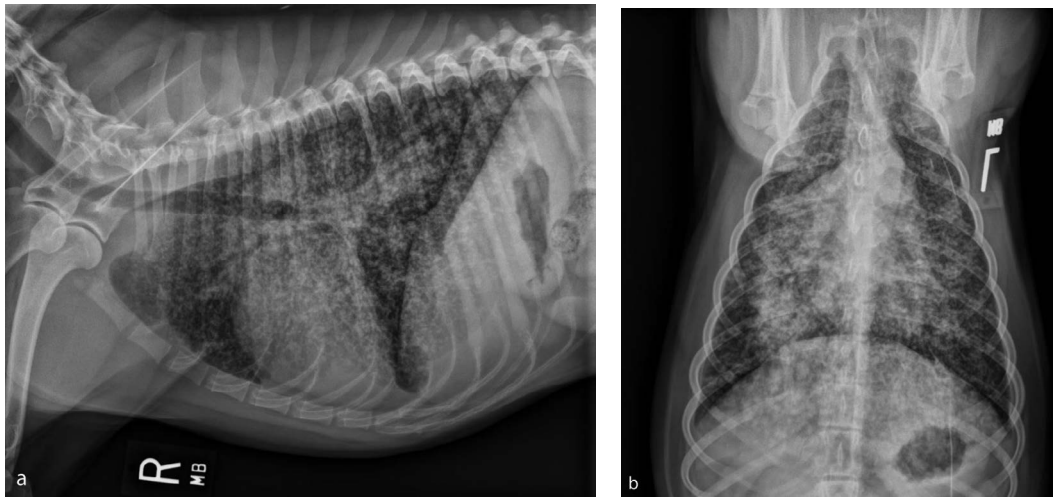


FIGURE 21.1.21 a, b Thoracic radiographs (lateral and DV) of 3-year-old female spayed Dalmatian with a week-long history of inappetence, lethargy, gagging, and coughing episodes. There is a severe, diffuse, miliary pulmonary pattern with a structured component characterized by multifocal, ill-defined, round, soft tissue opaque nodules measuring up to 2 cm in diameter.

inflammation are present (Figures 21.1.22–21.1.24). Samples for cytology include bone marrow, lymph node, and body fluid (BAL, CSF, urine, etc.) aspirates. Fungal morphologic features, including size, shape, budding pattern, presence or absence of septations, and branching pattern, provide valuable information when attempting to correctly identify the microorganism in question. Similarly, histopathology is used to describe both the fungal morphology, the presence or absence of tissue invasion, and the host reaction to the infection.

Fungal culture is not routinely performed in the case of true pathogenic fungi due to risk of exposure to laboratory workers and because fungal organisms are slow growing (i.e., long turnaround times between sampling and results). Culturing of opportunistic fungal infections from obtained clinical specimens (i.e., tissue, sputum, urine, wound, or blood) ensures isolation of the causative fungal agent and determination of the sensitivity of the isolated fungi to antifungal agents. Given that both cytology and histopathology may be invasive tests and give false-negative results, alternative tests have now been developed. Antibody tests are used for the diagnosis of coccidioidomycosis (Table 21.1.22). These tests are not useful in the diagnosis of histoplasmosis and blastomycosis due to their low sensitivity and specificity. More recently, antigen testing for systemic histoplasmosis, blastomycosis, and aspergillosis has become available through MiraVista Diagnostics, Indianapolis, IN. These tests are not only useful in the diagnosis of fungal infections but also useful for monitoring of disease response

TABLE 21.1.22 Preferred diagnostic assays for systemic fungal disease

	Diagnostic assay					
Organism	**Cytologic examination**	**Histopathology**	**Fungal culture**	**Antibody serology**	**Antigen assay**	**Real-time PCR**
Blastomycosis	**	*	–	–	**[a]	–
Histoplasmosis	**	*	–	–	**[b]	–
Coccidioidomycosis	*	*	**	**	–[c]	–
Sporotrichosis	**	*	**	–	–	–
Cryptococcosis	**	*	**		**[d]	–
Aspergillosis	**	*	**		**[e]	–
Phaeohyphomycosis	***	**	**	–	–	**
Hyalohyphomycosis	***	**	**	–	–	**
Eumycotic mycetoma	***	**	**	–	–	**

[a] *Blastomyces* cell wall galactomannan quantitative antigen EIA (MiraVista Diagnostics, Indianapolis, IN). Sensitivity: Urine (93.5%) > serum (87%). Cross-reactivity with histoplasmosis and other fungal pathogens may occur.

[b] *H. capsulatum* antigen (MiraVista Diagnostics, Indianapolis, IN). Sensitivity: Urine > serum. Cross-reactivity with blastomycosis and other fungal pathogens may occur.

[c] Clinical sensitivity for diagnosis is low (< 40%). Antibody testing is preferred for initial testing.

[d] Latex agglutination assay for detection of cryptococcal polysaccharide capsular antigen. Highly sensitive and specific (> 95%) test for cryptococcosis in dogs and cats.

[e] *Aspergillus* galactomannan antigen ELISA assay highly sensitive for diagnosis of disseminated aspergillosis (serum or urine).

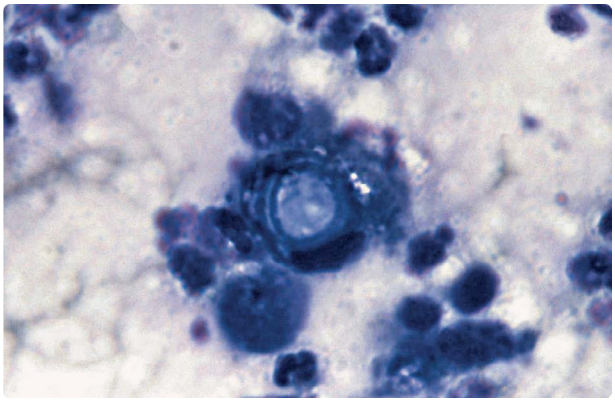


FIGURE 21.1.22 Microscopic appearance of a *Blastomyces* spore taken on a "touch prep" sample from the dog's nasal lesion. (*Courtesy of M. Schaer.*)

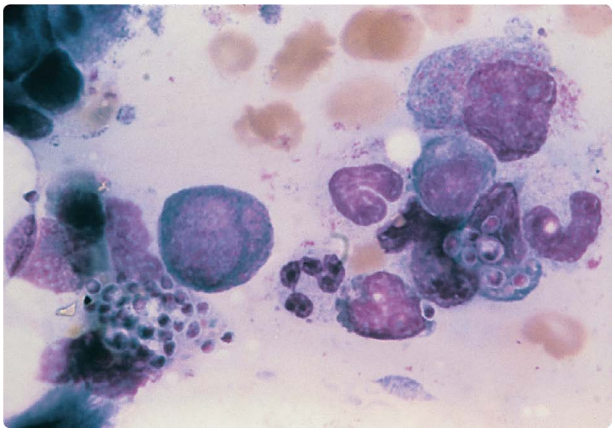


FIGURE 21.1.23 Clusters of *H. capsulatum* in the macrophages in the bone marrow of dog with diffuse histoplasmosis.

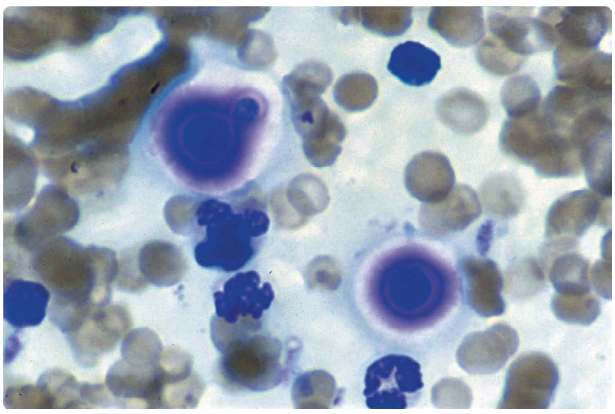


FIGURE 21.1.24 A cytology specimen stained with new methylene blue showing *Cryptococcus neoformans* spores. Note the thick capsule and the daughter spore. (*Courtesy of M. Schaer.*)

to antifungal therapy. Both urine and serum may be used as specimens, with urine being more sensitive. Cross-reactivity between different fungal antigens can occur, especially between *Blastomyces* and *Histoplasma* antigens, and among mold pathogen antigens. Other alternative diagnostics currently receiving increased attention include molecular diagnostics (e.g., real-time PCR assays), especially when dealing with opportunistic fungal infections or when classical methods for fungal detection (i.e., cytopathology, histopathology, and culture) have failed to identify fungal organisms.

Management

Treatment/Prognosis

Prognosis is variable and is dependent upon the immune status of the dog and whether disease is localized or disseminated. Cure is most likely in dogs with localized disease or in dogs where infection is secondary to medical immunosuppression. It should be noted that cost associated with treatment and disease severity may ultimately determine the prognosis. Systemic corticosteroids are indicated to reduce inflammation associated with severe disease. Nonsteroidal anti-inflammatory drugs (NSAIDs) are utilized when there is significant lameness and bone pain associated with infection. Triazole antifungals are considered "first-line therapy" for true fungal pathogens. These drugs inhibit ergosterol synthesis, resulting in cell wall damage, increased cell permeability, and eventual cell lysis. Triazoles commonly used include itraconazole, fluconazole, and voriconazole. Newer azoles (e.g., posaconazole) are generally cost prohibitive. Use of compounded azoles should be avoided due to variable drug concentrations within formulations. Single-agent itraconazole is considered first-line therapy in most situations, especially when bone lesions are present. In cases where there is CNS or urinary involvement, fluconazole is considered to be first-line therapy.

In dogs with rapidly progressive disease or when conventional antifungal therapy has failed, treatment with amphotericin B (AMB) should be considered. It is administered intravenously or subcutaneously. Adverse effects are associated with dose-dependent nephrotoxicity, attributable to the drug's vasoconstrictive and tubulotoxic effects. Newer lipid formulations are less nephrotoxic, allowing for higher cumulative drug doses and improved effectiveness.

Therapy for opportunistic fungal infection is challenging and often consists of aggressive surgical resection and prolonged medical treatment with antifungals (≥ 6 months). Immunosuppressants should be either discontinued altogether or tapered to the lowest effective dose possible to allow the immune system to fight infection. Failure to taper/discontinue immunosuppressant therapy may result in either progression of disease or patient death. Aggressive surgical excision with wide margins (≥ 2 cm) or amputation of a distal extremity is the treatment of choice for phaeohyphomycosis, localized hyalohyphomycosis, and mycetomas. New modalities, such as CO_2 lasers, have been utilized at the author's workplace for cutaneous fungal infections of the digits and nasal planum in both dogs and cats. The laser allows for precise ablation of the abnormal tissue without causing harm to the healthy tissues around the lesion, making it ideal for the digits, around the eyes, and nasal planum. Wounds created from these procedures are left open to heal through secondary intention. The treatment protocols for dogs infected with systemic mycoses are summarized in Table 21.1.23.

TABLE 21.1.23 Recommended treatment protocols for systemic mycotic infections

Mycotic infection	Treatment protocol
Blastomycosis[a]	**Mild-to-moderate cases** – Itraconazole[b] at 5 mg/kg p.o. q.12–24 h.[c] **Severe cases** – Amphotericin B (deoxycholate or lipid-complexed)[d] combined with Itraconazole at 5 mg/kg p.o. q.12–24 h.[e]
Histoplasmosis	**Mild-to-moderate cases** – Itraconazole[f] at 5 mg/kg p.o. q.12–24 h. **Severe cases** (i.e., pulmonary, acute disseminated, or CNS disease) – Amphotericin B combined with itraconazole – Fluconazole at 5 mg/kg p.o. q.12 h. can be substituted with itraconazole if CNS disease[e]
Coccidioidomycosis	**Mild-to-moderate cases** – Fluconazole at 5 mg/kg p.o. q.12 h. in patients with CNS disease – Itraconazole at 5 mg/kg p.o. q.24 h. in patients with bone involvement[g] **Severe or refractory cases** – Amphotericin B (deoxycholate or lipid-complexed) alone or in combination with an azole therapy (itraconazole/voriconazole/posaconazole)
Sporotrichosis	– Itraconazole at 5 mg/kg p.o. q.12–24 h. – Fluconazole at 5–10 mg/kg p.o. q.12–24 h. – Ketoconazole at 10–15 mg/kg p.o. q.12 h.[h] **Refractory cases** – Alternative antifungal therapy supersaturated potassium iodide (SSKI), potassium iodide at 2.5–20 mg/kg p.o. q.24 h.[i]

Cryptococcosis	– Itraconazole at 5 mg/kg p.o. q.12–24 h.
	Disseminated or CNS disease
	– Amphotericin B (deoxycholate or lipid-complexed) and fluconazole at 5–10 mg/kg p.o. q.12–24 h.
	– Alternatives to fluconazole
	  – Voriconazole 4–5 mg/kg p.o. q.12 h.
	  – Posaconazole 5–10 mg/kg p.o. q.12–24 h.

Aspergillosis	– Itraconazole at 5 mg/kg p.o. q.12–24 h. as monotherapy (2 months to 3 years survival) – Posaconazole at 5–10 mg/kg p.o. q.12–24 h. as monotherapy (6 weeks to 17 months survival) – Itraconazole at 5 mg/kg p.o. q.12–24 h. or voriconazole at 4–5 mg/kg p.o. q.12 h. or posaconazole at 5–10 mg/kg p.o. q.12–24 h. in combination with terbinafine at 30–40 mg/kg p.o. q.24 h. – Amphotericin B (deoxycholate or lipid-complexed) in combination with azole therapy (itraconazole/posaconazole/voriconazole)
Phaeohyphomycosis[j]	– Aggressive surgical resection in combination with itraconazole at 5 mg/kg p.o. q.12–24 h. or posaconazole at 5–10 mg/kg p.o. q.12–24 h. or voriconazole at 4–5 mg/kg p.o. q.12 h.
Hyalohyphomycosis[j]	**Immunosuppressed** – Taper/discontinue immunosuppression and combine with oral azole therapy (itraconazole, voriconazole, or posaconazole) **Localized disease** – Aggressive surgical resection in combination with itraconazole at 5 mg/kg p.o. q.12–24 h. or posaconazole at 5–10 mg/kg p.o. q.12–24 h. **Systemic disease** – Amphotericin B (deoxycholate or lipid-complexed) in combination with itraconazole at 5 mg/kg p.o. q.12–24 h.
Eumycotic mycetoma[j]	Surgery in combination with itraconazole at 5 mg/kg p.o. q.12–24 h.

[a] Duration of therapy based upon clinical signs, serial serological, and radiographic image monitoring (e.g., every 4–8 weeks).

[b] First-line therapy.

[c] Equivalent efficacy to 5 mg/kg p.o. q.12 h.

[d] Prior to each treatment, blood and urine should be collected for a CBC, renal panel, and urinalysis. Use three times a week (4 weeks) or until azotemia develops.
Deoxycholate may be administered IV or *SC.

IV protocol: Prior to and after treatment (1 hour), 0.9% NaCl administered IV at 1.5–2 times maintenance rate. Infusion lines should be flushed with D5W before treatment. 0.5 mg/kg of amphotericin B is transferred to a 500 mL bag of D5W and administered IV over 4–6 hours.

SC protocol: 0.8 mg/kg of amphotericin B is transferred to a 500 mL bag of 0.45% sodium chloride in 2.5% dextrose.

* Sterile injection site abscesses may form with this protocol.

Lipid-complexed administered IV.

Amphotericin B (3 mg/kg) is diluted to 1 mg/mL in D5W and administered IV over 1–2 hours.

[e] Supportive care with supplemental oxygen, nebulization, coupage, and tapering dose of systemic anti-inflammatory glucocorticoids (0.5–1 mg/kg prednisone equivalent).

[f] Itraconazole over fluconazole treatment.

[g] Itraconazole preferred in patients failing to respond to fluconazole treatment.

[h] More likely to result in relapses.

[i] Toxic side effects common (anorexia, vomiting, diarrhea, and lethargy).

[j] Discontinue or taper immunosuppressive therapy to the lowest effective dose.

Prevention

Preventing exposure to fungal organisms is difficult, especially in endemic areas, given that most fungal organisms are ubiquitous.

Public Health Implications

Both humans and animals can be infected with all of the organisms discussed in this section. There is no known transmission from dogs or cats to humans or other animals.

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CHAPTER 21

Infectious Diseases

CHAPTER 21.2 Cats

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BACTERIAL INFECTIONS

FELINE RESPIRATORY TRACT

FELINE CHLAMYDIOSIS

See also Chapter 19.

Definition/Overview

Feline chlamydiosis is caused by the obligate intracellular Gram-negative organism *Chlamydia felis*. The organism, which is relatively unstable outside the host, is associated with upper respiratory and ocular (conjunctival) infections. Limited studies suggest that chlamydiosis infection comprises approximately 5% of upper respiratory infections in cats in the United States. In the United Kingdom, it is estimated that up to 30% of respiratory disease in cats is associated with *C. felis* infection.

Etiology

Genomic classification of Chlamydiaceae had divided this family into two genera: *Chlamydophila* and *Chlamydia*. However, full genome sequencing has resulted in a recommendation to revert to a single genus, *Chlamydia*.

Pathophysiology

There is still limited information on the pathogenesis of this infection in cats; however, chronic infections, particularly among households of cats, have been documented. *C. felis* has been isolated from experimentally infected cats for periods of up to 18 months, suggesting the development of a carrier state subsequent to recovery.

Clinical Presentation

C. felis infection in cats is most commonly associated with unilateral or bilateral conjunctivitis (acute or chronic) and chemosis (**Figure 21.2.1**). Ocular ulceration is not common and can increase suspicion of other infectious agent involvement (e.g., feline herpesvirus-1 [FHV-1]). Occasional sneezing (much less than that associated with viral upper respiratory disease) is also reported. Systemic illness is uncommon. Currently, there is no known direct association between *C. felis* infection and feline reproductive disease.

Differential Diagnosis

Infections with FHV, feline calicivirus (FCV), *Bordetella bronchiseptica*, and/or *Mycoplasma felis*; conjunctival injury.



FIGURE 21.2.1 Bilateral conjunctivitis in a 2-year-old cat with chlamydiosis.

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Diagnosis

Polymerase chain reaction (PCR) detection of *C. felis* from conjunctival swabs is the preferred method of diagnosis. Since the organism is intracellular, it is important to submit swabs that contain sufficient cellular material. Cotton swabs should be used; plain sterile tubes without transport medium are required for transport. Cats suspected of having chlamydiosis could also be tested for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) infection.

Management

Treatment/Prognosis

Tetracyclines are regarded as the most effective antibiotics for use against *C. felis* infection in cats. Because this organism is known to disseminate, systemic treatment is more effective than local topical treatment. Oral doxycycline (5 mg/kg p.o. q.12 h. or 10 mg/kg p.o. q.24 h. for at least 4 weeks, or at least 2 weeks after clinical resolution, whichever is longer) can also be given. Oral doxycycline should be followed with 5 mL of water when administering this antimicrobial to cats due to esophagitis risk. Azithromycin treatment has not been shown to completely eliminate *C. felis* infection and is not currently recommended. In young kittens, clavulanate-potentiated amoxicillin may be preferred to avoid side effects.

Prevention

The most effective means of preventing chlamydiosis in cats is to limit exposure of susceptible kittens and cats to any cat with signs of respiratory or conjunctival disease. However, within catteries, animal shelters, and boarding catteries, preventing contact with infected carrier cats may be difficult or impossible to achieve. Both killed adjuvanted and live nonadjuvanted *C. felis* vaccines are approved for use in cats (Table 21.2.1). These vaccines appear to give reasonable protection against clinical signs of disease, but not against infection. The current recommendation for administration of *C. felis* vaccine is limited to those cats with known or suspected risk of exposure and in households with a history of disease.

Public Health Implications

C. felis is generally regarded as a pathogen unique to the cat. Isolated reports of human self-limiting conjunctivitis with *C. felis* have raised concern regarding occasional zoonotic infection, but *C. felis* is not regarded as an important zoonotic disease. *Chlamydia psittaci* primarily infects birds and is an important zoonotic agent of atypical pneumonia in humans via birds.

STREPTOCOCCAL INFECTIONS

Streptococcal species are occasionally considered as a cause of respiratory disease in cats. *Streptococcus canis* is most prevalent in cats and exists as a commensal but can be associated with upper respiratory tract disease, neonatal septicemia, abscesses, pneumonia, osteomyelitis, and polyarthritis. *Streptococcus equi* subsp. *zooepidemicus* has been recognized as an emerging feline respiratory pathogen associated with bronchopneumonia and pneumonia, as well as meningoencephalitis, often with a fatal course. Close confinement of cats, such as in shelters, appears to be a major risk factor. Horses are common carriers of this bacterium, and so contact with horses is a potential source of infection. PCR and culture are used for diagnosis, and treatment with broad-spectrum antibiotics (trimethoprim–sulfamethoxazole has been used) should be initiated as soon as possible and, if appropriate, adapted to the results of culture and sensitivity tests.

FELINE BORDETELLOSIS

Definition/Overview

Evidence that *B. bronchiseptica* is a significant primary respiratory pathogen of cats is lacking in the clinical literature but has been shown experimentally. The most compelling evidence supporting *B. bronchiseptica* as a respiratory pathogen in naturally infected cats is limited predominantly to clusters of kittens with concurrent viral upper respiratory infection, especially calicivirus. In these cases, *B. bronchiseptica* infection was associated with severe, frequently fatal, bronchopneumonia in kittens. Bordetellosis could also be considered in the differential diagnosis list for cats presented with acute or chronic coughing.

Etiology

Bordetella bronchiseptica is an aerobic, Gram-negative coccobacillus associated with respiratory infections in a variety of species. The organism is frequently found as part of the normal oral and upper respiratory tract flora in cats. Therefore, its role as a primary pathogen is debated but is an accepted secondary pathogen.

Pathophysiology

Bordetella bronchiseptica colonizes the ciliated respiratory epithelial cells in the trachea and nasal cavity and as such is shed in oral and nasal secretions of infected cats (experimentally 19 days post infection). Upon infection, both endotoxins and exotoxins are released, and these together with other injuries cause stasis of respiratory cilia, significantly compromising clearance mechanisms (mucociliary apparatus), often leading to chronic infections. As it affects both dogs and cats, cross-infection can occur.

Clinical Presentation

The predominant clinical signs include cough, fever, sneezing, purulent ocular/nasal discharge, and regional

TABLE 21.2.1 General vaccination recommendations of pet cats/kittens (based on the 2020 AAHA/AAFP Feline Vaccination Guidelines and the 2020 European ABCD Vaccination Matrix)

Core vaccines	Primary course start	First booster and thereafter

– Feline panleukopenia (FPV), herpesvirus (FHV), and calicivirus (FCV)
– Both MLV and killed vaccines exist with and without adjuvant
  – MLV often favored for more rapid onset of action and usual lack of adjuvant
  – Intranasal MLV vaccines exist for FHV and FCV in some countries, which give very rapid protection in high-risk situations
	– *Primary kitten (≤16 weeks of age) series:* Administer 1 dose as early as 6 weeks of age, then every 3–4 weeks until 16–20 weeks of age
	  – MDA interferes with vaccine efficacy
	– *Primary adult (>16 weeks of age):* Administer 2 doses 3–4 weeks apart
		– At 6–12 months of age, consider younger age for first booster if concern that MDAs may have been present at the time of last primary kitten vaccination
		– Thereafter, revaccinate every 3 years for FPV
		– For FHV and FCV, can revaccinate every 3 years if low risk (indoor only, visits to vet occasionally) or annually if higher risk (regular contact with other cats with outdoor access)

– Rabies – Can be noncore in countries free from rabies/pets that do not travel – Both recombinant and killed rabies vaccines exist	– Follow state/local/provincial or government (e.g., for pet travel) laws and manufacturer's recommendation	– Follow state/local/provincial or government (e.g., for pet travel) laws and manufacturer's recommendation (vaccines are licensed with 1 or 3-yearly intervals)

– Feline leukemia virus (FeLV)
– Both recombinant and killed vaccines exist, without and with adjuvant
– Core in kittens and young adults due to age-related susceptibility
  – Thereafter, can be considered as noncore dependent on risk
– In some countries, some FeLV vaccines are licensed with 3-yearly intervals
	– *Primary kitten (≤16 weeks of age) series:* Administer 2 doses, from 8 weeks of age and 3–4 weeks later
	– *Primary adult if required (>16 weeks of age):* Administer 2 doses, 3–4 weeks apart
		– 12 months after last vaccine
		– Thereafter, revaccinate according to risk
		  – Annually if regular exposure to FeLV infected cats or cats of unknown FeLV status
		  – Every 2–3 years* if low risk of exposure to FeLV-infected cats
		  – No requirement if no risk of exposure to FeLV
		* ABCD recommends yearly boosters until the cat is 3 years of age due to age-related susceptibility—then frequency adjusted based on risk

Noncore vaccines	**Primary course start**	**First booster and thereafter**
– FeLV	– 2 initial doses 3–4 weeks apart, can begin at 8 weeks of age	– 1 year later, booster every 1–3 years depending on circumstances (see references)
– *Chlamydia felis* – Both nonadjuvanted MLV and adjuvanted killed vaccines available	– 2 initial doses 3–4 weeks apart, if indicated, from 8–9 weeks of age	– 1 year later and then booster annually where there is documented risk of exposure or history of disease – Indications for use of this product are limited
– Feline *Bordetella bronchiseptica* – Attenuated live intranasal nonadjuvanted vaccine, not routinely used	– A single dose, administered intranasally, as early as 4 weeks of age, if indicated	– 1 year later and then booster annually where there is documented risk of exposure – Indications for use are limited to multicat households where there is history of disease

Guidelines to be consulted directly for further information as well as recommendations for shelter and/or breeding cats. Core vaccines are recommended for all cats. Noncore vaccines are recommended based on an individualized risk–benefit assessment.

Notes:

- Route for administration is SC unless specified as intranasal administration.
- The feline infectious peritonitis and feline immunodeficiency virus vaccines are not recommended.
- Inactivated (killed) adjuvanted vaccines can be considered when vaccination of a pregnant queens, but manufacturer's recommendations must be followed.
- When considering any vaccination or injection, the development of a feline injection site sarcoma (FISS) is a consideration. There is no definitive proof of the pathogenesis of FISS despite extensive research, but the most widely accepted hypothesis suggests that chronic inflammation at the site of an injection of an irritating substance acts as a trigger for subsequent malignant transformation. Therefore, an assessment of the infection risk is recommended for all vaccines in cats.

AAFP, American Association of Feline Practitioners; ABCD, Advisory Board for Cat Diseases; MDAs, maternal-derived antibodies; MLV, modified live virus.

lymphadenomegaly (Figures 21.2.2 and 21.2.3). Clinical signs are reported to resolve within 10 days, assuming coinfections and/or complications of pneumonia do not develop. Kittens (< 10 weeks) appear to be most prone to developing serious bronchopneumonia associated with feline bordetellosis. Clinical signs include dyspnea, cyanosis, and death. Coughing is more likely to be reported in kittens with bordetellosis than in adults.

Differential Diagnosis

Clinical illness associated with bordetellosis is characteristically associated with other respiratory pathogens such as FCV or FHV. Other differential diagnoses include cleft palate associated with aspiration pneumonia and bacterial pneumonia (e.g., *M. felis*).

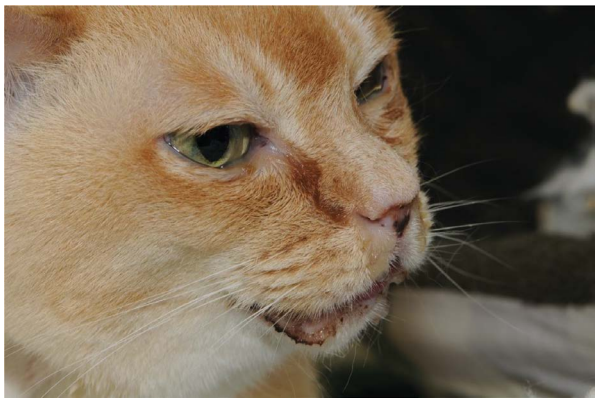


FIGURE 21.2.2 The upper respiratory signs associated with *Bordetella* infection are difficult to distinguish from other causes of feline infectious respiratory disease such as feline calicivirus or feline herpesvirus. (*Courtesy of S. Taylor.*)

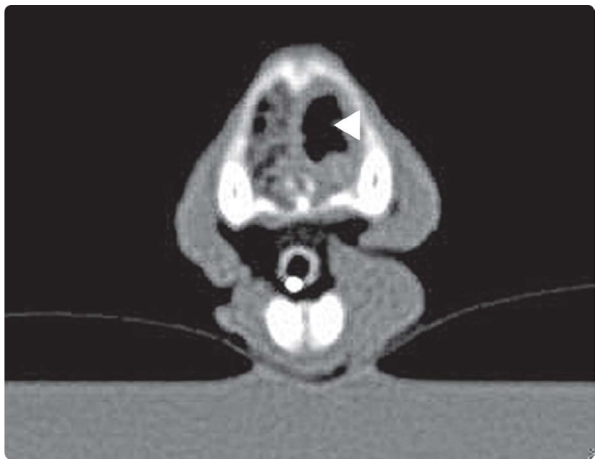


FIGURE 21.2.3 CT of the nasal and sinus areas of a Siamese cat with chronic rhinosinusitis and positive bacterial culture results for *Bordetella* spp. Note the absence of turbinates, perhaps due to the destructive nature of a primary feline herpesvirus infection, which is particularly visible on the right side (arrowhead). (*Courtesy of M. Schaer.*)

Diagnosis

The identification of *B. bronchiseptica* in the lower respiratory tract of clinically affected cats is considered diagnostic. Samples can be collected by bronchoalveolar lavage (BAL) or transtracheal wash and submitted for PCR and culture. Routine cytology of BAL samples often yields polymorphonuclear leukocytes, macrophages, and bacteria.

Bordetella bronchiseptica can be detected from respiratory secretions in the oropharynx, nasal cavity, or conjunctival sulcus of kittens and cats with upper respiratory disease and healthy cats; therefore, positive bacterial culture or PCR test results do not equate to causation of clinical signs in these cases.

Management

Bordetella bronchiseptica is susceptible to commonly used disinfectants. In a multicat household or shelter, stress management, including reduction of overcrowding to reduce disease transmission and thorough cleaning and disinfection to reduce fomite transmission of upper respiratory pathogens, should be instituted.

Treatment/Prognosis

Several antimicrobial agents are appropriate for use in kittens and cats with clinical signs associated with *B. bronchiseptica*. Considering the potential outcome for kittens concurrently infected with viral upper respiratory infection (e.g., FCV or FHV), antimicrobial therapy is justified in affected kittens to prevent development of bronchopneumonia. Doxycycline (5 mg/kg p.o. q.12 h. or 10 mg/kg p.o. q.24 h. with 5 mL water to follow; permanently stained dentition is a possible adverse effect in young kittens) is the initial treatment of choice. Other options include amoxicillin–clavulanate and pradofloxacin[1], both of which have published efficacy in the treatment of feline bordetellosis. In both dogs and cats, *B. bronchiseptica* can persist for as long as 12 weeks following the initial infection. Extended treatment durations of 4 weeks or longer are not unusual. In addition, many cats require additional supportive therapy, including intravenous fluid and nutritional support; some require more intensive care.

Prevention

A modified live *B. bronchiseptica* vaccine has been licensed for topical (intranasal) administration in cats and kittens. Considering the overall low incidence of clinical disease and the difficulty in documenting infections attributable to *B. bronchiseptica* in kittens, it is currently recommended that this vaccine be limited to use in multicat households where there are documented clinical infections with *B. bronchiseptica*, either as a single pathogen or as a comorbid infection with FHV and/or FCV. Currently, there appears to be little indication for the routine vaccination of adult cats against feline *B. bronchiseptica* (see Table 21.2.1).

Public Health Implications

Although there are limited reports of *B. bronchiseptica* infections occurring in people, some of which included exposure to dogs, there is no evidence to support direct transmission from cats to humans. However, transmission between cats and dogs has been documented using molecular techniques. One should follow dosage recommendation by manufacturer in your country as this varies due to licensing.

MYCOPLASMA FELIS INFECTION

Definition/Overview

Mycoplasma felis has been isolated from the upper respiratory tracts of cats with clinical signs of upper respiratory tract disease and also from healthy cats, so it is considered an upper respiratory tract commensal.

Whether acting as a primary pathogen or secondary opportunistic invader, *Mycoplasma* spp. are important infectious agents in feline upper and lower respiratory tract disease.

Etiology

Mycoplasma spp. are intracellular bacteria bound by a single limiting cell membrane (i.e., they lack a cell wall). *Mycoplasma* spp. have been recovered from the normal flora of the upper respiratory tract, conjunctiva, and genital tract of cats.

Pathophysiology

Mycoplasma infections are generally spread by direct contact or fomite transmission. They often act as opportunistic pathogens where cats are stressed or overcrowded or when there are comorbid infections.

Clinical Presentation

The most common clinical signs are upper respiratory and ocular: Sneezing, nasal discharge, conjunctivitis, and/or ocular discharge. Pyrexia and inappetence can occur. Lower respiratory tract infections have also been reported, accompanied by coughing, dyspnea/tachypnea, bronchopneumonia, and/or suppurative bronchitis. Screening for this pathogen in cats presenting for chronic respiratory disease, especially those poorly responsive to antimicrobials is recommended. Rare reports of association with polyarthritis exist.

Differential Diagnosis

The most common pathogens causing upper respiratory tract disease in cats are FHV-1, FCV, *M. felis*, *B. bronchiseptica*, and *C. felis*. Other causes of feline pneumonia include bacterial, fungal, and parasitic pathogens; aspiration pneumonia; and neoplasia.

Diagnosis

The identification of *M. felis* in the lower respiratory tract of clinically affected cats is considered diagnostic, for example via BAL. Commercially available PCR testing is thought to be the most sensitive diagnostic tool available. Consideration of contamination from the upper respiratory tract as a cause false-positives is important. Quantitative PCR results can aid in assessing clinical relevance.

Because of their fastidious nature and limited ability for survival outside the host, bacterial culture of *Mycoplasma* spp. is challenging so not routinely performed.

Management

Treatment/Prognosis

Doxycycline (10 mg/kg p.o. q.24 h.; 5 mL water should be administered after every dose; permanently stained dentition is a possible adverse effect in young kittens) is the treatment of choice. Prolonged courses (up to 6 weeks) might be necessary to reduce pathogen load to undetectable levels using quantitative PCR testing, but clinical resolution of infection typically occurs in 1–2 weeks. *M. felis* also has published in-vitro and in-vivo susceptibility to fluoroquinolones such as marbofloxacin (2.7–5.5 mg/kg p.o. q.24 h. for 6 weeks), macrolides (azithromycin), and lincosamides (clindamycin 10–15 mg/kg p.o. q.12 h.).

There are no antimicrobial regimens that are proven to clear infection, and *M. felis* persists in the host for extended periods, resisting clearance using intracellular localization, immunomodulatory effects, and surface antigen variations. For this reason, clinical resolution might be more important than achieving negative PCR results post treatment.

Prevention

Stress management is paramount to environmental control, and special attention should be given to reducing overcrowding to reduce disease transmission. Thorough cleaning and disinfection is required to reduce fomite transmission of upper respiratory pathogens. *M. felis* is susceptible to routine disinfectants as it lacks a cell wall. Population management is the main prevention tool in multicat environments. There are currently no vaccines available for the prevention of *M. felis* infection.

Public Health Implications

There have been isolated case reports of human infections with *M. felis*, but the vast majority of human *Mycoplasma* infections have been due to *Mycoplasma* spp. not found in cats or dogs.

OTHER

HEMOPLASMAS (HEMOTROPIC MYCOPLASMAS)

See also Chapter 16.

Definition/Overview

Mycoplasma haemofelis (formerly *Haemobartonella felis*) belongs to a genus of small (0.3–1 μm) wall-less bacteria that live on red blood cells (RBCs) closely related to mycoplasmas; they are sometimes called the "hemoplasmas." Acute infections are characterized by rapid-onset hemolytic anemia, hence the name "infectious anemia." While chronic *M. haemofelis* infection is characterized by episodes of fluctuating parasitemia, clinical anemia does not usually occur in the absence of comorbidities. Persistent Coombs-positive autoagglutination by antibodies bound to RBCs can be found in cats with acute anemia due to *M. haemofelis* infection.

Other species of hemoplasmas known to infect cats are "*Candidatus Mycoplasma haemominutum*" and "*Candidatus Mycoplasma turicensis*." However, infections with these species appear to be subclinical in cats unless concurrent disease is present. "*Ca. M.*

haemominutum" is usually the most common species found in studies followed by *M. haemofelis* and "*Ca. M. turicensis*." Infections with more than one hemoplasma species are relatively common.

Etiology

The natural mode of hemoplasma transmission in cats is not known. Older, male nonpedigree cats, outdoor access, and a history of fighting have been associated with infection. Direct cat-to-cat infection by casual contact, such as mutual grooming, is thought to be unlikely, while transfusion of blood from apparently healthy carrier cats is an effective means of transmitting *M. haemofelis*. Vectors such as fleas and ticks may be involved in transmission, although this has not yet been conclusively shown. Vertical transmission has been shown for other hemoplasmas but has not been definitively shown for feline hemoplasmas.

Pathophysiology

Acute *M. haemofelis* infection can be fatal if left untreated due to severe hemolytic anemia (usually extravascular), although in some cases only mild anemia results. Cats that ultimately recover from acute infections can remain chronically infected for years, although long-term carrier status may be more common with "*Ca. M. haemominutum*" infections. Depending on the intrinsic immunologic and phagocytic responses, chronic carrier cats may manifest small numbers of organisms on the surface of RBCs or may manifest no evidence of infection until stressed (e.g., chronic corticosteroid therapy, FeLV/FIV-positive status). Other factors such as the health status of the cat and possibly even the transmission route of infection may play a role in the outcome of hemoplasma infection with any species.

Clinical Presentation

While acute infections are often associated with significant anemia, many cats with chronic infections are asymptomatic or show only mild anemia and manifest few, if any, clinical signs. When clinical signs are present, they are most likely related to anemia (i.e., weakness, lethargy, pallor, and splenomegaly). Intermittent pyrexia may be present. Cats are only occasionally noted to be icteric.

Differential Diagnosis

Primary immune-mediated hemolytic anemia (IMHA), secondary IMHA (e.g., secondary to drugs, neoplasia, infections), cytauxzoonosis, retroviral infection, babesiosis, Heinz body-associated hemolysis, hypophosphatemia, and inherited red blood cell disorders such as pyruvate kinase deficiency are important differential diagnoses.

Diagnosis

Pathogenic hemoplasma infections typically cause a regenerative anemia that is macrocytic and hypochromic, although reticulocytosis is not always evident. Positive Coombs test results have been reported in acute hemoplasmosis. Hyperbilirubinemia is seen occasionally due to hemolysis, and hypoxic damage to the liver may result in increased activities of alanine aminotransferase (ALT). Hyperproteinemia is sometimes seen in cats. Retrovirus testing may be positive in cats (particularly FIV).

Definitive diagnosis of hemoplasma infection relies upon PCR diagnosis, which can identify with species is present as well as bacterial loads present in the blood if a quantitative PCR assay is used. Hemoplasmas may also be visible on blood smear cytology (Figure 21.2.4), but this method is known to have very poor sensitivity, as well as an inability to reliably differentiate between species. Stain precipitate and Howell–Jolly bodies are commonly mistaken for hemoplasma organisms on blood smear examinations performed in-house.

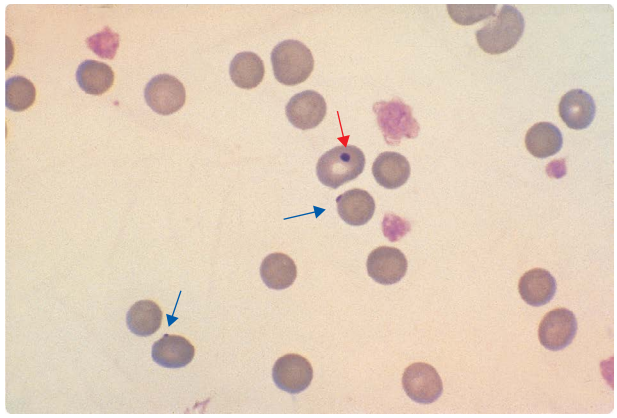


FIGURE 21.2.4 Peripheral blood smear from a cat demonstrating faint staining *Mycoplasma haemofelis* on the red blood cell surface (blue arrows) with a nearby Howell-Jolly body (red arrow), which is a nuclear remnant. Romanowsky-type stains can be used (e.g., Wright, Giemsa, Diff-Quik®) to stain blood smears.

Management

Treatment/Prognosis

Transfusion of whole blood or packed red blood cells if available may be required in severely anemic cats with marked clinical signs associated with acute-onset anemia.

Doxycycline (5 mg/kg p.o. q.12 h. or 10 mg/kg p.o. q.24 h. for 2–4 weeks, followed at each administration by 5 mL water) is recommended for treatment in cats showing clinical signs associated with *M. haemofelis* infection. If this is the first episode of hemoplasmosis in a cat which shows a rapid clinical response to treatment, 2 weeks of doxycycline may be adequate with no further monitoring. However, if the patient is a more complex case (e.g., repeated episode, concurrent disease, and/or clinical signs do not improve within 3 days), blood organism numbers can be monitored by quantitative PCR to ensure they are decreasing with treatment. Repeat hematology profiles are also helpful to assess response to treatment.

Fluoroquinolones such as marbofloxacin (2–5.5 mg/kg[1] p.o. q.24 h.) and pradofloxacin (3–4.5 mg/kg[1] p.o. q.24 h.) can be used as second-line agents if there has been inadequate clinical response to doxycycline.

Although clinical signs of infection can improve with appropriate antibiotic treatment, clearance of infection does not always result. This needs to be considered as chronic infection can result in relapses of clinical disease, although this is not believed to be common. However, a recent treatment protocol to clear chronic *M. haemofelis* infection has been published, comprising 4 weeks of doxycycline followed by 2 weeks of marbofloxacin for any cats that remain positive by quantitative PCR (as determined by repeated testing on multiple occasions) after doxycycline treatment. Treatment breaks of up to 4 weeks between the courses of doxycycline and marbofloxacin did not influence outcome. This may be of value to use in cats with *M. haemofelis* infection that have had particularly severe disease and/or reactivation of infection.

Immunosuppressive glucocorticoid treatment to suppress any IMHA associated with hemoplasmosis is not recommended because antibiotic treatment and supportive care alone are usually adequate, even in animals with positive Coombs testing. Glucocorticoids may cause hemoplasma infection reactivation.

The prognosis for uncomplicated *M. haemofelis* infection in cats is good, assuming that treatment can be administered and is tolerated by the cat.

Prevention

Since vectors may be involved in the transmission of feline hemoplasmosis, ectoparasiticide prevention is advised. Blood donors should be screened for hemoplasma infection by PCR before use. There is no vaccine available for hemoplasmosis.

Public Health Implications

Infections have been described in humans with novel hemoplasma species, as well as very occasional case reports documenting infection with species that have possibly originated in cats. This raises the possibility of zoonotic infections, and so good hygiene measures should be adopted when handling infected cats.

FELINE MYCOBACTERIA

Definition/Overview

Mycobacterial infections are a global health problem in animals and humans with geographical variation worldwide. They are intracellular acid-fast aerobic bacilliform bacteria (AFB), usually slow growing, that can be resistant in the environment. Those of feline importance are in the tuberculosis (TB) complex group (these form tubercles on pathology) or the nontuberculous mycobacteria (NTM) group, which includes feline leprosy (FL) organisms. Mycobacterial taxonomy is complex. Geographical variation exists in prevalence.

Etiology

The TB complex group are obligate pathogens and include *Mycobacterium tuberculosis* (mainly infects humans, not seen in cats), *Mycobacterium bovis* (infects cattle, cats, and rarely humans), and *Mycobacterium microti* (infects small rodents and cats). *Mycobacterium bovis* and *M. microti* can be transmitted via bites with small rodents, ingestion of infected milk or meat (e.g., raw meat diets), and occasionally via direct cat-to-cat contact or indirect contact. The NTM group comprise many slow-growing (e.g., *Mycobacterium avium-intracellulare* complex [MAC]) or rapid-growing (e.g., *Mycobacterium fortuitum*) species, and the FL group includes *Mycobacterium lepraemurium*. The NTM have pathogenic potential but are generally saprophytic or opportunistic, e.g., soil contamination of wounds or following rodent bite. MAC transmission may be possible via ingestion of infected meat or contact with bird feces.

Pathophysiology

Mycobacterial infections center on macrophages and are characterized by granulomatous and pyogranulomatous inflammation. TB complex species can result in tubercle formation and systemic disease with disseminated internal lesions (with *M. bovis* more than *M. microti*) as well as skin lesions. NTM infections typically involve the skin and subcutaneous tissues, rarely causing systemic disease except for MAC infections. Rapid-growing species often result in panniculitis due to their preference for adipose tissue. FL infections in cats are restricted to the skin, with localized and rarely disseminated cutaneous nodules resulting.

Clinical Presentation

TB and FL often occur in adult male cats with outdoor access (likely due to hunting and fighting) without evidence of immunosuppression. Obese outdoor cats are at increased risk of non-FL NTM infections. Siamese, Abyssinians, and Somalis are at increased risk of disseminated MAC infection. A recent outbreak of *M. bovis* in the UK occurred via ingestion in indoor-only pedigree cats that were fed a commercial raw wild venison diet.

Cats with TB usually present with cutaneous signs: Nodules (± ulceration) or nonhealing draining wounds, primarily on the head, extremities, or tail base. Regional or generalized lymphadenopathy is common. Systemic pulmonary involvement can occur, although outward signs of respiratory disease (coughing, tachypnea, dyspnea) may not occur. Weight loss and anorexia may occur. Bone involvement can result in lameness and/or pain. Occasionally ocular uveitis occurs.

NTM infections usually present as cutaneous/subcutaneous nodules ± ulceration (resembling localized TB) and/or granulomatous panniculitis (multiple punctate draining tracts; "pepper pot" appearance), which can progress to involve significant areas of painful, ulcerated and nonhealing tissue (often inguinal fat pads,

flanks, and/or tail base). Systemic signs sometimes occur, e.g., with MAC infection, such as neurological or pulmonary signs.

Cats with FL NTM have nodular cutaneous signs; alopecic or ulcerated nonpainful nodules that are mobile on palpation, typically on the head or limbs. Regional lymphadenopathy may occur, but systemic involvement is very rare.

Differential Diagnosis

Conditions which affect the skin should be considered as differential diagnoses such as bacterial infections (abscesses, actinomycosis, nocardiosis, rhodococcosis, etc.), fungal infections (blastomycosis, cryptococcosis, mycetoma, histoplasmosis, etc.), neoplasia, foreign body granuloma. Systemic signs involving the lungs and gastrointestinal tract should have relevant differential diagnoses considered such as inflammatory disease (e.g., feline asthma, inflammatory bowel disease), infectious disease (e.g., toxoplasmosis, feline infectious peritonitis, salmonellosis), and neoplastic disease (e.g., lymphoma, adenocarcinoma, metastatic disease).

Diagnosis

Hematology and biochemistry changes are nonspecific, although hypercalcemia due to granulomatous disease may occur. Thoracic imaging is variable and nonspecific, ranging from no abnormalities to bronchial, alveolar, or interstitial nodular mixed patterns and/or mediastinal and perihilar lymphadenopathy. Appendicular radiographs may show bone osteolysis or proliferative lesions. Abdominal ultrasonography can be useful in finding mesenteric lymphadenopathy or other abnormalities (e.g., in kidneys, liver). It can also be used a guide to obtain fine-needle aspirates (FNAs) of observed abnormalities.

FNAs or smears from skin lesions (nodules, ulcers, draining tracts) or lymph nodes show granulomatous changes and should be stained for AFB using, e.g., Ziehl-Neelsen (ZN) staining, although a negative cytology result does not rule out mycobacterial infection. If cytology suggests granulomatous inflammation with or without ZN-positive staining, a biopsy for histology should be obtained, as well as fresh nonfixed samples for culture and PCR. Histopathology in affected cases can vary depending on the mycobacterial species involved (pyogranulomatous or granulomatous inflammation, necrosis, panniculitis, etc.) and allows acid-fast staining with ZN, although organism numbers may be too few to allow visualization. If mycobacterial infection is suspected, it is mandatory to keep fresh biopsy samples frozen without formalin for subsequent culture and PCR. Gloves and aseptic practice are required to handle cytology or biopsy samples from suspected cases due to zoonotic risk.

A positive culture from a fresh tissue sample or FNA is most useful to confirm the diagnosis and identify the species to help guide treatment, prognosis, and assessment of zoonotic risk. However, culture needs to be done in a specialized laboratory, and many species take a long time to grow (2–3 months) or even fail to grow (such as FL species and some forms of NTM infection). Due to these limitations, PCR has evolved as a useful adjunctive test on fresh samples (tissue but also on FNAs and stained smears) that can identify the species quickly, and a positive result can be followed by sequencing in specialized laboratories investigating outbreaks. The availability of PCR testing is limited. Both culture and PCR testing are costly.

Feline interferon gamma (IFN-ɣ) release assay blood testing, currently available in the UK, shows promise for the antemortem diagnosis of TB. The test measures the T-cell response (IFN-ɣ production) in peripheral blood mononuclear cells to three different antigens. The pattern of any positive results identifies whether the cat is infected with a pathogenic or less pathogenic TB complex species and/or whether it has been exposed to environmental NTM species. It is useful to determine whether *M. bovis* and *M. microti* infection is most likely to determine the zoonotic risk to guide treatment in suspected cases.

Management

Treatment/Prognosis

In the case of a diagnosis of disseminated *M. bovis*, it is important to discuss whether cats should be treated at all due to zoonotic implications and concern around antimicrobial resistance developing in human TB as a result of antimicrobial use in cats. In some countries, euthanasia of confirmed cases of *M. bovis* is mandatory. In others, if treatment is being considered, the costs and compliance issues of the long treatment need to be carefully discussed with owners, as well as the recommendation for keeping the cat indoors during treatment. Additionally, owners are advised to contact their own doctor for screening. TB complex treatment comprises 2 months of oral triple therapy with rifampicin (10 mg/kg q.24 h.), a fluoroquinolone (although marbofloxacin [2 mg/kg q.24 h.] may be effective, pradofloxacin [3–5 mg/kg q.24 h.; different dose for tablets versus liquid] is now preferred), and a macrolide (azithromycin (5–15 mg/kg q.24 h.] or clarithromycin (7–15 mg/kg q.12 h.]) is recommended, followed by a further 4- to 7-month treatment with two of these drugs (usually fluoroquinolone and macrolide). If triple therapy is not possible, then two of the drugs should be given for 6–9 months. Hematology and biochemistry should be monitored for possible side effects, especially hepatotoxicity with rifampicin. Rifampicin can discolor body fluids orange and cause anorexia, erythema, pruritus, and anaphylaxis. Clarithromycin can cause pinnal/generalized erythema. More recently, a 3-month course of triple therapy alone, or triple therapy given for 2–3 months beyond resolution of clinical signs or static thoracic imaging abnormalities (typically comprising 4–6 months of treatment), has been described as unpublished observations for the treatment of TB in cats. To aid compliance, medications can be given combined

within a single gelatin capsule, as liquid formulations, or via an esophagostomy tube. Surgery is sometimes used to treat solitary cutaneous lesions but is difficult for diffuse cutaneous disease due to wound dehiscence and local recurrence.

Treatment of MAC complex, slow and rapidly growing NTM depends on the infecting species. Culture and susceptibility results are useful to guide treatment choice, if available. Oral clarithromycin and rifampicin or clofazimine (4–8 mg/kg q.24 h. or q.48 h.) are given for *M. avium* cases, alongside, if possible, doxycycline (5 mg/kg q.12 h. or 10 mg/kg q.24 h.) or pradofloxacin. Other NTM species show variable responses to antibiotics, but generally two or three antibiotics are used. Clarithromycin and pradofloxacin together are good for certain species (e.g., *M. chelonae-abscessus*), while a fluoroquinolone and doxycycline are better for others (e.g., *M. smegmatis*). Treatment should continue 1–2 months beyond clinical resolution; up to 12 months of treatment needed for extensive/systemic infections. Surgical resection may comprise part of the treatment for severe panniculitis case, with reconstructive surgery sometimes needed.

Treatment of FL NTM comprises surgical removal of solitary lesions, which may be curative. If further treatment is required, dual or triple antibiotic treatment should include clarithromycin, rifampicin, pradofloxacin, and/or clofazimine, typically for 2–3 months.

It is hard to assess prognosis accurately, as not all reported cases have been treated appropriately. TB infections have remission rates of 70%–90%, although outbreaks in younger cats have a poor prognosis. Imaging abnormalities only resolve in a few cases. The prognosis for MAC, slow and rapidly growing NTM is variable; good to guarded, depending on the species involved (*M. avium* infections and those with extensive panniculitis, especially due to *M. fortuitum*, are particularly poor). For FL NTM, the prognosis varies from good to poor.

Prevention

There is currently no vaccine available for mycobacteriosis in cats. Restriction of access to potential sources of infection (e.g., prey species) may be difficult in outdoor cats. Although an uncommon source of infection, avoiding the feeding of raw meat diets and unpasteurized milk from sources where TB is endemic is important. Prevention of transmission within veterinary clinics involves the use of hand washes and disinfectants that are mycobactericidal, e.g., 60%–90% alcohols (e.g., Sterillium), halogenated tertiary amines (e.g., Anigene, Anistel), and 3% iodine preparations. Investigations on suspected cases should be performed at the end of the day in well-ventilated rooms, with breathing systems and endotracheal tubes disposed of after use. Strict asepsis is very important, as nosocomial spread of mycobacterial infections has been reported.

Public Health Implications

Despite *M. bovis* being zoonotic and infecting humans, cat-to-human transmission is of very low risk and very rarely reported. *M. microti* is less of a zoonotic concern, with cat-to-human transmission never reported. Of the NTM, only *M. avium* can be zoonotic (in immunosuppressed people). Cat-to-human transmission of NTM has not been reported.

Despite the very low transmission risk with *M. bovis*, the zoonotic potential of this agent is important to be aware of and discuss with owners and personnel in clinics dealing with TB cases. People are at heightened risk of TB infection if they are under 5 years old, are pregnant, are HIV positive, or have other immunocompromising condition. It is generally thought that protracted exposure is required for cat-to-human infection. A single high-dose inoculation could result in transmission of infection, so care is always required. When collecting samples from cats, the zoonotic risk should be considered; inhalation of organisms from cats with respiratory signs/coughing and/or contact with organisms present in draining wounds. A fitted filtering face mask should be worn when in close proximity of coughing cases (e.g., during intubation, collecting BALs) to prevent inhalation. Gloves and protective clothing should be used when handling cases with draining skin lesions to avoid spread to other cats, as well as covering of any open sores/wounds in personnel to prevent zoonotic transmission. If open surgery is required on a suspected TB patient, an appropriately filtered airflow helmet is required. Following euthanasia of a TB patient, cremation rather than burial should be recommended to reduce the risk of environmental contamination.

FELINE LEPTOSPIROSIS

Definition/Overview

Although a significant disease of dogs and humans, the pathogenic role of *Leptospira* in cats in unknown and currently not often clinically recognized.

Etiology

Leptospirosis is mainly a disease of dogs caused by spirochetes of the genus *Leptospira*. Antigenically related serovars are grouped into serogroups. These bacteria are maintained in the environment by mammalian reservoir hosts who shed *Leptospira* in their urine (mainly rodents). Hosts become infected by direct contact with infected urine or indirectly via contaminated soil or surface water. Cats can become infected by these routes but also through ingestion of rodents. They develop antibodies (4%–33.3% depending on geographical location) and shed *Leptospira* in their urine with a prevalence of up to 68%. Therefore, their role as a healthy reservoir host is poorly understood. Outdoor cats are considered to be higher risk. The presence of another cat in the household significantly increases the likelihood of seropositivity.

Pathophysiology

Leptospirosis spreads hematogenously, enabled by the ability to evade the host immune system. Leptospiremia

then occurs, usually lasting around 7 days, creating an often multisystemic disease. After 10 days, *Leptospira* have entered the renal tubules and start to be eliminated in the urine. How long they are shed in the urine of cats is currently unknown, but it has been shown to occur up to 8 months post infection with little to no association with clinical disease. Interstitial nephritis has been documented on renal histopathology of affected cats. Whether this goes on to cause chronic renal damage and insufficiency is unclear.

Clinical Presentation

Clinical signs of acute disease in cats is rare. Further understanding of *Leptospira* as potential pathogen in feline renal disease (both acute and chronic) is needed. In the few case reports available, a possibly longer incubation period compared to dogs has been suggested. Therefore, perhaps there is more of a role as a trigger for chronic kidney disease we are yet to fully understand. Other reported clinical signs in confirmed infected cats have included polyuria, polydipsia, hematuria, uveitis, lameness, lethargy, anorexia, gastrointestinal signs (vomiting and diarrhea), presence of effusions, inflammatory lesions of skin and digits, and nonspecific pain. Hepatic lesions appear to be much less common in cats compared to dogs.

Differential Diagnosis

Chronic kidney disease, urinary tract infection, urolithiasis, pyelonephritis, calicivirus, FIP, leishmania, and other inflammatory/infectious diseases, including babesiosis.

Diagnosis

The need to screen for this disease in cats is debatable given our limited understanding of the importance of the disease in this species. Most affected cats are moderately to severely azotemic on presentation and hyperphosphatemia has been reported. Diagnosis is usually based on demonstration of antibodies (microscopic agglutination titer [MAT] or enzyme-linked immunosorbent assay [ELISA]) and/or *Leptospira* deoxyribonucleic acid (DNA) by blood or urine reverse transcription PCR (RT-PCR; care as previous antibiotic therapy often causes false negatives for this test). For further information, see the canine section.

Management

Treatment/Prognosis

As the pathogenic role is poorly understood in cats, no treatment is currently recommended unless other causes of presenting clinical signs are excluded. The approach to treatment is the same as described in dogs, with additional care over administration of oral doxycycline and risk of esophagitis. Prognosis depends on the severity of organ damage.

Prevention

Vaccination is not currently advised for cats. Reduction or prevention of exposure to stagnant water, predation opportunities, and keeping the cat indoors can help.

Public Health Implications

Leptospirosis is a recognized zoonotic disease as such the role of cats as chronic reservoir hosts/carriers needs further investigation.

FELINE ACTINOMYCOSIS AND NOCARDIOSIS

Definition/Overview

Actinomycosis and nocardiosis are rare chronic infections, reported in both dogs and cats. Disease is caused by a variety of anaerobic (actinomycosis) and aerobic (nocardiosis) actinomycetes.

Etiology

Actinomyces spp. and *Nocardia* spp. are branching, filamentous, Gram-positive bacteria. Both organisms are ubiquitous found in soil. *Actinomyces* spp. also inhabit the oral cavity of cats as normal flora. Infections are opportunistic and usually occur subsequent to mechanical disruption of mucosal barriers, such as inoculation of skin with contaminated plant material or, less often, bite wounds. Actinomycosis is more prevalent, especially in cats, than nocardiosis.

Pathophysiology

Entry and spread of infection depend on the host's immunocompetence. In both infections, hematologic and biochemical findings are nonspecific and typical of any pyogenic inflammatory process. There is usually a leukocytosis with a left shift.

Clinical Presentation

Feline Actinomycosis

Feline actinomycosis is most often associated with subcutaneous cat bite abscess formation or pyothorax. Lymphadenopathy, fever, and weight loss may occur. A viscous, opaque, foul-smelling exudate is characteristic.

Feline Nocardiosis

Feline nocardiosis infections are characterized by suppurative or pyogranulomatous inflammation that can be localized (cutaneous–subcutaneous or pulmonary) or disseminated (systemic with lesions in two or more separate sites such as joints, central nervous system [CNS]). The cutaneous form is the most common and often presents with abscess formation and fistulous tracts with serosanguineous discharge or nonhealing

wounds. The pulmonary form is associated with coughing, dyspnea, fever, and pyothorax.

Differential Diagnosis

Penetrating (subcutaneous) injury, neoplasia, and mycobacterial infections (especially those associated with panniculitis) are among the most important differential diagnoses for actinomycosis. Pneumonia (bacterial, parasitic, viral, or protozoal [toxoplasmosis]) is an important differential diagnosis for nocardiosis. As *Actinomyces* spp. and *Nocardia* spp. are opportunistic pathogens, all infected cats should be tested for FeLV and FIV.

Diagnosis

Feline Actinomycosis

Recovery of multiple bacterial pathogens from the exudate is common. Cytology of samples, e.g., an exudate may reveal so-called yellow sulfur granules (aggregates of bacteria), which can occasionally be visualized without microscopy (Figures 21.2.5 and 21.2.6). Cytologic assessment of exudates is complicated by the presence of mixed bacterial populations, but typically, pyogranulomatous inflammation is present. *Actinomyces* in the exudate may be difficult to visualize, but they should appear as Gram-positive filamentous organisms. Attempts to culture *Actinomyces* spp. from exudates are complicated by bacterial overgrowth and the need for anaerobic conditions.

Feline Nocardiosis

Cytology of exudates can reveal the Gram-positive filamentous organisms, although the presence of mixed bacterial populations is rare. Microscopically, filaments are finer than fungal filaments (less than 1 µm) and can be identified using Bourke's modification of Gram stain. Filaments do not stain with Romanowsky stains. Culture confirms the diagnosis.

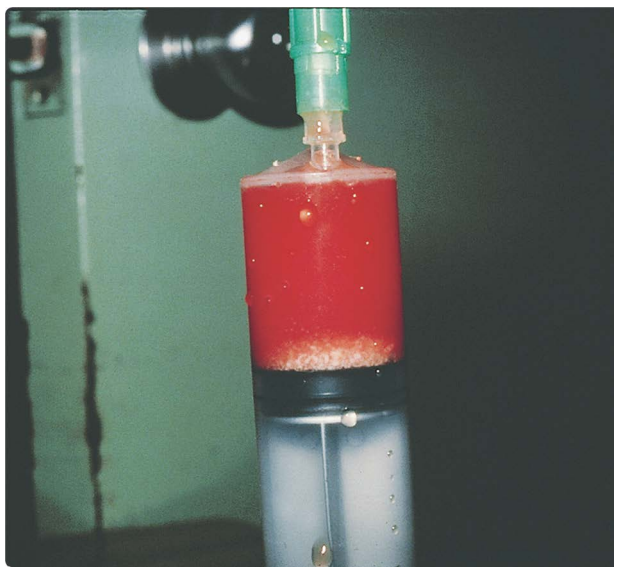


FIGURE 21.2.5 Suppurative exudate containing "sulfur" granules, taken from a feline patient with suppurative pleuritis caused by *Actinomyces* infection, is shown in the syringe.



FIGURE 21.2.6 The cat is having thoracic exudate aspirated through chest drains.

Management

Treatment/Prognosis

Both diseases are best treated with surgical drainage and debridement of affected areas (e.g., abscesses, effusion drainage), except in cases with disseminated infection. Treatment with antimicrobials is essential for weeks because of limited drug penetration of the dense granulomatous tissue.

Feline Actinomycosis

Penicillin G (100,000 U/kg IV or SC q.6–8 h.) or penicillin V (phenoxymethylpenicillin, 40 mg/kg p.o. q.8 h.) is the recommended treatment for feline actinomycosis. Clindamycin, minocycline, erythromycin, and amoxicillin are good alternative antibiotics. Antimicrobial penetration of the granulomas is difficult and, therefore, dictates extended therapy. Once effective drainage has been established, treatment should continue for a minimum of 2 weeks or as long as necessary for clinical and microbiological cure. Once treatment has been initiated, the volume of discharge is frequently reduced. The clinician should attempt to identify the extent of draining tracts and the possibility of a foreign body within the wound site or tract. Treatment is significantly complicated by infections associated with migrating foreign bodies. Animals that fail to respond to initial drainage and antimicrobial therapy should undergo exploratory surgery in an attempt to identify the underlying cause. Assuming that effective drainage can be established, the inciting foreign material removed, and antibiotic therapy administered appropriately, the prognosis for cure is excellent.

Feline Nocardiosis

Feline nocardiosis has a considerably poorer prognosis than actinomycosis. Sulfonamides are the recommended drugs in the management of nocardiosis (e.g.,

trimethoprim-sulfadiazine: 15–30 mg/kg p.o. q.12 h.) and should be administered in gelatin capsules or reformulated for cats to avoid salivation on administration. Doxycycline (5 mg/kg p.o. q.12 h. or 10 mg/kg p.o. q.24 h., with water to follow), in combination with amoxicillin (20 mg/kg p.o. q.12 h.) has also been used. Paradoxically, amoxicillin–clavulanate and fluoroquinolones are not effective. Although response to therapy may be noted within 7–10 days following the onset of treatment, extended treatment periods of 2 months or longer are usually required. Cats that do not have easily resectable nocardial lesions have a poor prognosis.

Prevention

There is currently no vaccine on the market for the prevention of either actinomycosis or nocardiosis in cats.

Public Health Implications

Although human cases of actinomycosis and nocardiosis are reported, human infections are not directly transmitted from infected dogs or cats. Individuals handling material from draining wounds should use normal routine precautions to avoid inadvertent contact with infectious material.

For discussion of tetanus, refer to Chapter 13.

VECTOR-TRANSMITTED PATHOGENS

FELINE BARTONELLOSIS

Definition/Overview

Feline bartonellosis is a flea-borne disease generally attributed to infection with *Bartonella henselae*. Although infected cats rarely show obvious clinical signs of illness, the relationship between feline *B. henselae* infection and human cat scratch disease (CSD) has prompted intensive research. Over 20 species of *Bartonella* are now recognized worldwide, although their role as pathogens in feline and human disease is still poorly understood.

Etiology

Bartonellae are small, Gram-negative intracellular bacteria. Cats are primary reservoirs of three species: *B. henselae*, *B. clarridgeiae*, and *B. koehlerae*. *B. henselae* is present within RBCs ingested by the flea on feeding but is mainly transmitted by inoculation of the skin by infected flea feces (infective for approximately 9 days) present on the cat's claws through scratching. Successful transmission by *Ixodes ricinus* has also been described. In Europe, the antibody prevalence is reported to be 8%–53%.

Pathophysiology

A prolonged (> 1 year), fluctuating bacteremia occurs in infected cats, which are usually young (< 2 years old). When the infection is first acquired, animals may have a transient lymphadenopathy and low-grade fever. Despite the duration of bacteremia, there seem to be no long-lasting effects.

Clinical Presentation

Many infected cats are asymptomatic. In the small number of cases documented, bartonellosis was described as a self-limiting, febrile illness lasting for 2–3 days, with clinical signs of lethargy and mild postural reaction deficits in all limbs. In all cases, the clinical signs resolved without the administration of antimicrobial therapy. Chronically bacteremic cats are typically healthy, as cats act as reservoirs of infection for the host-adapted *B. henselae*. A number of studies have attempted to link clinical signs or laboratory abnormalities with *Bartonella* seropositivity, including hyperglobulinemia, urinary tract disease, hematuria, CNS disease, and osteoarthritis, but the strength of evidence in these reports has been variable. Additionally, response to treatment for *Bartonella* has been documented in case reports of feline uveitis, endocarditis, and myocarditis.

Differential Diagnosis

Since experimental infections have demonstrated transient pyrexia, mild anemia, localized or generalized lymphadenopathy, and/or mild CNS signs, bartonellosis could reasonably be included in the differential diagnosis list for cats with any of those presenting signs. FeLV and FIV testing is indicated.

Diagnosis

Seropositivity (IFA or ELISA) is common among healthy cats and generally only denotes prior exposure to any of several genetic varieties of *Bartonellae*. Positive serologic results do not appear to be related to bacteremia. Therefore, serology is more useful to exclude *Bartonella* from the differential diagnosis list. Currently, blood or tissue culture remains the preferred means of confirming the diagnosis, but these tests might need to be performed repeatedly to avoid false-negative results from fluctuating bacteremia and again do not prove disease causation due to high prevalence in healthy cats. PCR testing can be performed on blood, aqueous humor, oropharyngeal swabs, and CSF or tissue aspirates, and submission of multiple specimen types from a single case increases test sensitivity.

Management

Treatment/Prognosis

Although marbofloxacin (5 mg/kg p.o. q.12–24 h. for 6 weeks) or doxycycline (5 mg/kg p.o. q.12 h. or 10 mg/kg p.o. q.24 h. for 2–4 weeks) is the recommended treatment, failure to clear infection is still common. Azithromycin (10 mg/kg p.o. q.24 h. for 7 days,

followed by 10 mg/kg p.o. q.48 h. for 6–12 weeks) and amoxicillin–clavulanate (62.5 mg p.o. q.12 h. for 2 months) have also been reported to resolve infection. However, because clinical disease is seldom associated with infection, the value of treating infected cats may be limited to households in which cats reside with immunocompromised humans.

Prevention

There is currently no vaccine available for bartonellosis in cats. However, effective flea and tick management is deemed to be a prudent means of minimizing the risk of infection. Blood donors should be screened for *Bartonella* antibodies. Avoid rough play and ensure cats' claws remained trimmed.

Public Health Implications

A variety of clinical disorders in humans (e.g., bacillary angiomatosis, peliosis, relapsing fever, neuroretinitis, uveitis, endocarditis, and neurologic disorders), as well as CSD, have been associated with *Bartonella* spp. infection. Infections are most profound in people with human immunodeficiency virus (HIV) and other causes of immunosuppression. Although infections do develop in immunocompetent individuals, these infections tend to be subclinical or localized to regional lymph nodes.

There is a strong relationship between *B. henselae* infection and human CSD. Despite the fact that CSD in humans has for years been associated with cat scratches, there is considerable speculation as to the actual means of transmission between cats and humans. Currently, it appears that feline saliva is not an effective means of transmitting *B. henselae* to humans. However, there is increased awareness of the important role played by fleas in human infections, so the risk of exposure to arthropod vectors, not only to cats, should be considered in suspected human infections.

PLAGUE

Definition/Overview

Plague is an uncommon infection of cats caused by the facultative anaerobic, Gram-negative bacterium *Yersinia pestis* transmitted by *Xenopsylla cheopis* fleas. The organism has been sustained for centuries by chronic bacteremia in wild rodents and prairie dogs. In the United States, reported cases of plague have a seasonal distribution, corresponding to when rodents and fleas are most active, and humans are most likely to be outdoors (February–August).

Although infections in domestic animals are uncommon, the fact that both domestic and feral cats are susceptible to *Y. pestis* infection, and that cats are a documented source of human infection, means that plague must be regarded as a significant zoonotic infection of cats. Although dogs can become infected, their susceptibility is considerably less than cats.

Etiology

Transmission of the bacterium to susceptible hosts occurs predominantly through flea bites or the ingestion of infected rodents or lagomorphs; humans, dogs, and cats are usually accidental hosts and are not responsible for the transmission of infection. However, infection can also be transmitted directly through contact with broken skin or by inhalation of infectious microdroplets from cats or humans infected with the pneumonic form of plague.

Pathophysiology

The incubation period depends on the route of entry of the organism: 2–6 days with flea bites; 1–3 days after inhalation or ingestion. Typically, there is evidence of neutrophilic leukocytosis with a left shift and lymphopenia, hyperglycemia, azotemia, hypokalemia, hypoalbuminemia, hyperglobulinemia, hypochloremia, hyperbilirubinemia, and increased alkaline phosphatase (ALP) and alanine aminotransferase (ALT) activity.

Clinical Presentation

Three clinical forms of *Y. pestis* infection have been recognized in cats: Bubonic (most common), septicemic, and pneumonic. Following ingestion of infected rodents, cats that become infected typically develop fever, necrotic stomatitis, and lymphadenomegaly (due to suppurative lymphadenitis), particularly around the head and neck. Lymph nodes may rupture and drain through to the skin surface. Subsequently, septicemia may develop in a small number of cats (septicemic plague). Fever, shock, disseminated intravascular coagulation (DIC), and pneumonitis are short-lived signs that precede death. Hematogenous spread of the organism to the lungs in cats culminates in pneumonic plague, which is particularly likely to be fatal.

Within endemic areas (particularly the Southwestern United States and western coastal states), cats presented with persistent fever, lymph node enlargement, tonsillar enlargement, necrotic stomatitis, facial ulceration, or abdominal distension should be evaluated for plague.

Differential Diagnosis

Any cat living in, or from, a plague-endemic area should be considered suspect if presented for stomatitis, chronic respiratory disease, and/or lymphadenomegaly. Feline frontal sinusitis/rhinitis, sepsis, neoplasia, toxemia, pyometra, and lymphoma are important differential diagnoses for feline plague.

Diagnosis

Diagnosis of feline plague is based on identification of the organism collected from cultured tissue, fluid, or blood. Smears can be made from aspirates collected from draining lesions and enlarged lymph nodes; Gram-negative bacteria with a bipolar safety pin shape can be visualized. Cultures from tonsils are reported to

be particularly important in confirming a diagnosis; however, recent antimicrobial treatment might cause false-negative results. Colonies might take 48 hours to appear; they are a significant biohazard and should be sent to recommended laboratories obtained on the advice of local public health authorities. Acute and convalescent antibody titers can also be used to document infection. Since the incubation period is relatively short (1–6 days), seronegative results can occur initially in infected cats. A fourfold rise in antibody titer over 3–4 weeks is necessary to distinguish active disease from prior exposure. Because of the zoonotic potential of feline plague, attempts to culture the organism in a veterinary practice are discouraged. IFA testing can be performed on heat fixed slides of tissue aspirates or on impression smears collected at necropsy and submitted to recommended testing facilities. Specimens should not be shipped to routine veterinary diagnostic laboratories; local public health authorities should be contacted regarding approved testing laboratories and specific shipping instructions.

Management

Treatment/Prognosis

Because of the time delay involved in confirming a diagnosis, treatment is typically initiated pending results. Medical management of suspected cases includes treatment for fleas, flushing abscesses or draining lymph nodes, and administering antimicrobial therapy for a minimum of 10 days. It is particularly important that all cats suspected of having plague be handled by persons wearing full personal protective equipment, including examination gloves, gowns, and a surgical mask and goggles or a full face mask. Extreme care should be taken when working with cats that manifest signs of pneumonia. All suspect cases should be isolated for at least the first 4 days of antimicrobial therapy, and the number of people in contact with the case should be reduced to the bare minimum.

Although several antimicrobials have been effective against *Y. pestis* in cats, drug resistant strains are being isolated with increasing frequency. Administration of doxycycline (10 mg/kg IV or p.o. q.24 h. 10 days; administer IV diluted in 100 mL of lactated Ringer's solution over 2 hours) is recommended. Parenteral treatment is recommended for at least the first 72 hours to avoid contact with the oral cavity of infected cats. Alternatively, aminoglycosides (gentamicin [5–8 mg/kg IV, IM, or SC q.24 h. for 10 days], chloramphenicol [25–50 mg/kg p.o. q.12 h. for 10 days; 12–30 mg/kg IV, IM, or SC q.12 h. for 10 days], and trimethoprim–sulfamethoxazole [30 mg/kg p.o. q.12 h. for 10 days]) also have efficacy against *Y. pestis*. Cats that have been exposed to plague may be treated prophylactically with doxycycline (10 mg/kg IV or p.o. q.24 h. for at least 7 days). The prognosis for cats with clinical signs associated with plague depends on treatment status. Up to 75% of infected cats may die if untreated, but > 90% of cats treated with appropriate antimicrobial therapy survive.

Prevention

Effective flea control is the best means of preventing infection. In addition, dogs and cats should be restricted from hunting and access to carcasses of dead rodents or rabbits.

Public Health Implications

Humans most commonly become infected by infected flea bites, but inhalation and direct contact are other possible routes of infection. The risk of human exposure to plague appears to be greatest in the Western United States, particularly California, Arizona, and New Mexico. Because human plague infection, particularly pneumonic plague, has a significant mortality rate, veterinarians working in endemic areas should be particularly alert to potential infections in cats. Because domestic animal cases are now relatively rare, underrecognition could be problematic. Furthermore, there appears to be an increased risk of exposure when maintaining and treating nondomestic cats living in endemic areas. Attempts should be made to limit exposure to these potential carriers.

FELINE BABESIOSIS

See also Chapter 21.1.

Definition/Overview

Cats appear less predisposed to babesiosis when compared to dogs, so little is known about common clinical signs and/or disease course. Multiple *Babesia* species have been identified in cats, but *Babesia felis sensu stricto* is the most clinically important. Younger cats (< 3 years old), Siamese, and Oriental cats appear predisposed, with the disease being more prevalent in the summer months, most likely due to increased activity of the assumed tick vector.

Etiology

Babesia is a protozoa piroplasm endemic worldwide, mostly South Africa. The small *Babesia felis sensu stricto* is the important pathogenic species in cats. The definitive tick vector has not yet been identified. Transmission studies are also lacking.

Pathophysiology

Babesia species replicate in red blood cells (RBCs) to form merozoites. Ticks are infected by ingesting merozoites during feeding. Merozoites replicate within the tick salivary gland to form sporozoites. Maturation of the sporozoites occurs at the time of tick attachment, thus requiring an attachment time of 2–3 days before transmission can occur. When infected ticks feed, the sporozoites are then regurgitated into the host bloodstream. The subsequent intraerythrocytic infection leads to a hemolytic anemia. Blood transfusions are another possible method of transmission.

Clinical Presentation

Most clinical signs are attributable to the hemolytic anemia (e.g., pale mucous membranes, lethargy). Pyrexia and jaundice are uncommon. However, clinical signs may be mild due to the chronicity of infection and the cat's ability to adapt to the level of anemia (experimentally does not peak until 3 weeks post infection). More severe clinical signs occur in the presence of coinfections, such as with FeLV/FIV and splenectomized cats. Life-threatening complications include acute kidney injury, hepatopathies, pulmonary compromise, and neurological disorders.

Differential Diagnosis

Primary immune-mediated hemolytic anemia (IMHA); secondary IMHA (to drugs, neoplasia, infections, cytauxzoonosis, retroviruses, babesiosis, Heinz bodies, hypophosphatemia); pyruvate kinase deficiency, and other inherited hematological disorders.

Diagnosis

Whole blood PCR is the diagnostic test of choice. Due to low level of parasitemia, direct visualization of merozoites on blood smear is rare. Bloodwork often reveals a regenerative macrocytic hypochromic anemia, hyperbilirubinemia, moderate-to-marked increases in ALT activity, and increased total protein/hyperglobulinemia due to a polyclonal gammopathy. Coombs and autoagglutination tests can be positive. Serology is not recommended for diagnosis.

Coinfection with other erythrocytic pathogens, including *Mycoplasma* spp., and *Cytauxzoon felis*, has been reported in up to 30% of cases. As vectors for *Bartonella* spp. and *Babesia* spp. overlap, coinfection may also exist in cats, but it has yet to be documented.

Management

Treatment/Prognosis

Primaquine phosphate (0.5–1 mg/kg p.o., IV or IM once or daily for 3 consecutive days). Recrudescence can occur a few weeks later, which if associated with continued clinical signs, repeat treatment is recommended. Doses exceeding 1 mg/kg can be lethal in cats. Chronic, persistent infections and cyclical disease recurrence can occur. Treatment for asymptomatic chronic carriers with persistent parasitemia is not recommended at this time. However, monitoring via routine complete blood count (CBC) evaluation and blood smear analysis is indicated. Mortality rates of 15%–20% are reported in acute severe disease.

Prevention

Effective tick control and reduced exposure to ticks.

Public Health Implications

Feline babesiosis is not a known zoonotic disease.

FELINE ANAPLASMOSIS

Definition/Overview

Anaplasmosis is a tick-borne disease caused by *Anaplasma phagocytophilum*. Estimated prevalence varies widely depending on the geographical location. Although clinical signs are nonspecific, moderate-to-marked thrombocytopenia is the common hematological finding.

Etiology

Anaplasma phagocytophilum is an intracellular Gram-negative bacteria transmitted by the *Ixodes* tick species within 24–48 hours of tick attachment. Rodents and wild ruminants are the most common reservoirs. Blood transfusions are another potential source of infection. Transplacental infection in cats has not been described. In Europe, estimated serological prevalence is 0%–33.3% and in the United States 4.3%–37.6%. Direct pathogen detection via PCR or within a blood smear in Europe is 0%–23.1% and 0%–6.9% in the United States and in a recent study of UK ticks 0.9%. Outdoor cats have an increased risk of disease due to tick exposure. Increased self-grooming of cats compared to dogs may also contribute to species differences.

Pathophysiology

Infection is spread via an infected tick bite. The bacteria invades neutrophils, forming morulae, where it is then spread hematogenously and via lymphatics. The immune function of the neutrophil is compromised, leading to further dissemination of the organism.

Clinical Presentation

Clinical signs of acute disease develop after a 1- to 2-week incubation period, often after only a few days postvector contact. Usually, signs are nonspecific, including lethargy, pyrexia, anorexia, and conjunctivitis. Painful abdomen and limbs have also been reported in up to 30% of cats within one case series. Gingivitis, calculus, weight loss, and neurological signs are also reported but in < 10% of cases. Asymptomatic and chronic infections are rare.

Differential Diagnosis

Feline upper respiratory tract disease (e.g., chlamydia, FHV, FCV), FeLV/FIV, immune-mediated thrombocytopenia (primary or secondary), and other tick-borne disease (including Ehrlichiosis).

Diagnosis

Mild-to-moderate thrombocytopenia is the most common finding, followed by anemia, and should raise suspicion of this disease. Visual detection of morulae within neutrophils raises suspicion but must be confirmed with PCR. PCR can be performed on whole blood, buffy

coat, bone marrow, or splenic samples. False-negative PCR results can occur in chronic infections due to low levels of parasitemia. Rapid serological testing, such as the SNAP 4DX Plus Assay (IDEXX) ELISA are available and can be used in cats. False-negative serology tests could occur early in the course of infection (seroconversion taking approximately 2 weeks' post infection to occur), but false positives can occur due to cross-reaction with other pathogens, such as *Ehrlichia* spp.

Management

Treatment/Prognosis

Doxycycline (10 mg/kg p.o. s.i.d. for 28 days) is the treatment of choice. This should always be administered with food or water to prevent esophagitis. Clinical signs usually rapidly improve following antimicrobial treatment. The exact duration of treatment to ensure clinical resolution in cats is unknown.

Prevention

Effective tick control, regular checking for and removal of ticks and reduced exposure to ticks.

Public Health Implications

Possible cause of granulocytic anaplasmosis in humans.

FELINE CYTAUXZOONOSIS

Definition/Overview

Cytauxzoonosis is mainly a disease found in the United States, but occasionally cats from Europe are affected, although likely caused by different species. Literature suggests that different species vary in their pathogenicity, thus causing both symptomatic and asymptomatic disease. *Cytauxzoon felis* is a tick-borne pathogen causing hemolytic anemia and subsequent jaundice in cats from endemic areas and is further discussed later.

Etiology

Bobcats and pumas are the main reservoir host of this disease and are subclinically affected. The main tick vector in the United States is *Amblyomma americanum*, but *Dermacentor variabilis* has also been shown to be a competent vector. Blood transfusion is another possible method of transmission.

Pathophysiology

In the acute phase of disease, schizont-infected macrophages obstruct blood vessels, disrupting blood flow to various tissues leading to circulatory impairment and multiorgan failure. In addition, merozoites released from macrophages infect red blood cells. This intraerythrocytic infection leads to a hemolytic anemia. The pathogenesis and route of transmission of other *Cytauxzoon* spp. requires further investigation.

Clinical Presentation

Incubation period is 5–20 days. Cats usually present with pyrexia, anorexia, vomiting, depression, icterus, signs of anemia, dyspnea, hepatosplenomegaly, and occasionally coagulation disorders.

Differential Diagnosis

Primary immune-mediated hemolytic anemia (IMHA); secondary IMHA (to drugs, neoplasia, infections, retroviruses, babesiosis, Heinz bodies, hypophosphatemia, and hemoplasmosis); pyruvate kinase deficiency; and other inherited hematological disorders.

Diagnosis

Detection of the organism either cytologically on blood smears, tissue histopathology or PCR from blood, spleen/liver aspirates, bone marrow, or lymph node aspirates. Serology is not commercially available. Routine blood work often reveals a regenerative anemia, neutrophilia, thrombocytopenia may or may not be present, and hyperbilirubinemia. A recent study showed that despite severe histologic evidence of disease there are no pathognomonic thoracic radiographic findings in cats with acute cytauxzoonosis. However, pulmonary infiltrates can occur.

Management

Treatment/Prognosis

Combination therapy with atovaquone (15 mg/kg p.o. q.8 h.) and azithromycin (10 mg/kg p.o. q.24 h.) is the treatment of choice. Diminazene or imidocarb do not perform as well. Other supportive treatment, such as blood transfusions, as necessary. It was previously considered a fatal disease, but many cats will survive and become subclinical carriers with chronic asymptomatic parasitemia.

Prevention

Housing indoors or regular tick prevention is advised. The consensus statements of the European Advisory Board on Cat Disease (ABCD) and the American College of Veterinary Internal Medicine (ACVIM) recommend that in endemic areas only PCR-negative cats should be used as donors.

Public Health Implications

Cytauxzoon felis is not a known zoonotic pathogen.

FELINE LEISHMANIA

Definition/Overview

The prevalence of *Leishmania infantum* in cats is significantly lower than in dogs. Although a rare disease in this species, it still has significance clinically and possibly in disease transmission, with cats being potential reservoirs of infection for sandflies.

Etiology

The disease is transmitted by an infected sandfly feeding on the host. Blood transfusion is another possible method of transmission.

Pathophysiology

The vector infects the host with promastigotes, which transform into amastigotes able to replicate within macrophages and trigger a granulomatous inflammatory reaction. The outcome of infection is based on host immune response, as in dogs. The production of high-level antibody levels also contributes to presenting signs through deposition of immune complexes, for example in the kidneys. The disease is never cured but can remain in a latent/subclinical state for prolonged periods.

Clinical Presentation

Feline leishmaniosis (FeL) is a chronic disease with an incubation period of months to years that is more commonly associated with subclinical infection. However, cats can present similarly to dogs. Nodular, ulcerative, or scaly skin lesions and lymphadenopathy are the most common presenting signs with weight loss, uveitis, and lethargy. Most cases of feline leishmaniosis are immunocompromised due to concurrent FeLV/FIV infection, medication, or other significant comorbidities.

Differential Diagnosis

Conditions which affect the skin should be considered as differential diagnoses such as bacterial infections (abscesses, actinomycosis, nocardiosis, rhodococcosis, mycobacteria, etc.), fungal infections (blastomycosis, cryptococcosis, mycetoma, histoplasmosis, etc.), poxvirus, neoplasia, and foreign body granuloma. Other differentials include leptospirosis, toxoplasmosis, glomerulonephritis, neoplasia, and other chronic immune-mediated/infectious disease.

Diagnosis

Initially, a quantitative antibody test should be performed if clinical signs of FeLV are present. A high antibody titer in this situation is considered diagnostic. If low positive or negative results are obtained, then tests to detect the parasite are warranted. These parasitological tests include cytology/histopathology of skin lesions, PCR (lesions, lymph node, conjunctival swab, or blood), or culture.

Routine blood and urine screening most commonly identifies hyperglobulinemia, mild-to-moderate nonregenerative anemia and proteinuria.

Management

Treatment/Prognosis

Empirical treatment protocols are the same as in dogs; however, controlled clinical studies are lacking. Side effects are also similar, in addition to pruritus in one study. It should also be considered that propylene glycol is among the excipients of the oral miltefosine (Editors' Note: Might not be readily available in the United States) licensed for the treatment of dogs with leishmaniosis, which has been linked to Heinz body formation and decreased feline RBC life span. Prognosis is considered good unless there are significant comorbidities but does not appear to be affected by concurrent FIV infection in one study.

Prevention

General sandfly bite prevention, bearing in mind pyrethroids are toxic to cats. The only pyrethroid formulation licensed for cats is the flumethrin collar, which in field studies did reduce the incidence of FeLV.

Public Health Implication

Leishmaniosis is a zoonotic disease the role of the cat as a potential reservoir of disease requires further study.

VIRAL INFECTIONS

FELINE VIRAL UPPER RESPIRATORY INFECTION

Definition/Overview

Feline viral upper respiratory infection is generally attributable to either or both of two viruses: Herpesvirus (FHV-1) and calicivirus (FCV). It is important to acknowledge that bacterial upper respiratory tract infections with *B. bronchiseptica*, *C. felis*, *M. felis*, *Staphylococcus* spp., and/or *Streptococcus* spp. may concurrently infect cats with FHV-1 or FCV, thereby complicating the course of clinical disease.

While FHV-1 causes fairly uniform clinical disease, several strains of FCV have been identified and are known to vary in their clinical effects, anatomic localization, virulence, and antigenicity. Despite widespread vaccination against FHV-1 and FCV, these viruses still occur very frequently in the domestic cat population, particularly in multiple cat households and animal shelters.

Etiology

Transmission from infected to susceptible cats occurs most commonly by direct contact via ocular/nasal and respiratory secretions and through fomites; airborne transmission is not thought to be important, although sneezed droplets can spray over 1–2 meters. FCV has also been detected in the urine and feces of infected cats and in flea feces. Cats living in high-density populations are known to be particularly susceptible to infection because crowding facilitates viral transmission, and stress reduces immune function as well as precipitating reactivation and shedding. Young kittens may, therefore, acquire infection at an early age, depending on maternally derived antibodies and

subsequent immunity. Those that recover from the acute infection are likely to develop a chronic carrier state with either FHV-1 or FCV. This chronic carrier state usually persists for months to years (likely for life in the case of FHV-1 carriers) and contributes significantly to the persistence of the virus within cat populations, particularly in multicat environments. FHV-1 shedding by carriers is intermittent but can be precipitated by stress or immunosuppressive therapy; FCV shedding is usually constant but can fluctuate in individuals.

Pathophysiology

After initial acute infection, FHV-1 is carried as a latent virus, usually in the trigeminal ganglia. Reactivation and thus intermittent periods of shedding in oronasal and conjunctival secretions may occur for 1–3 weeks following a "stressful" episode (e.g., boarding, general anesthesia, corticosteroid therapy, parturition). During this time, cats may manifest mild clinical signs, but they are capable of shedding virulent virus. High positivity rates (25%–50%) are found in acute upper respiratory tract disease cats when sampled.

It has been reported that 50% of FCV-recovered cats develop a carrier state and shed virus for at least 75 days after infection. Although chronic FCV carriers may shed virus for weeks to possibly years following the initial infection and be clinically well, they shed virus continuously from conjunctival, nasal, and oral secretions and, as such, pose a significant risk to susceptible kittens and adults.

Clinical Presentation

The hallmark clinical sign of acute viral upper respiratory disease (URD) is sneezing and hypersalivation frequently accompanied by a serous to mucopurulent nasal and ocular discharge, dehydration, anorexia, and varying degrees of conjunctival hyperemia and chemosis (Figures 21.2.7 and 21.2.8). Acute URD being defined as < 10 days in duration.



FIGURE 21.2.8 Cat with unilateral conjunctivitis and photophobia due to feline herpesvirus.

Oral ulceration can be common among FCV-infected cats but is relatively uncommon in FHV-1 infections. Ocular signs of conjunctivitis, keratitis, dendritic ulceration (Figure 21.2.9), corneal sequestra, and profound chemosis are more likely to occur in cats with FHV-1 than with FCV. Self-resolving polyarthropathy and pyrexia (limping kitten syndrome) can occur in juvenile cats infected with FCV (Figure 21.2.10), often following acute oral/respiratory signs, but has not been reported in association with FHV-1.

However, attempting to distinguish one viral infection from another on the basis of clinical signs is particularly difficult, and coinfections (predominantly causing pneumonia in kittens) also occur. Clinical signs and history are usually sufficient to make a clinical diagnosis of viral upper respiratory infection. Given the treatment options available, it is not always important to distinguish one viral infection from another, although environmental disinfection requires compounds capable of inactivating enveloped viruses in FCV outbreaks.

FHV-1 carrier cats may manifest with chronic rhinitis because of permanent viral turbinate lysis. Clinical signs characteristically resolve during periods



FIGURE 21.2.7 Bilateral conjunctivitis and keratitis in a kitten caused by an upper respiratory virus. (*Courtesy of M. Schaer.*)



FIGURE 21.2.9 Keratoconjunctivitis and dendritic ulcer in an adult cat with recrudescent feline herpesvirus infection.



FIGURE 21.2.10 Siamese cat with a hunched posture associated with diffuse polyarthropathy caused by feline calicivirus. (*Courtesy of M. Schaer*.)

of antimicrobial administration, only to reappear following discontinuation of the drug. Chronic immune-mediated signs associated with viral infection, such as stromal keratitis (FHV-1) and gingivostomatitis (FCV) can occur.

Virulent-systemic feline calicivirus (VS-FCV) strains have different pathogenesis and clinical presentation. They are detailed in further section.

Differential Diagnosis

Ocular signs of acute viral upper respiratory infection in kittens, such as severe conjunctivitis and chemosis, may be consistent with *C. felis* infection, although the viral infection is characteristically associated with more severe respiratory signs. *Bordetella bronchiseptica* may cause opportunistic infections culminating in pneumonia and sudden death among kittens with acute viral respiratory disease. *M. felis* infection can cause acute upper respiratory and/or ocular signs and is a cause of bacterial pneumonia in cats.

Diagnosis

Commercial veterinary laboratories offer PCR testing for feline upper respiratory tract pathogens, including FHV-1 and FCV. A sterile cotton-tipped swab with a plastic (not wooden) stem is used to collect specimens from the conjunctival sac and tongue/oropharynx (preferred if only one site possible). The swab should be transported in a plain sterile tube that does not contain transport medium. Because of the high number of vaccinates and the frequency of chronic carrier cats, serology has not been a valuable aid. Due to its high sensitivity, a quantitative PCR can further guide on the importance of a positive sample and must always be interpreted in view of the presenting clinical signs. Topical anesthetics and fluorescein could affect the PCR sensitivity. A negative result does not rule out infection. Other pathogens can also be screened for using the same sample. Serology is of limited value for diagnosis.

Management

Treatment/Prognosis

The focus of treatment for cats with viral upper respiratory infection, whether it be FHV-1 or FCV, centers around the ability to provide good nursing care, enteral nutrition, fluid and electrolyte replacement, and antimicrobial therapy to combat secondary bacterial infection. Doxycycline (10 mg/kg p.o. q.24 h. for 7–10 days) is a good empiric choice, as it is also effective against *C. felis*, *B. bronchiseptica*, and *M. felis*. Dehydration results from reduced food and fluid intake and losses via secretions, which can be copious. In severe cases, dyspnea can occur. Placement of a nasoesophageal or esophagostomy feeding tube facilitates the administration of fluids and calories to affected cats (Figure 21.2.11). Regular saline nebulization (q.4–6 h. for approximately 15 minutes) can help loosen secretions, reduce congestion, and improve comfort. Intermittent saline nasal flushing, eye drops, and mucolytic agents (e.g., bromhexine) can also be helpful. There is no evidence for the use of maropitant specifically for these pathogens, but it is sometimes used in cats with upper respiratory tract disease. Following rehydration, NSAIDs could be considered if necessary to reduce pain and pyrexia.

There is no antiviral therapy registered for use in FHV-1- or FCV-infected cats. The popular anti-herpesvirus drug used in human herpesvirus infection, acyclovir, has been studied in cats and shown not to be effective against FHV-1. It can cause leukopenia and anemia, which are reversible when therapy is discontinued. There have been promising reports of favorable responses to treatment with famciclovir in cats naturally infected with FHV-1, but these have mostly been anecdotal or the result of uncontrolled studies. Dose and dose frequency are critical with this drug, and the cost of therapy at the currently recommended dose rate of 90 mg/kg q.12 h. is prohibitive in most cases. However,



FIGURE 21.2.11 A nasoesophageal tube being used to provide fluids and calories to an anorexic cat with acute viral upper respiratory tract infection. (*Courtesy of the Feline Centre, Langford Vets, University of Bristol*.)

in cats with ulcerative keratitis associated with FHV-1, ophthalmic trifluridine (1% solution) can be administered topically at 4- to 6-hour intervals until 1 week beyond resolution of clinical signs. A commercially available hyperimmune serum containing antibodies to FHV-1, FCV, and FPV is available in some countries. In the limited studies available, cats showed more rapid clinical improvement initially when compared to placebo. However, this benefit was lost at day 7, so the treatment benefit is questionable. Studies do not suggest the use of feline interferon-omega or oral L-lysine show any additional benefit beyond routine symptomatic treatment in acute respiratory disease.

The prognosis for recovery from acute viral upper respiratory infection is excellent if supportive care is provided and the cat housed to avoid known risk factors for clinical disease, such as stress due to overcrowding. In the absence of treatment, most infections are self-limiting in 10–14 days. However, secondary bacterial infections can become severe. Complicating pneumonia is especially devastating in kittens, particularly if *B. bronchiseptica* is involved, and may culminate in high mortality rates among litters of affected kittens. The long-term prognosis is dependent on the establishment of a chronic carrier state and, potentially, anatomic damage to the eye and turbinates (FHV-1) or the development of chronic oral conditions, which are thought to be FCV related. Associated clinical signs of infection in cats recovered from acute infection are usually intermittent (sneezing, ocular and nasal discharge) but can be continuous (ocular and/or nasal discharge, sneezing, gingivostomatitis). Following recovery from acute infection, development of a carrier state is common for both viruses. It is thought that many FCV-infected cats will develop a carrier state for months to years following infection, and almost all FHV-1 infected cats develop a carrier state following recovery that will persist for the life of the cat.

Prevention

Environmental and hygiene factors are important. FHV-1 is an enveloped DNA virus that is extremely labile outside the host, being inactivated within a few minutes at 56°C and by most commercial disinfectants, so except in situations with densely housed cats (e.g., catteries), environmental contamination is not a common source of infection. FCV, on the other hand, is an unenveloped ribonucleic acid (RNA) virus that can survive outside the host for up to a month on dry surfaces at room temperature and is not susceptible to some commonly used disinfectants, such as quaternary ammonium compounds. Effective substances include sodium hypochlorite (5% bleach diluted at 1:32), potassium peroxymonosulfate, chlorine dioxide, and other virucidal approved commercial products. Washing of laundry including bedding at > 60°C is also advised. Limiting cat group sizes, quarantine of new cats, separating sick cats, limiting new cat introductions, and regular flea prevention also all help in prevention by reducing stress and exposure.

Parenteral (killed and modified live) and topical (intranasal/intraocular) vaccines are commercially available in some countries. Vaccination helps protect cats from the severe effects of clinical disease but not against infection/becoming carriers. Intranasal vaccination should only be administered with a vaccine approved for use by this route, and mild sneezing is common for 3–5 days after vaccination. However, severe clinical upper respiratory signs can occur if injectable vaccines are administered intranasally. Current recommendation is that boosters are administered every 3 years from 1 year after the primary series (Table 21.2.1). Measurement of antibody testing against FHV-1 or FCV can be used before vaccination to determine if a booster is required, as effective immunity against both of these agents requires both an antibody response and cell-mediated immunity, and correlation between antibody levels and protection is poor.

Public Health Implications

Despite concerns that human infection can result from contact with an infected cat, the infections must be considered independent. Neither FHV-1 nor FCV is considered to be a human pathogen and, as such, poses no risk to human health.

VIRULENT SYSTEMIC CALICIVIRUS INFECTION

Definition/Overview

A small number of infectious disease outbreaks within cluster households of cats has been associated with a VS-FCV. Initially reported as "hemorrhagic FCV," the limited number of infections caused by this highly infectious emerging pathogen has resulted in mortality rates of up to 70% in previously healthy adult cats. Prior vaccination with a combination FHV-1/FCV vaccine for the prevention of upper respiratory infections may not provide cross-protection against the VS-FCV because in every outbreak of VS-FCV, a genetically distinct strain of FCV has been involved.

Etiology

The ability of FCV to infect cats whether or not they are vaccinated, and for infected cats to develop a chronic carrier state associated with persistent shedding from the nasopharynx, explains the high prevalence of calicivirus in the general cat population. Although each VS-FCV has been associated with a separate mutation of one of the feline caliciviral strains, similar clinical presentations have been reported. Outbreaks have been reported among both vaccinated and unvaccinated cats. Index cases from all reported outbreaks have come from crowded, high-stress environments, such as shelters, rescues, and sometimes veterinary clinics. This highly contagious virus is transmitted by infected cats and their fomites; just a few hairs have acted as fomites and transmitted infection in some outbreaks.

Pathophysiology

Changes in the capsid gene of FCV, or in virus–host interactions, are thought to be responsible for VS-FCV infection. Affected cats develop severe acute systemic illness caused by multiorgan damage, likely due to widespread vasculitis and vascular compromise, systemic inflammatory response syndrome (SIRS), and DIC. Unlike the usual field strains of FCV, adult cats are particularly affected by VS-FCV, perhaps because the immune response to the virus is responsible for some of the clinical manifestations of disease.

Clinical Presentation

Initially, the infection may present as moderate-to-severe upper respiratory infection. However, the disease rapidly progresses, and clinical signs include fever, facial, limb edema, ulceration, and crusting of the face, muzzle, feet, and pinnae. Viral invasion of both epithelium and endothelium occurs, and visceral involvement (lungs, pancreas, liver) with jaundice can occur. DIC can ensue (with overt hemorrhage in some cases), and mortality rates are high (up to 70%), especially among adult cats. Laboratory findings are nonspecific. Necropsy findings include necrosis of major organs such as the liver, spleen, pancreas, lung, and GI tract. Laboratory testing cannot distinguish VS-FCV from regular field strains of FCV, and carriage rates for FCV are high (approximately 25%–30%) among the general feline population.

Similar clinical signs occur in a less fatal manifestation of FCV known as "paw and mouth disease." Whether this is caused by less pathogenic but similar strains of the virus is unknown.

There are currently no specific diagnostic assays for VS-FCV.

Differential Diagnosis

The differential diagnosis includes sepsis, vasculitis, systemic toxicity, envenomation, cutaneous neoplasia, or severe viral upper respiratory infection. Systemic signs may include laboratory and clinical evidence of acute pancreatitis or acute liver failure (e.g., jaundice). Feline panleukopenia virus is a differential diagnosis for sudden death and can also be a comorbid infection, especially in shelter outbreaks.

Diagnosis

In order to identify cases of VS-FCV, it is advisable to both demonstrate FCV infection and confirm antigen in what are otherwise considered unusual sites such as the liver.

Management

Treatment/Prognosis

Because of the high morbidity and mortality associated with outbreaks, deaths usually occur over a relatively short initial period, followed by prolonged clinical recovery for severely ill but surviving cats. If an outbreak can be contained within a population, spread of the virus is typically limited. However, VS-FCV is extremely easily transmitted to other cats by fomites (hands, hair, clothing, food dishes); therefore, strict control procedures, including isolation, quarantine, thorough disinfection with appropriate agents, and the use of disposable personal protective equipment by all personnel in contact with infected or exposed cats must be implemented in order to effectively contain an outbreak. Sadly, there is no clearly defined quarantine period after which cats are guaranteed to be safe. Supportive care is indicated, although the rapid course of infection may not yield effective patient care and long-term survival. If possible, infected cats should be cared for on an outpatient basis by a minimum number of staff. Ideally, catteries, rescues, shelters, and veterinary hospitals should be closed for at least 4 weeks to prevent disease transmission until the outbreak is under control.

Prevention

Population management by reduction of overcrowding in multicat housing and adoption of healthy cats into low-density homes reduces the risk of a VS-FCV outbreak. Vaccines have been introduced into the UK and the United States for the prevention of VS-FCV infection. However, every reported outbreak of VS-FCV has been due to a genetically distinct viral strain. Additionally, protection is not provided until at least 2 weeks after the second vaccination with VS-FCV vaccines because they are inactivated.

Public Health Implications

VS-FCV poses no known threat to human health.

FELINE LOWER RESPIRATORY TRACT VIRAL INFECTION

FELINE POXVIRUS

Definition/Overview

Feline poxvirus is an orthopoxvirus and an emerging feline respiratory pathogen, endemic within Northern Europe.

Etiology

Hunting cats are considered most at risk due to exposure to wild rodent reservoir hosts, with disease incidence peaking in the autumn. There are two forms of clinical feline cowpox that occur as a result of disease, cutaneous and pulmonary. Transmission between cats has been reported, and dry scabs can hold their infectivity in the environment for several months.

Pathophysiology

The primary lesion/site of inoculation is cutaneous, with replication within macrophages and monocytes in local lymph nodes. Following a period of viremia, secondary lesions develop in the lungs and sometimes spleen.

Clinical Presentation

In feline cutaneous poxvirus, lesions are most commonly found on the head, ears, and paws, as infection is most often associated with rodent bite/contact. Multifocal discrete nodular (Figure 21.2.12) or ulcerative/crusting skin lesions and/or dermatitis occur, developing approximately 10 days post infection. Ulcerative oral lesions can develop in up to 20% of infected cases, which contributes to oral pain and anorexia. As ulcerative skin lesions heal, usually spontaneously after 4–5 weeks, round areas of alopecia remain (Figure 21.2.13). Nonspecific systemic signs of viremia follow, including lethargy, pyrexia, and inappetence. In cats affected with the pulmonary poxvirus form, clinical signs will occur due to the effects of a necrotizing pneumonia with or without pleural effusion and/or lung lobe consolidation. The presence of skin lesions and lung lobe consolidation on imaging increases suspicion. Cats in this phase of disease will often present with a cough, and progressive dyspnea will occur.

Skin lesions in pox cases can continue to develop for 6–8 weeks after infection and may take up to 12 weeks to fully resolve.

Multifocal discrete nodular (Figure 21.2.12) or healing ulcerative skin lesions with circular areas of alopecia remaining (Figure 21.2.13).



FIGURE 21.2.12 Multifocal discrete nodular skin lesions with circular areas of alopecia in a cat with feline cutaneous poxvirus.

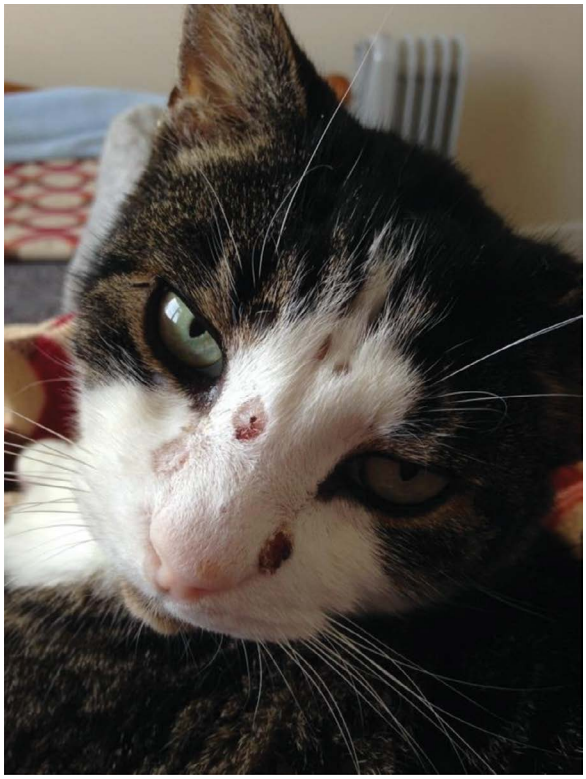


FIGURE 21.2.13 Multifocal discrete healing ulcerative skin lesions on the face of a cat with feline cutaneous poxvirus. Note the circular areas of alopecia surrounding the healing ulcers.

Differential Diagnosis

Dermatologic cryptococcosis; other mycoses, mycobacteriosis, nocardiosis, neoplasia (e.g., squamous cell carcinoma), herpetic dermatitis, and eosinophilic granuloma complex.

Diagnosis

For feline cutaneous poxvirus, diagnosis revolves around sampling of the abnormal skin lesions. Samples of skin lesions (dry scab/skin biopsy) are submitted for virus detection using PCR (most common; rapid result), culture (> 7 days until result), electron microscopy, or visualization of inclusion bodies on histopathology. Paired serology is possible, with titers rising 2 weeks following infection, but is not commonly available.

In diagnosis of feline pulmonary poxvirus, similar diagnostic tests are available for fluid or tissue samples obtained. Those most likely available would be pleural or bronchoalveolar lavage (BAL) fluid. Other options include lung fine-needle aspirate or oropharyngeal swabs. Cytology of respiratory fluid samples are usually predominantly neutrophilic.

Thoracic imaging can assist in the diagnosis and treatment through detection of pneumonia, pleural effusion, and lung lobe consolidation, which increases index of suspicion.

Management

Treatment/Prognosis

Barrier nursing of the affected patient is required. As a virus, no specific treatment is available; therefore, supportive therapy is paramount. Cats suffering with pleural effusion and subsequent respiratory compromise require oxygen therapy and therapeutic thoracocentesis. If tolerated, saline nebulization can help expel excessive respiratory secretions associated with the necrotizing pneumonia. In addition, nutritional support, such as a nasoesophageal feeding tube, and antinausea medication may be required. Skin nodules often progress to ulcers to ulcerated scabs, so it is important to prevent secondary skin infections through topical management/skin cleaning if needed. There is no current supportive evidence for antiviral or interferon treatment. In the few case studies available, some cats had coinfections with other pathogens, which caused more severe clinical signs (e.g., FeLV/FIV, herpesvirus), so testing for these should also be considered.

There are a few factors considered to affect prognosis. These include the poxvirus strain, the route and site of infection (pulmonary is worse), dose of inoculated virus, and the presence of systemic immunosuppression (e.g., FeLV/FIV or concurrent immunosuppressive glucocorticoid treatment).

Prevention

There is no vaccination currently available. Reducing exposure to reservoir hosts and keeping cats indoors are potential options. Prolonged survival in the environment can occur, as such appropriate disinfection of affected areas is needed following a confirmed case.

Effective products against feline poxvirus include 0.8% sodium hydroxide, 1% sodium hypochlorite (bleach), quaternary ammonium compounds, 3% iodine and phenolic compounds, 0.2% chloramine T.

Public Health Implications

Feline poxvirus is a known zoonosis, usually causing mild and self-limiting pustular skin lesions of the hands and face (contact areas) in humans. However, severe and fatal cases can occur. Gloves must be worn at all times during handling of suspected cases.

FELINE RETROVIRUS INFECTION

FELINE LEUKEMIA VIRUS

Definition/Overview

FeLV is a single-stranded RNA virus (oncornavirus) belonging to the retrovirus group. FeLV is a pathogenic, oncogenic (tumor-producing) virus that replicates within numerous tissues in cats, including bone marrow, salivary glands, and epithelial cells.

Etiology

The virus is spread both vertically (in utero or through milk) and horizontally (from cat to cat) usually through "friendly" contact, such as mutual grooming, but also through bites. FeLV does not survive for long outside the host under dry conditions and is readily inactivated by disinfectants, soap, heating, and drying. Although transmission via fomites is very unlikely, small amounts of virus can survive for at least 48 hours if kept moist at room temperature. Transmission via blood transfusions can also occur. Subtypes A, B, C, and T exist; the FeLV-A subtype is ubiquitous and present in all infections. The virus has worldwide distribution.

Pathophysiology

The biology of FeLV infection in cats is highly complex. Susceptibility to FeLV infection is greatest in kittens under 4 months of age. Following FeLV infection, usually via the oronasal mucosa after constant exposure to chronically shedding cats or via a bite wound, FeLV viral replication occurs in local lymphoid tissues. During replication, FeLV RNA integrates into the host feline cells, producing proviral DNA via FeLV reverse transcriptase; this proviral DNA can be detected by PCR testing. The FeLV can then spread via circulating monocytes and lymphocytes to other lymphoid tissues. This equates to the "primary viremia," which is associated with the presence of free p27 FeLV antigen in the blood, detectable by screening tests. If the FeLV is not contained by the immune response and is able to reach the bone marrow, viral replication occurs in the bone marrow so that neutrophil and platelet precursors become FeLV infected. This bone marrow stage is associated with the presence of cell-associated p27 FeLV antigen in the blood, which can be detected by the immunofluorescence antibody (IFA) test. Thereafter, if the FeLV is still not contained, other granulocytes become infected, and the "secondary viremia" occurs, which allows spread of FeLV throughout the body, including in epithelial cells. FeLV virus is shed in high amounts in saliva and nasal secretions with lower amounts in urine and feces (and milk if lactating). This full course of infection is only completed in progressively infected cats. In cats in which the immune response is able to contain the FeLV before this course is completed, regressive or abortive infection results, depending on the time at which the cat's immune response is effective.

The outcome of FeLV infection is influenced by factors such as age of the cat (younger cats more susceptible to progressive infection), the strain/pathogenicity of FeLV, the infectious pressure, and the immune response of the host. These factors influence the balance between the host and the virus. Although suppression of the virus by the host immune response, when it occurs, usually happens within a few weeks of FeLV exposure, it can take many weeks or months for the immune response to gain the upper hand over the virus.

There are three main possible outcomes of FeLV infection in cats:

1. *Progressive infection:* Extensive virus replication occurs in the lymphoid tissues and then in the bone marrow and epithelial tissues, with shedding of infectious virus. Progressively infected cats become p27 antigen positive within 2–3 weeks (and always by 6 weeks) of FeLV exposure and remain so lifelong, with persistent high levels of FeLV (viral) RNA and proviral DNA in the blood. Indeed, FeLV proviral DNA and plasma viral RNA are usually detectable by PCR in the blood within 1–2 weeks of FeLV exposure, often before blood FeLV p27 antigen is detectable. These cats are usually confirmed as being progressively FeLV infected by repeat positive p27 antigen testing after several weeks.

Progressive infected cats often develop FeLV-associated disease, e.g., lymphoma, nonregenerative anemia, leukemia, opportunistic infections, and/or immunodeficiencies, after which the prognosis is poor, although some can survive for long periods with proper care.

2. *Regressive infection:* Fortunately, most FeLV infected cats undergo regressive infection and are unlikely to develop FeLV-related disease. Here, sufficient FeLV-specific immunity (viral neutralizing antibodies and cytotoxic T-lymphocytes) occurs so that FeLV replication is contained before or at the time of bone marrow infection. Despite the FeLV-specific immunity that occurs in regressive infections, FeLV is still integrated into the genome of infected cells permanently, and this may or may not be accompanied by transient viral shedding (i.e., a transient viremia). Cats that do not undergo viral shedding remain negative on p27 antigen blood tests throughout. Cats that do undergo transient viral shedding are transiently p27 antigenemic within 2–3 weeks of FeLV exposure, with shedding usually completed by 4 weeks (but can be up to 16 weeks) post infection. The length of this transient shedding determines the optimal time period between repeat p27 antigen testing following a positive result to differentiate between progressive (continually p27 antigen positive) and regressive (becomes p27 antigen negative) infections. Waiting 16 weeks for retesting is quite lengthy, so a compromise of 6 weeks before retesting is advised. The eventual negative p27 antigen test that occurs in regressive infection readily distinguishes it from progressive infection. Additionally, blood loads of FeLV proviral DNA and viral RNA also eventually distinguish between progressive and regressive FeLV infection because, although both progressive and regressive infections are associated with similar high blood proviral DNA and viral RNA loads during initial infection, levels of proviral and viral RNA subsequently fall in regressively infected cats compared to progressively infected cats.

It had been thought that regressively infected cats were at little risk of developing FeLV-associated diseases, with provirus presence contributing to protection from FeLV-associated disease, but reactivation of infection and ensuing viral replication in cats has been reported, albeit uncommonly, and can be associated with lymphoma. The risk of reactivation of viremia is said to decrease over time. Others have suggested that the regressive state itself, without reactivation of viremia, may be associated with clinical disease such as lymphoma and bone marrow suppression.

3. *Abortive infection:* These cats mount an effective immune response on exposure to low doses of FeLV early in infection. They never test provirus PCR positive or p27 antigen positive at any stage but are identified by the presence of anti-FeLV antibodies (more specifically antibodies to FeLV p15E protein, an envelope transmembrane protein), a test for which has recently become available. It used to be thought that abortive outcome of FeLV infection was rather uncommon compared to regressive and progressive infection, but more recent data suggest that it is a very common outcome of FeLV infection, unless there is intense infectious pressure, comorbidities, or stress, in which case regressive or progressive infections are more common.

Additionally, focal or atypical infections have been rarely described where anatomically localized viral replication (e.g., in the bladder, eyes, mammary glands) exists that can result in intermittent p27 antigenemia, with accompanying positive p27 ELISA test results. Weak positive, discordant, or fluctuating positive/negative p27 ELISA results can occur.

Clinical Presentation

FeLV infection risk factors identified include mixed-breed, outdoor access, male gender, entire status, living in multicat environments with five or more cats, originating from geographic areas with a high FeLV prevalence, and/or lack of FeLV vaccination and being sick. Clinical signs of FeLV infection are highly variable and potentially involve any organ system. FeLV-infected cats are at risk of developing solid tumors (e.g., lymphoma) or leukemia, bone marrow suppression involving leukocytes and erythrocytes, and increased susceptibility to bacterial, viral, and/or fungal infections. Immune complex disease affecting renal function and causing polyarthritis has also been documented, as have reproductive (including embryonic deaths and stillbirths) and CNS disorders.

Differential Diagnosis

Cats presenting with any chronic, debilitating illness, fever, or weight loss should be tested for FeLV, regardless of age. Chronic upper respiratory infection, stomatitis, gingivitis, and periodontitis are common respiratory/oral signs that justify testing. Since FeLV has oncogenic potential, cats with neoplasia, especially lymphoid tumors, should be tested. Hematologic abnormalities such as nonregenerative anemia, lymphoblastic leukemia, leukopenia, thrombocytopenia, or thrombocytosis (> 1 million platelets/mm^3) can be associated with FeLV.

Diagnosis

Because of the nonspecific nature of clinical signs associated with FeLV infection, it is essential that FeLV testing is performed on sick cats presented for evaluation that may have been exposed to FeLV. Additionally, FeLV testing is recommended after cats are acquired, before FeLV vaccination and following potential exposure to an infected cat. Testing is done on blood samples.

Most point-of-care tests detect free FeLV p27 antigen in the blood of infected cats, often as an ELISA or rapid immunomigration tests, and these are used as screening tests. Many have good sensitivity and specificity, with positive results occurring 2–3 weeks after FeLV infection. However, disease prevalence affects the positive and negative predictive value of any diagnostic test, so false-positive results with these tests are more likely in areas of low FeLV prevalence and in cats with a low risk of infection (e.g., if testing is done in healthy cats pre-vaccination).

IFA testing detects cell-associated FeLV p27 antigen in the blood, within leukocytes on smears, and is a highly specific test, although it only becomes positive about 3 weeks after p27 antigen tests become positive; this is because IFA is only positive if bone marrow infection (which occurs usually about 4–7 [but up to 16] weeks after infection). False negatives are possible with leukopenias. IFA-positive cats are usually progressively infected as most, but not all, with bone marrow infection go on to develop progressive infection rather than revert to regressive infection.

FeLV PCR assays detect either viral RNA (in free virus particles and cell-associated during viral replication) or DNA (provirus, integrated into the cellular genome of the cat) in blood following DNA and RNA extraction. Standard PCR detects FeLV proviral DNA, whereas reverse-transcriptase (RT-)PCR detects FeLV viral RNA. Cats become blood RNA positive within 1 week of FeLV exposure and blood provirus DNA positive within 2 weeks of FeLV exposure. FeLV proviral PCR assays are widely available and generate positive results with both progressive and regressive infections. However, in regressive infections, FeLV proviral loads are lower, and p27 antigenemia and IFA tests are negative, in contrast to progressive infections in which FeLV proviral loads are high, and p27 antigenemia or IFA tests are positive. FeLV viral RNA RT-PCR assays are not widely available but have been used on pooled saliva swabs to determine FeLV prevalence in large-scale studies without blood sampling. An isothermal PCR point-of-care test that amplifies FeLV provirus ± RNA has been described showing some promise, but extraction of DNA and RNA is required, complicating its point-of-care test use.

If initial screening testing with point-of-care screening tests is inconclusive for any reason, testing should be repeated, preferably by a veterinary diagnostic laboratory using IFA or PCR. If a positive result is confirmed, consideration of whether repeat testing (6 weeks later) is indicated to differentiate between regressive and progressive infection. The cat's health status, clinical signs, signalment, and history at the time of testing will all factor into how likely the cat is to have progressive FeLV infection and its associated poor prognosis.

Management

Treatment/Prognosis

Healthy FeLV-infected cats should be housed indoors (or with confined outdoor access), neutered, not fed raw meat, and be kept away from other cats to limit the risk of disease transmission, ideally in single cat households. If this is not possible, cats in contact with an FeLV-infected cat that do not show any evidence of FeLV infection (regressive nor progressive infection) should be vaccinated, although protection cannot be guaranteed. Veterinary checks should be performed on infected cats at least every 6 months. Weight loss, lymphadenopathy, clinical signs of upper respiratory infection (e.g., ocular or nasal discharge), and oral health are particularly important to note, as well as ophthalmic examinations. Routine hematology, serum biochemistry, urinalysis, urine culture, and fecal examination may be indicated and can be done annually.

The prognosis for infected cats is highly variable depending on the stage of infection, host immunity, FeLV strain and specific disease manifested during the course of infection, and the availability of supportive treatment for secondary infections. Although a small percentage of FeLV-positive cats may remain healthy for several years, the prognosis for progressive FeLV is poor. Most progressive infected cats living within cluster households are expected to die within 3 years from the time of diagnosis. One study confirmed that cats infected with FeLV, or dual FeLV and FIV, survived significantly shorter times than uninfected or cats infected with FIV alone. Reduced red blood cell counts at the time of diagnosis of either FeLV or FIV infection is associated with reduced survival time compared to infected cats with normal counts at diagnosis. Progressive infected single household cats given supportive medical care could potentially have longer survival times.

Specific treatment modalities for FeLV-infected cats are directed at the clinical manifestation of illness. Immunomodulatory and antiretroviral treatments have been attempted (Table 21.2.2). Results of treatment are highly variable and have not yet been subjected to controlled studies. As in FIV-infected cats, azidothymidine (AZT) and recombinant interferon have been used to treat FeLV-infected cats. The dosage regimens recommended for these products are outlined in Table 21.2.2. Lymphoma is the most common solid tumor associated with FeLV infection. Several chemotherapeutic combinations have been recommended, and administration of corticosteroids is minimally effective as a single-agent treatment modality for FeLV-induced cancer. CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], and prednisone) and CHOP-based protocols are widely used in cats diagnosed with lymphoma and can be successful. A recent study showed an excellent response rate with a novel multidrug

TABLE 21.2.2 Treatment protocols in the management of FeLV

Immunomodulation therapy

- Recombinant human interferon-alpha (rHu-IFN) (Roferon-A, Hoffmann LaRoche) or recombinant feline interferon-ω (rIFN-ω) (Virbagen Omega; Virbac) (the availability of these drugs varies, but the feline product is preferentially used as human products can induce neutralizing antibodies)
  - Various dosing regimens are described for rHu-IFN
    - *High dose:* 1,000–10,000 U/kg IM q.24 h. for 3–7 weeks; treatment beyond this period is associated with anti-interferon antibody
    - *Low dose:* 30 U p.o. q.24 h. for life
  - Various dosing regimens are described for rIFN-ω
    - *High dose:* 1 million U/kg SQ s.i.d. for 5 consecutive days for 3 courses starting on days 0, 14, and 60 (the licensed protocol for Virbagen Omega); has been associated with improved clinical scores and survival, especially in cats that were sick at the start of treatment
    - *Low dose:* 100,000 U/cat p.o. s.i.d. for 90 days

Antiviral therapy

- Azidothymidine (formerly called AZT) (5 mg/kg p.o. or SQ q.12 h.; some use 10 mg/kg p.o. or SQ q.12 h., and this higher dose should be used carefully as side effects can develop—bone marrow toxicity [anemia, neutropenia]—so monitor hematology)
  - Better for FIV infection than FeLV infection, though mild benefits have been reported
  - For SQ injection, the lyophilized product should be diluted in isotonic saline solution to prevent local irritation
  - For p.o. application, syrup or gelatin capsules can be used
- Raltegravir, an oral integrase inhibitor, has been used in experimental FeLV infection but with limited long-term results
  - Treatment was associated with significantly reduced plasma FeLV RNA loads, but then levels rebounded 4 weeks following termination of treatment; this agent does not prevent FeLV viremia

Cytopenia therapy

- Recombinant human erythropoietin (100 IU/kg SC q.48 h. for 2 weeks or until the desired hematocrit is reached)
  - Anti-erythropoietin antibody may develop against exogenous and endogenous erythropoietin, but this appears to be less likely with the longer acting recombinant human erythropoietin (rHuEPO) darbepoetin

lomustine-based chemotherapy protocol (LOPH [lomustine, vincristine, prednisolone and hydroxydaunorubicin]) for cats with high-grade multicentric or mediastinal lymphoma in an area in Brazil endemic for FeLV. In most cases, only cats that achieve complete remission after induction chemotherapy go on to have long-term disease-free status. FeLV status does not affect initial response to chemotherapy, but positive retroviral status negatively affects long-term survival, mostly because of the occurrence of other FeLV-related disorders.

Cats with myelosuppressive disease have a particularly poor prognosis and are best managed with transfusions as needed to resolve the anemia, although this is costly and is needed repeatedly. Recombinant human erythropoietin can be used for clinical signs associated with anemia (hematocrit < 0.2 L/L [20%]) (see Table 21.2.2). FeLV-infected cats with immune-mediated diseases (e.g., immune-mediated hemolytic anemia, immune-mediated polyarthritis) can benefit from the cautious use of oral prednisolone (2 mg/kg per day). FeLV-infected cats with severe gingivostomatitis are most likely to benefit long-term from full mouth extraction, including tooth roots rather than medical management, although appropriate short-term medical options (e.g., recombinant IFN, AZT, or lactoferrin topically [40 mg/kg q.24 h.]) to the oral mucosa can be tried.

RetroMAD1 is a commercially available recombinant chimeric protein. Oral administration of 0.4 mg/kg p.o. q.24 h. to symptomatic cats with progressive FeLV infection in a multicenter trial in Brazil found some improvement in clinical signs (gingivitis, anemia, upper respiratory tract disease) and survival rate compared to untreated cats, although further controlled studies are necessary to corroborate these results before this drug can be recommended.

Prevention

Currently, several vaccine types are available that offer relatively good protection against FeLV. Adjuvanted killed whole virus, recombinant subunit, and a genetically engineered subunit recombinant canary pox vector vaccine exist. FeLV vaccines are usually considered noncore, although the 2020 American Animal Hospital Association and the American Association of Feline Practitioners (AAHA/AAFP) feline vaccination guideline recommends FeLV vaccines as core vaccines for kittens and young adults due to their age-related susceptibility (see Table 21.2.1). Routine testing, as well as vaccination of cats determined to be at risk, are key factors in FeLV prevention. Adult indoor cats are least susceptible to infection. As with any vaccination decision, risk assessment for infection should be made on an individual basis, based on lifestyle factors and local prevalence. None of the currently available FeLV vaccines will cause false-positive tests for FeLV antigen on either screening or IFA tests. FeLV testing should ideally be performed before vaccination to establish FeLV infection status, although the prevalence of FeLV in healthy cats will be low, affecting the positive predictive value of a positive screening test result in this situation. Routine vaccination with core vaccines (e.g., calicivirus) are indicated in FeLV-infected cats that need protection based on their lifestyle. Although killed inactivated, rather than MLV, vaccines are recommended by some for retrovirus infected cats, there is no evidence confirming killed vaccines to be safer.

Public health implications

FeLV in cats is not regarded as a human health hazard.

FELINE IMMUNODEFICIENCY VIRUS

Definition/Overview

First described in 1987, FIV is an RNA retrovirus (lentivirus) infection unique to cats.

Etiology

Transmission among cats occurs primarily through bite wounds and fighting. Blood transfusions can also transmit infection. Vertical transmission of FIV has been reported but is not common. The virus survives only minutes outside the host and is susceptible to all disinfectants.

Pathophysiology

FIV is a lentivirus and, therefore, shares many properties with other retroviruses such as HIV. Many different FIV subtypes with marked nucleotide sequence differences exist with worldwide geographical variation. FIV replicates in lymphoid organs and spreads to other tissues of the body via mononuclear cells during which time the cat may show mild illness (e.g., anorexia, malaise, lymphadenopathy, pyrexia). Viremia peaks a few (8–12) weeks post-infection, after which the level of infection decreases to low levels as the cat mounts an immune response to FIV. Antibodies are produced about 2–6 weeks post infection (although can up to 12 weeks) but are ineffective at clearing infection. Following the initial viremia, the cat enters an asymptomatic period of variable duration (often several years and can be lifelong) during which time progressive dysfunction of the immune system occurs with a reduction in the CD4+-to-CD8+ (T-helper-to-cytotoxic lymphocyte) ratio. This can eventually lead to the development of feline acquired immunodeficiency syndrome (AIDS) characterized by risk of tumors, secondary infections, stomatitis, immune-mediated diseases, and neurologic disorders.

Clinical Presentation

The major risk factors for infection are male gender, entire status, and outdoor access. Cats with illness due to FIV manifest a wide variety of nonspecific clinical signs. Dermatitis, stomatitis, ocular disease, renal insufficiency, lower urinary tract infections, neurologic abnormalities, and opportunistic infections have been reported (Figures 21.2.14 and 21.2.15). FIV infection is significantly associated with the development of lymphoma. However, many cats with FIV infection manifest no clinical signs and can eventually die of unrelated causes. Laboratory findings in cats with FIV infection are often nonspecific and contribute little to establishing a diagnosis of FIV infection. Mild, nonregenerative anemia, neutropenia, lymphopenia, and hypergammaglobulinemia (with a hyperproteinemia) are commonly found on routine hematology and serum biochemistry.

Differential Diagnosis

Any adult cat presented for chronic or debilitating illness, fever, or weight loss should routinely be tested for FIV, as well as FeLV. Cats with anemia, neutropenia, stomatitis, glossitis, lymphoma, or chronic upper respiratory infection should be evaluated for FIV infection. FIP is an important differential diagnosis among FIV-infected cats with significant hypergammaglobulinemia.



FIGURE 21.2.14 Chronic inflammatory skin disease is sometimes diagnosed in cats infected with FIV.

Diagnosis

Detection of FIV-specific antibodies in blood or serum is the most widely accepted means of establishing a diagnosis. Point-of-care ELISA and rapid immunomigration tests are reliable as screening tests for the detection of anti-FIV antibodies, although kits vary in the type of specific FIV antibodies (typically one or two) they test for. However, any positive screening FIV antibody result must be confirmed, especially if the FIV exposure risk is low in the tested cat, due to lower positive predictive value of a positive test with decreasing prevalence of FIV in a population. Interpretation of a positive antibody test in kittens under 6 months of age



FIGURE 21.2.15 Chronic stomatitis in a cat.

is complicated by the fact that maternal antibody from an infected queen may be transferred via the colostrum to kittens. Indeed, most kittens born to an FIV-infected queen will not be infected. Additionally, cats vaccinated against FIV, using the commercially available inactivated (killed) vaccine available in some countries (currently only Australia, New Zealand, and Japan), can be antibody positive on some screening tests in the absence of FIV infection due to vaccine-induced antibodies that can last for at least 7 years after vaccination. In these cases, PCR is indicated to determine true FIV infection.

In some countries Western blotting (WB) and immunofluorescence tests are available to detect a wider range and number of specific FIV antibodies, increasing sensitivity and specificity compared to screening tests that typically detect only one or two specific FIV antibodies. Recent work confirmed the increased sensitivity of WB over screening ELISA tests, suggesting that if cats with a high suspicion of FIV infection are negative on a screening test, they should be further investigated with a more sensitive test such as WB, i.e., unexpected negative results for FIV on screening tests should be followed up as well as unexpected positive results.

FIV PCR tests generally detect FIV provirus, whereas RT-PCR detects FIV RNA; those commercially available usually detect provirus. A positive result is regarded as confirmation of positive FIV status. However, negative FIV PCR results do not necessarily mean that the cat is not infected, as PCR might not detect all subtype strains as there is much variation in sequence among FIV subtypes, making it impossible for single PCR assays to identify all subtypes. Additionally, FIV proviral and viral loads may be low in cat, especially during the asymptomatic period. PCR testing does not detect vaccine virus. As for FeLV, an isothermal PCR point-of-care test that can amplify FIV provirus and RNA has been described, but limitations exist around its use.

Management

Treatment/Prognosis

Healthy FIV-infected cats should be housed indoors (or with confined outdoor access), neutered, not fed raw meat, and be kept away from other cats to limit the risk of disease transmission, ideally in single cat households. Veterinary checks should be performed as for FeLV-infected cats.

It can be many years before an FIV-infected cat develops feline AIDS, and until this time, the cat's quality of life can be excellent, so diagnosis of FIV in a healthy cat is not a reason for euthanasia. Indeed, studies have increasingly shown that FIV-infected cats can survive as long as uninfected cats and that the management and housing conditions of cats might impact on disease progression and survival in FIV-infected cats. This may be due to stress and exposure to (opportunistic) pathogens. Reduced red blood cell counts at the time of diagnosis is associated with reduced survival time.

There is currently no FIV-specific antiviral therapy available. The use of azidothymidine (AZT) as for FeLV (see Table 21.2.2 for dosages) can cause clinical improvement, particularly in FIV-infected cats with stomatitis or neurological disease, and increased CD4+-to-CD8+ ratios in a small number of published studies, but significant side effects, particularly anemia, can occur. AZT-resistant mutant FIV viruses can arise during long-term (years) treatment. Recombinant interferon treatment (see Table 21.2.2) has been associated with improved clinical scores, especially in cats showing clinical signs of gingivitis/gingivostomatitis. Recombinant human erythropoietin (see Table 21.2.2) has improved red and white blood cell counts in experimentally-infected FIV cats.

FIV-infected cats can be susceptible to chronic inflammatory and secondary infections. Supportive treatment is indicated and may, in those cats that respond to treatment, extend the life of the clinically infected cat for several months or years. As for FeLV, routine vaccination with core vaccines should be given in FIV-infected cats that need protection based on their lifestyle.

Prevention

The most effective means of preventing FIV infection is to limit exposure to, and agonistic encounters with, FIV-infected cats that could result in biting. Published studies have demonstrated that casual contact between harmoniously cohabiting FIV-positive and FIV-negative cats over years may not result in viral transmission, despite mutual grooming, minor episodes of aggression, and sharing food and water dishes, litter pans, and bedding. However, careful management is required when cats are first introduced to one another, as the potential for agonistic interactions that could result in FIV transmission is increased. Because of this, it is important to determine FIV status before cats are introduced to one another and then to observe interactions until the likelihood of aggression resulting in penetrating bite wounds is remote. If there is a reasonable suspicion that such agonistic interactions will occur when the cats are unobserved, FIV-positive and FIV-negative cats should be segregated from one another, and the most reliable method of preventing transmission is to keep FIV-infected cats away from non-infected cats.

One FIV vaccine is licensed for use in cats (see Table 21.2.1); it was available in the United States and Canada until 2015 and is now only available in Australia, New Zealand, and Japan. However, it has only shown protective rate of 56% under field conditions, and its use interferes with FIV screening test interpretation, and so it is not commonly used.

ENTERIC VIRAL INFECTION

FELINE CORONAVIRUSES

Definition/Overview

Feline infectious peritonitis (FIP) is a serious disease in cats caused by virulent mutations of an enteric feline coronavirus (FCoV) in the genus *Alphacoronavirus*.

The recently emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is very distinct and different to FCoV, belonging to a different genus *Betacoronavirus* and is described separately later.

As mutations arise in FCoV, the viruses can lose their tropism for enterocytes and can gain both tropism for monocytes and macrophages as well as an ability to replicate at high levels within with cells that have an affinity for the endothelium of venules in the serosa, omentum, pleura, meninges, and uveal tract. Varied mutations in the 3, 7b and spike genes of FCoV have been implicated the switch to a pathogenic virus associated with FIP. Clinical FIP is characterized by widespread immune-mediated vasculitis and/or pyogranulomas, manifesting as high-protein effusions in body cavities and/or tissue granulomas. While the disease course from the onset of clinical signs until death can be variable, ranging from weeks to months, it is usually shorter in younger cats and those with effusions. The mortality rate is extremely high.

Etiology

Feline coronaviruses are large-enveloped RNA viruses commonly isolated from the feces of cats, particularly those in multicat households. Infection is typically acquired by kittens or young cats from exposure to shedding cats via the fecal–oral route. Mutation from a less virulent FCoV to a virulent form associated with FIP is thought to occur at some point after FCoV infection between viral replication in enterocytes and with efficient replication in macrophages. Direct transmission of FIP between cats is thought to be extremely rare, since cases are generally believed to arise as a result of in vivo mutation in an FCoV-infected cat.

Pathophysiology

Initially, the virus replicates in oropharyngeal tissues and in the enterocytes at the tips of the intestinal villi. The manifestation of infection depends on several predisposing factors, including the immune response and genetic factors in the host and the strain and dose of virus. A vigorous cell-mediated immune response is required for protection from FIP, while antibodies produced in response to infection enhance the uptake and replication of FCoV in macrophages and contribute to the immune-mediated vasculitis, which results in effusions. If the antibody-mediated immune response predominates, effusions tend to result, whereas if a cell-mediated immune response also occurs, the development of effusions may be suppressed. It is important to remember that there is overlap between the effusive and noneffusive forms of FIP, and these manifestations should be considered as a spectrum; brief episodes of effusive disease can occur before a noneffusive form predominates, and conversely, in the terminal stages of a noneffusive form, effusions may form.

Clinical Presentation

FIP most commonly occurs in cats of 2 years of age and younger. A recent history of stress (e.g., adoption, being in a shelter, neutering, upper respiratory tract disease, vaccination) is commonly apparent. Nonspecific clinical signs care common and include lethargy, anorexia, and weight loss (or failure to gain weight/stunted growth in kittens). A fever, which can be fluctuating and that is moderate and typically < 40°C (but sometimes can be higher) and that is refractory to many drugs and nonresponsive to antibiotics, is commonly present. Icterus can occur, more commonly in cats with effusions, but the degree of hyperbilirubinemia is often not high enough to result in clinical jaundice. When effusions form, they comprise viscous, high protein-content fluid in the abdominal and/or, less often, the pleural cavity and pericardial sac, resulting in clinical signs of abdominal swelling (**Figure 21.2.16** and **21.2.17**) and/or tachypnea/dyspnea. Effusions can also result in scrotal swelling in entire male cats (**Figure 21.2.18**). Pyogranulomatous lesions occur predominantly in the abdominal cavity, particularly in the liver, mesenteric lymph nodes, intestines, spleen, and kidney, where irregular outlines and/or enlargement may be appreciated on abdominal palpation. Pyogranulomatous lesions can also occur in the thoracic cavity, eyes, or CNS. Ocular signs of FIP can include anterior and/or posterior uveitis; hyphema, hypopyon, keratic precipitates ("mutton fat" deposits on the ventral corneal endothelium; **Figure 21.2.19**), retinal detachment, perivascular cuffing, hemorrhage, and retinitis. A variety of neurologic signs can develop, depending on the particular site(s) within the CNS in which lesions occur, and include ataxia, hyperesthesia, nystagmus, seizures, behavioral and mental state changes, and cranial nerve deficits.

Cats with suspected FIP in a veterinary clinic should be handled and housed like any other cat with routine infection control measures, as any cat is a potential source of FCoV infection; it is not necessary to isolate the cat.

Differential Diagnosis

Differential diagnoses for cats with abdominal effusions include hepatic- or cardiac- (rare) associated



FIGURE 21.2.16 Eight-month-old neutered male Siamese cat with effusions due to FIP. Note the abdominal distension due to the peritoneal effusion.



FIGURE 21.2.17 Eight-month-old neutered male Siamese cat with effusions due to FIP. Note the abdominal distension due to the peritoneal effusion.

ascites, cholangiohepatitis complex, septic peritonitis, neoplasia, and pregnancy. Among cats with significant accumulation of pleural fluid, neoplasia, cardiac failure, exudative pleuritis (pyothorax), and chylothorax are reasonable differential diagnoses that should be considered. Neoplasia and toxoplasmosis can both cause bicavity effusions in the abdomen and thorax. Differential diagnoses for cats with FIP in the absence of an effusion are extensive depending on the organ system(s) involved (e.g., neurologic/ocular signs [seizures, posterior paralysis, toxoplasmosis, neoplasia, idiopathic encephalomyelitis/meningitis, retinitis with or without retinal detachment, uveitis ± keratic precipitates and hyphema], and mesenteric lymphadenopathy [mycobacterial infection, neoplasia]).



FIGURE 21.2.18 Eight-month-old neutered male Siamese cat with effusions due to FIP. Note the scrotal effusion.



FIGURE 21.2.19 Keratic precipitates in the right eye of a cat with FIP.



FIGURE 21.2.20 Splenic pyogranulomas in a cat with nonefusive FIP.

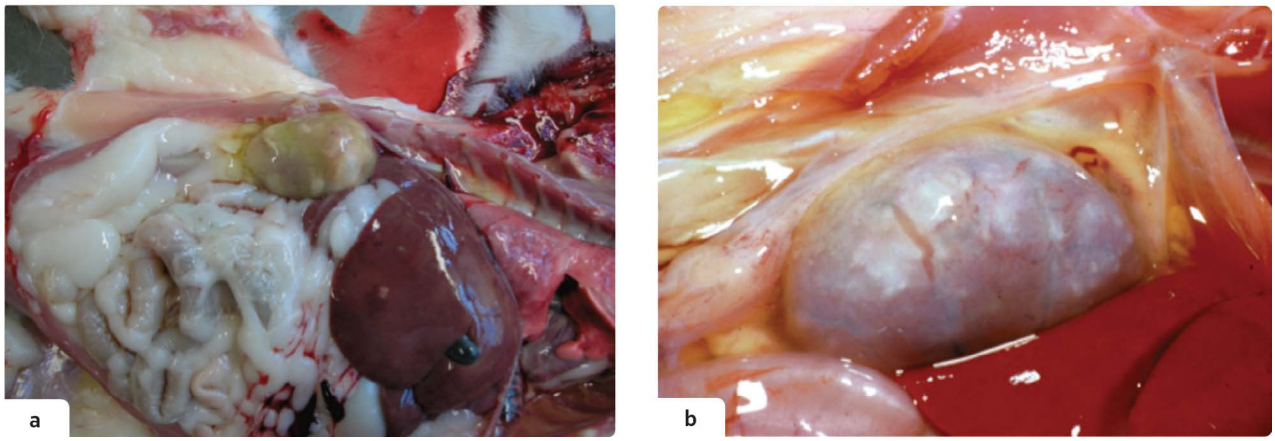


FIGURE 21.2.21 (a) Necropsy from the cat with effusive FIP shown in Figures 21.2.17 and 21.2.18. (b) Note the glistening proteinaceous fluid and subcapsular pyogranulomas on the renal surface.

Diagnosis

Immunostaining for FCoV Antigen in Association with Pathology

The only reference method for definitively diagnosing FIP antemortem is histopathology with immunohistochemistry on biopsy specimens showing pyogranuloma formation and/or vasculitis associated with the presence of FCoV antigen (Figures 21.2.20 and 21.2.21a, b). While this method is highly specific, its accuracy is dependent on specimen (showing pathology) selection and the expertise of the pathologist reading the slides. Additionally, it may be difficult to justify collection of large biopsy specimens in sick cats, and so other less invasive diagnostic methods, particularly effusion analysis, are often used to help the veterinarian decide on the likelihood of FIP. The presence of FCoV antigen in macrophages can also be demonstrated by immunocytochemistry or immunofluorescence on effusion (Figure 21.2.22a, b) and fine-needle aspirate (FNA) (as well as cerebrospinal fluid [CSF] and ocular aqueous humor in neurologic and ocular cases) samples that show cytological features consistent with FIP, i.e., the presence of neutrophils and macrophages. This is widely used in Europe and Australia where positive results performed by reputable diagnostic laboratories are consistent with a diagnosis of FIP, although a negative result does not rule out FIP due to the paucity of cells and/or FCoV antigen in some samples.

Approach to Cases with and without Effusions

When an effusion is present, a likelihood of FIP can be determined quickly antemortem by examination of an effusion sample recovered from any body cavity and showing it to be consistent with FIP. Ultrasonography or radiography can be used to identify or confirm the presence of effusions and to assist in sample collection. The effusions in FIP are highly viscous with a high protein content (> 35 g/L [3.5 g/dL]) (Figure 21.2.23). Cytologic evaluation of the fluid usually reveals a relatively low cell count (< 5,000 nucleated cells/μL), although counts can be higher on occasion (up to 20,000 nucleated cells/μL). Cells comprise low-to-moderate numbers of neutrophils and macrophages and some lymphocytes

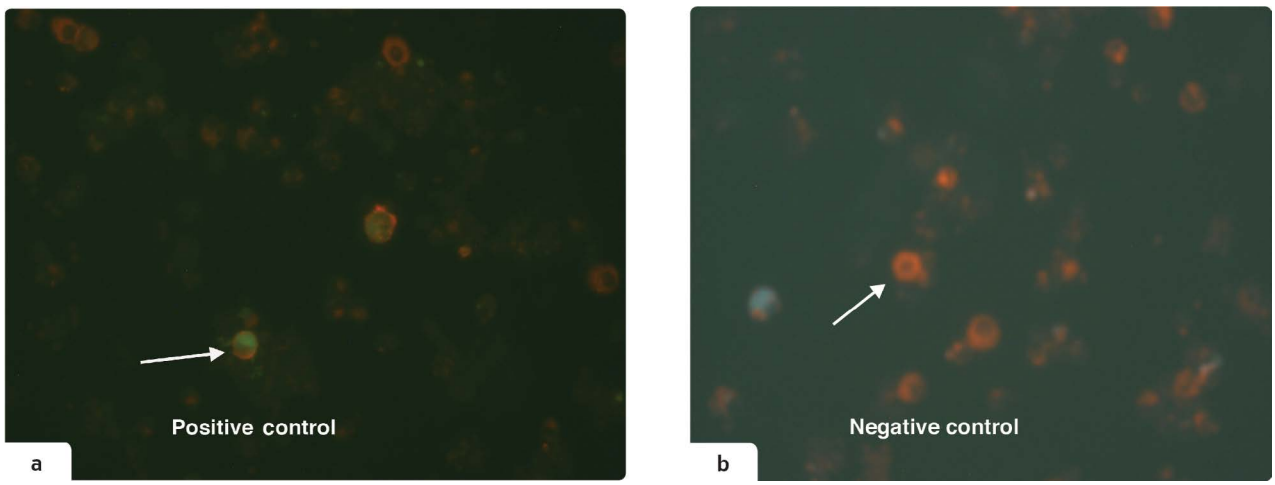


FIGURE 21.2.22 (a) Direct immunofluorescence staining of feline abdominal effusion—positive control specimen (arrow). (b) Direct immunofluorescence staining of feline abdominal effusion—negative control specimen (arrow).

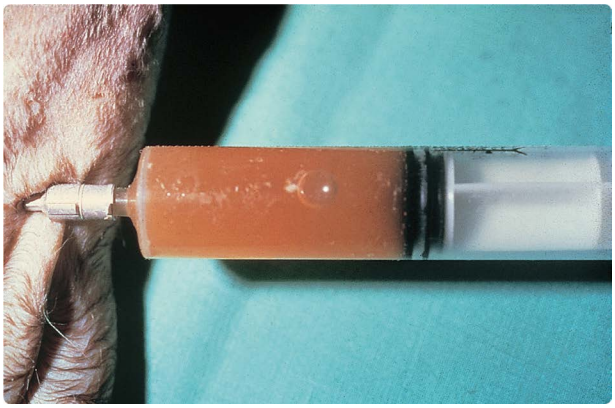


FIGURE 21.2.23 Abdominocentesis in a cat with FIP and an abdominal effusion reveals the characteristic viscous, high specific gravity exudate. Note that in some cases the globulin concentration of the fluid is sufficiently high that the sample might clot when exposed to air.

(Figure 21.2.24). The albumin-to-globulin ratio of the effusion is usually < 0.4, whereas a value of > 0.8 helps to rule out FIP.

The Rivalta test can be done as a point-of-care test (Figure 21.2.25). It involves placing a drop of effusion fluid into a tube containing weak acetic acid and watching for a characteristic clot to appear. This test gives positive results with FIP effusions but also with exudates collected from cases of lymphoma or septic effusions. It is limited by the subjective interpretation needed, although a negative Rivalta test can be useful to rule out a diagnosis of FIP.

When an effusion is not present in a suspected case of FIP, the diagnostic approach is more problematic due to difficulties accessing affected tissue sample biopsies, contraindications (such as the need for general anesthesia) to taking biopsies from a sick cat, and/or costs involved in tissue sample collection. Currently, there is no noninvasive, confirmatory test available for cats with FIP that do not have effusions, although in some cases valuable information can be gained through analysis

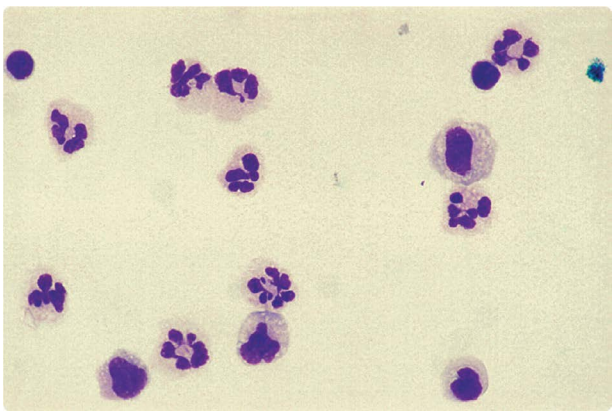


FIGURE 21.2.24 Cytopathology of abdominal fluid from a cat with FIP and an effusion, characterized as a relatively low cellular count fluid containing a mixture of neutrophils and macrophages (pyogranulomatous effusion).

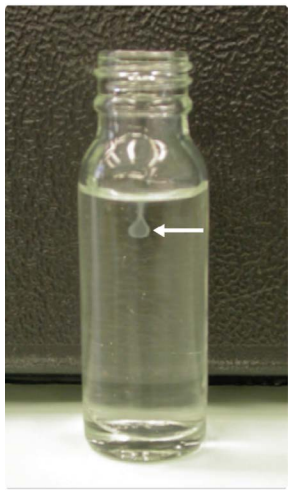


FIGURE 21.2.25 Positive Rivalta's test from a cat with effusive FIP showing clotted droplet of effusion (arrow) in weak acetic acid (made by combining 8 mL of distilled water at room temperature and one drop of 98% acetic acid).

of fine-needle aspirate (FNA) samples collected from affected organs, if accessible, as described in further section.

Hematology and Biochemistry

Routine hematology changes are nonspecific but can show lymphopenia, neutrophilia, a left shift, and/or a mild-to-moderate normocytic, normochromic anemia. An immune-mediated hemolytic anemia occasionally occurs. On serum biochemistry, elevated serum bilirubin may occur, with values are not always correlated with elevated liver enzymes. Hyperproteinemia may occur; a hyperglobulinemia is typical with a slight decrease in the albumin fraction is typical. When FIP disease prevalence is low, a A:G ratio > 0.6 can rule out FIP, but a low A:G ratio does not confirm a diagnosis of FIP. The hyperglobulinemia is due to a polyclonal hypergammaglobulinemia, and although serum protein electrophoresis provides a graphic portrayal of the serum proteins, this test does not provide definitive diagnostic information as other chronic infections (e.g., FeLV and FIV) may produce similar findings.

Acute phase proteins (APPs) are produced in the liver in many inflammatory and noninflammatory diseases, and so increases are not specific to FIP. Alpha-1-acid glycoprotein (AGP) is a major APP in cats, and assays are available for its measurement in some countries. Moderately elevated serum AGP concentration of > 1.5 mg/mL is frequently reported in cats with FIP and may be helpful in raising the suspicion of a diagnosis of FIP.

FCoV Antibody Serology

There is no reliable serologic test for the diagnosis of FIP; available serological assays detect antibodies against any FCoV, not just those associated with FIP. As FCoV infection is common in multicat households,

many healthy cats are seropositive, sometimes with very high titer, making it impossible to differentiate cats with and without FIP based on titer alone.

Reverse-Transcriptase Polymerase Chain Reaction for FCoV RNA Detection

The detection of FCoV antigen in samples by immunostaining, described earlier, shows the presence of the virus in pathological lesions and is a reliable test for FIP when positive. Polymerase chain reaction (PCR) assays detect FCoV RNA in samples by reverse-transcriptase (RT-)-PCR. RT-PCR can be performed on many sample types such as effusions, FNAs, and CSF where the presence of high levels of FCoV RNA in association with other features consistent with FIP (e.g., cytology) is highly supportive of a diagnosis of FIP. However, positive RT-PCR tests alone cannot confirm a diagnosis of FIP, as it is known that FCoV RNA can be present systemically in cats in the absence of FIP. Additionally, the levels of FCoV RNA present in samples from cats with FIP can be variable and may not be detectable in some cases. Recently, positive RT-PCR results on FNAs, particularly from mesenteric lymph nodes from cats without effusions, have proved highly supportive of a diagnosis of FIP. Other potential samples for FNA include the liver, spleen, and kidneys. Blood samples are not recommended for FCoV RNA testing due to the low levels present in cats with FIP. FCoV RT-PCR can also be performed on fecal samples, but this is primarily used to identify cats that are shedding FCoV for the management of infection in a multicat household, and it is not used to diagnose FIP, as it is known that many healthy cats without FIP shed FCoV.

FCoV Spike Gene Mutation Analysis Following FCoV RNA Detection by RT-PCR

Following detection of FCoV RNA in a sample by RT-PCR, varied molecular techniques can be used to derive spike (S) gene sequence data for the FCoV present. However, such techniques are not always successful in FCoV RT-PCR-positive samples, as low FCoV levels preclude sequence analysis, and FCoV sequence variability can prevent targeted sequencing techniques from generating sequence data. The reason for the focus on S gene sequences was because it was believed that specific sequence changes in this region were correlated with the development of FIP, thus potentially being a useful diagnostic test for FIP. Subsequent work suggested that S gene mutations were associated with the acquisition of monocyte/macrophage tropism to allow FCoV to spread systemically outside of the gut and contribute to the development of FIP rather than being diagnostic of FIP, per se, and thus their diagnostic usefulness was limited.

MRI and CSF Sampling

Advanced imaging using magnetic resonance imaging (MRI) may be helpful in neurologic cases of FIP, as can sampling of CSF for analysis via cytology, protein measurement, PCR, and/or immunocytochemistry.

Management of FIP

Treatment/Prognosis

Historically, no effective causal treatment was available for FIP, so cats with confirmed FIP had a grave prognosis, dying or being euthanized after only a few days to weeks. A variety of anti-inflammatory and immunosuppressive treatments have been recommended as palliative care (e.g., prednisolone, 2–4 mg/kg p.o. q.24 h., with reducing doses as needed, to control signs) although no controlled studies exist to document their benefit. Feline interferon-omega (IFN-ω) is used by some clinicians in the treatment of FIP; however, a randomized, placebo-controlled, double-blind treatment study in cats with confirmed FIP did not show any benefit of IFN-ω treatment.

In recent years, newer antivirals, especially protease inhibitors (which inhibit formation of FCoV viral proteins) and nucleoside analogs (which inhibit FCoV RNA formation), show huge promise for the effective treatment of FIP. Recent published studies have documented the efficacy of newer antiviral compounds, such as the protease inhibitor GC376, and especially the nucleoside analog GS-441524 (given subcutaneously or orally), in the treatment of naturally occurring FIP, with courses of GS-441524 given for at least 12 weeks appearing to be especially efficacious in young cats with effusions. Higher doses and longer courses of treatment are usually required for cases with ocular and/or neurological signs of FIP. However, neither GC376 nor GS-441524 are currently licensed for use in animals, making acquisition or administration of these agents by vets illegal in many countries. Thus, some owners are sourcing these agents online and administrating them to their cats themselves in the absence of veterinary care, which does pose animal welfare concerns. Some vets monitor cases receiving treatment from their owners to help ensure appropriate supportive care is available. Monitoring can include clinical signs, e.g., appetite, activity, weight, and temperature measurements, as well as hematology and biochemistry, e.g., globulin, albumin-to-globulin ratio, bilirubin, lymphocyte count, and/or hematocrit. Remdesivir (GS-5734) is a prodrug of GS-441524 and is licensed for use in humans but not animals. Evidence from field case descriptions suggests that injectable remdesivir (given intravenously and/or subcutaneously) is also effective for the treatment of FIP in cats. Thus, much promise exists for the use of these antiviral agents for FIP treatment, especially once licensed products become available.

Prevention

A modified live FIP vaccine is commercially available in some countries, but it is not recommended for use, as there is insufficient evidence that it induces clinically relevant protection.

Management of FCoV

Since FCoV is transmitted predominantly via the fecal–oral route, hygiene is the mainstay of FIP control in multicat environments. FCoV infection is maintained in households by continual cycles of infection and re-infection in the cats, the source of infection being feces in the litter tray. Reducing the FCoV infection pressure and risk of transmission is important and can be helped by keeping cats in small stable groups of three or less, observing strict hygiene (especially litter trays), and providing outdoor access if possible. Although FCoV is only rarely shed in saliva, food and water bowls should be cleaned daily using detergent or in a dishwasher at a cycle of at least 60°C because of the risk of fomite contamination. Fecal shedding of FCoV occurs over several months or sometimes lifelong, especially in multicat households. Identification of cats that are persistently shedding a high FCoV load and their separation from low shedders and fecal RT-PCR-negative cats has been suggested for reducing transmission rates. However, the optimal fecal sampling protocol for RT-PCR testing has not been determined, although at least three fecal samples collected at intervals between 1 week and 1 month has been suggested. Additionally, FCoV-infected cats should not be exposed to stressful situations.

Some studies described the successful use of an oral nucleoside analog to eliminate FCoV shedding (identified by fecal RT-qPCR) in cats in households with endemic FCoV infection where owners were wanting to eliminate FCoV shedding due to previous FIP cases in their households. A potential problem with this approach is that because FCoV is so common in multicat households, and can be carried on fomites, it is very difficult to maintain an FCoV-negative status long term. Additionally, the risk of the development of resistance to antiviral agents is present, and so many advise that the use of antivirals should be preserved only for the treatment of cats with FIP.

Public Health Implications

FIP and FCoV pose no known public health risk.

SARs-CoV-2

SARS-CoV-2 is very distinct and different to FCoV and is the cause of COVID-19 in humans. Felids have been shown to be susceptible to SARS-CoV-2 infection, and a few natural cases of feline SARS-CoV-2 infections have been described in cats living in households with COVID-19-positive people; however, these numbers are extremely low compared to the millions of human infections documented. Cats have not been shown to transmit infection to people. To reduce the risk of infection, close contact with pet cats should be avoided by people with COVID-19 alongside standard hygiene measures, but cats should not be re-homed or relinquished. Infections in cats are generally without clinical signs, but occasionally respiratory signs and/or enteric signs are described. The testing of cats for SARS-CoV-2 infection is not generally recommended unless required by regulatory authorities.

FELINE PANLEUKOPENIA (FELINE PARVOVIRUS)

Definition/Overview

Feline panleukopenia (FPL) is caused by a small, non-enveloped, single-stranded DNA parvovirus recognized in cats worldwide. Once a common fatal viral infection, feline panleukopenia virus (FPV) infection is a rare disease among vaccinated pet cats. However, FPV infection regularly occurs in cats housed in animal shelters and can also affect breeding catteries, and recent outbreaks in unvaccinated cats have been described in Australia. FPV can also replicate in dogs, although it is not shed in their feces. Canine parvovirus (CPV) type 2 arose from FPV via mutations, and although it initially could not replicate in cats, all current variants of CPV type 2 (i.e., a–c) can now infect and cause disease in cats.

Etiology

FPV infection is transmitted by contact with the feces, saliva, and/or secretions of infected cats, or by fomite (e.g., bedding, litter trays, food and water bowls, clothing) or in utero transmission, and fecal–oral transmission is most important. Virus is shed in feces for up to 6 weeks (but is typically much shorter) following recovery from clinical disease. The virus is very stable in the environment, capable of persisting outside the host or on fomites for at least 1 year, so even cats with an indoor only lifestyle cannot always avoid encountering FPV. Some unvaccinated adult cats can acquire natural immunity subsequent to subclinical infection via low-level viral exposure to infected cats or fomites. Kittens are more likely to become infected (Figure 21.2.26), but once clinical infection occurs, both kittens and adults have similar mortality rates.

Pathophysiology

The virus requires rapidly multiplying cells for replication, so it has a tropism for those tissues with a high

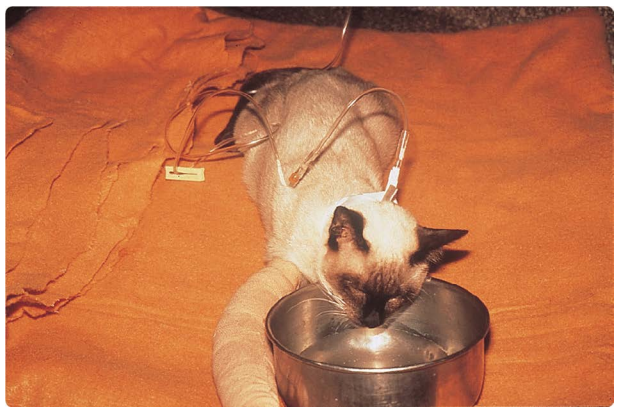


FIGURE 21.2.26 This young Siamese kitten had marked vomiting, diarrhea, and fever caused by feline panleukopenia virus. It was an unvaccinated cat that was hospitalized for a fracture repair. (*Courtesy of M. Schaer.*)

mitotic rate (e.g., bone marrow, lymphoid organs, and the intestinal crypts). Cellular depletion and immunosuppression occur when lymphoid tissue is infected, and myeloid cell populations are depleted by bone marrow infection; thus, panleukopenia results. Intestinal crypt infection (particularly in the jejunum and ileum) impairs regeneration of the epithelium, resulting in shortening or intestinal villi and malabsorption, increased permeability, and hemorrhagic diarrhea with translocation of intestinal bacteria. Fetal and neonatal infection targets the CNS, including the cerebrum, cerebellum, retinae, and optic nerves. Fetal death, fetal absorption, abortion, or mummified fetuses can occur in infected pregnant queens. Blindness and cerebellar hypoplasia, manifesting as nonprogressive hypermetria and ataxia are common among kittens infected as neonates.

Clinical Presentation

Following FPV exposure, clinical disease is more likely to develop in unvaccinated kittens under 5 months of age, as they are less likely to have protective antibody titers. It should be remembered that vaccinated kittens can be infected if maternal-derived antibodies (MDAs) were present at the time of their vaccination, as these can interfere with the response to vaccination. Kittens suckling queens with high antibody titers are likely to receive large amounts of anti-FPV antibodies, prolonging interference with the immune response to vaccination, sometimes until 16–20 weeks of age.

When clinical disease develops, the onset is acute and may culminate in death within 12 hours, sometimes without apparent clinical signs of disease. Infected cats generally present with clinical signs, including lethargy, anorexia, vomiting, diarrhea, fever, and/or dehydration. Death can result from shock, DIC, secondary bacterial infections, and/or profound dehydration. One retrospective study reported that clinical recovery most often occurred approximately 5 days after the onset of clinical signs (range 1–9 days), while in fatal cases, death occurred approximately 1 day after the onset of clinical signs (range 0–9 days). Cerebellar hypoplasia is a clinical finding among kittens born to queens infected during pregnancy. Affected kittens ambulate with a characteristic broad-based stance and manifest hypermetric movements, but mentation is normal. Intention tremors of the head may occur when food is offered to affected kittens. One or more of a litter of kittens may be affected. The condition is not progressive, so affected cats can make good pets if their clinical signs allow good quality of life.

One study reported that low leukocyte counts (< 1,000 leukocytes/μL), hypoproteinemia (less than 30 g/L [3 g/dL]), and hypokalemia (< 4 mmol/L) were poor prognostic indicators in FPV-infected cats, while another found that total thyroxine measurement at hospital administration was of prognostic value.

Differential Diagnosis

Intestinal parasitism, including coccidiosis, infectious enteritis, intussusception, and poisoning, are consistent with acute, enteric FPV infection, particularly in young cats. *Salmonella* infections can cause hemorrhagic diarrhea and panleukopenia. Sepsis and enteric foreign body may also be considered. Neurologic signs associated with cerebellar hypoplasia may be consistent with acute head trauma.

Diagnosis

Infected cats usually have a history of possible exposure to FPV and risk factors for infection, such as lack of a vaccination history and/or age less than 16 weeks.

The hallmark laboratory finding in kittens with FPV infection is a leukocyte count between 50 and 3,000 cells/μL; this can be determined in practice with microscopic examination of a simple blood smear showing profound neutropenia and lymphopenia. Thrombocytopenia is occasionally reported. Biochemical profiles are of little value in establishing a diagnosis of FPV infection but can document azotemia due to dehydration and hypoalbuminemia and/or hypokalemia due to intestinal losses and anorexia.

Point-of-care fecal antigen tests, e.g., ELISAs, exist for both FPV and CPV, with both being able to detect FPV antigen. A positive test result confirms infection in clinically affected cases. However, a negative test result does not rule out infection, since viral shedding is intermittent and may only be detectable in feces for 24–48 hours after infection. Polymerase chain reaction (PCR) assays can be used to detect FPV strains in fecal samples as well as whole blood, bone marrow, and tissue samples. However, healthy cats can test PCR positive in feces. Both fecal antigen and PCR tests can be positive for at least 4 weeks after vaccination with modified live virus (MLV) vaccines, although this is uncommon.

Virus isolation is an effective means of diagnosing infection but is not routinely available in clinical practice.

A full necropsy should be performed on any cat suspected to have succumbed to FPV infection, as histopathology of the intestinal tract can show characteristic intestinal crypt necrosis and dilate crypts filled with necrotic material. Neonatally infected cats may have cerebellar hypoplasia or retinal degeneration.

Management

Treatment/Prognosis

There is no specific antiviral therapy available for the treatment of FPV-infected cats. While feline recombinant interferon-ω has been used successfully to treat CPV, one feline study using the agent as a preventive measure before an FPV outbreak was unable to demonstrate improved outcomes in treated kittens. Intensive supportive therapy and nursing care offer the only reasonable means of treating clinically affected cats. A single dose of serum or plasma from an immune or recovered cat can be administered through a filter either subcutaneously or intraperitoneally, to cross-matched, exposed, unvaccinated kittens (2 mL in kittens < 12 weeks; 4 mL in kittens ≥ 12 weeks), although this is of most value when administered before the onset of clinical signs, i.e.,

for prevention following exposure rather than treatment. Only one dose can be administered, to prevent subsequent anaphylaxis, and vaccination against FPV should be delayed in treated kittens by 3–4 weeks to prevent antibody interference with the immune response. Once recommenced, the course of vaccination should continue 2–4 weeks longer than usual (up to 18–24 weeks old).

Parenterally administered balanced electrolyte solutions, such as lactated Ringer's solution, are of utmost importance in replacement of electrolytes and fluids in affected cats. Fluid therapy can be given intravenously or intraosseously (in small kittens). Parenterally administered metoclopramide (0.2–0.4 mg/kg SC q.6–8 h. or 1–2 mg/kg IV over 24 hours as a constant rate infusion) can be used in persistent vomiting. Maropitant (1 mg/kg SC q.24 h.) is an alternative antiemetic. Appetite stimulants, such as mirtazapine (2 mg per cat p.o. q.48 h.), can be used during the recovery phase. A highly digestible, bland diet can be offered once vomiting is under control.

Antimicrobial therapy may be indicated, since secondary bacterial infections and sepsis are common complications resulting from viral injury to the intestinal mucosa. Parenteral ampicillin (10–20 mg/kg IV or SC q.8 h.) is a good empiric choice.

Prognosis for peracute panleukopenia is poor because many cats die within 12 hours. Median survival time after hospitalization was 3 days in a study of shelter cats, with death more likely in cats that were lethargic, were hypothermic, and had poor body condition. Kittens with cerebellar hypoplasia can make suitable pets depending on the severity of their neurologic abnormalities.

Prevention

Excellent vaccines are available for immunization of kittens against FPV (see Table 21.2.1), and FPV vaccines are considered core vaccines. Current FPV vaccines appear to afford protection against CPV variants.

MDAs interfere with vaccination and typically wane by 12 weeks of age to allow an active immunological response to vaccination to occur. Thus, many vaccination datasheets for pets and breeding cats recommend an initial vaccination at 8–9 weeks of age followed by a second vaccination 3–4 weeks later for the primary course. However, MDAs can sometimes persist as far as 20 weeks of age, and so guidelines often recommend that the last FPV primary vaccine be administered at 16–20 weeks of age as by this age, in most kittens, MDA will have waned, although this is not always the case. In shelter or rescue cats that are unlikely to have MDAs and are vulnerable, they can receive their primary vaccination from 6 weeks of age. A booster vaccination is then recommended for all cats at 6–12 months of age to further enhance the likelihood of vaccine-induced immunity being induced in cats that did not adequately respond to the primary vaccination course due to MDA. Thereafter boosters are only required every 3 years for FPV, as solid immunity is known to last for many years after vaccination.

Cats that do recover from natural infection probably derive lifelong immunity.

Both MLV and killed adjuvanted parenteral vaccines are available (see Table 21.2.1). Although MLV vaccines are used predominantly in clinical practice due to their more rapid onset of protection and better resistance to MDAs, even a single dose of a killed FPV vaccine can rapidly induce good antibody responses in naïve cats quickly. MLV vaccines should not be administered to kittens < 4 weeks of age or pregnant queens, as vaccine virus may replicate in the cerebellum of unborn kittens and kittens < 6 weeks old and may cause neurologic signs after birth. It has been recommended that immunocompromised cats should not receive MLV vaccines, but one study in cats with retrovirus infection demonstrated no adverse effects and similar responses to healthy cats following a MLV FPV vaccine. Boosters every 3 years are recommended after the primary course; however, antibody testing can be performed before vaccination, as FPV-specific antibodies are strongly correlated with protection. Some commercially available point-of-care tests are available for FPV antibody testing. Cats which possess FPV antibodies do not need to be revaccinated at that time point, and it is known that many cats already have antibodies even if not vaccinated previously.

FPV is long lived in the environment and resistant to many disinfectants such as quaternary ammonium. Bleach (1:32 solution used within 24 hours of dilution and protected from light) or accelerated hydrogen peroxide- or potassium peroxymonosulfate-based disinfectants should be used with a contact time of at least 10 minutes, after thorough cleaning to remove all organic material.

Public Health Implications

FPV poses no risk to human health.

FELINE TOROVIRUS

Definition/Overview

Toroviruses are similar to coronaviruses and have been detected in several species. There is some evidence to suggest a link in cats to protrusion of the third eyelid and diarrhea.

Etiology

Toroviruses are members of *Torovirinae* of the family *Coronaviridae* and are large, enveloped, single-stranded RNA viruses. Toroviruses have been implicated in human diarrheal disease, but consensus on their importance is lacking.

Pathophysiology

Suspected fecal–oral infection transmission, but information is lacking.

Clinical Presentation

Suspected involvement occurs in mainly young cats with protruding third eyelids (nictating membranes) and concurrent mild enteritis. This usually self-resolves within a few days with or without supportive treatment. Vision may be temporarily impaired due to physical obstruction of the pupil by the third eyelid. Mild hyperthermia may be present at the time of presentation.

Differential Diagnosis

Screening for an underlying enteropathy and/or upper respiratory tract pathogens may be warranted.

Diagnosis

No tests are currently commercially available, so diagnosis is based on clinical suspicion. Experimentally RT-PCR on fecal samples can be performed.

Management

Treatment/Prognosis

Supportive treatment may or may not be required. Prognosis is considered to be good.

Prevention

Likely endemic in the feline population, practice basic hygiene practices.

Public Health Implications

No available information.

OTHER VIRAL INFECTIONS

FELINE RABIES

See also Chapter 14.

Definition/Overview

Feline rabies virus infection has worldwide importance, particularly in the United States, although similar to that described in the dog, the incidence of feline rabies has been greater since the mid-1980s. This is considered to be associated with cats' nocturnal behavior and encounters with wildlife vectors and probable lower rabies vaccination rates. It is also known that younger cats, as well as dogs, are more susceptible to rabies virus infection than adult animals. The high concentration of rabies virus in the saliva of infected cats poses a particular threat to humans because of their popularity as companion animal pets and their ability to penetrate skin with their teeth. It has been estimated that < 20% of domestic cats in the United States are ever vaccinated against rabies. This fact, combined with the increasing incidence of wildlife rabies in the Mid-Atlantic and Northeastern United States, justifies efforts to promote feline rabies vaccination.

Etiology

Rabies is caused by an RNA virus of the *Rhabdoviridae* family. In areas with good pet vaccination programs, wildlife tend to be the major reservoirs and vectors, whereas in areas with poor programs, domesticated animals are the major reservoirs and vectors.

Pathophysiology

After inoculation into the subcutaneous tissues and muscle, usually by a bite or a scratch from an infected animal, the virus replicates in muscle cells at the bite site for weeks to months before attaching to peripheral nerve endings and undergoing retrograde migration up nerve axons to the CNS. Rabies virus replicates in the spinal ganglia, from where it disseminates throughout the CNS and continues replicating. The virus is then transported out of the CNS to other body tissues, including the salivary glands, through peripheral, motor, and sensory nerves. An animal is infectious when the salivary glands are affected. Infectious virus may be shed in saliva for up to 13 days before clinical signs of illness are manifest. Although deemed an uncommon mode of transmission, contact transfer has been experimentally demonstrated.

Clinical Presentation

The average incubation period for rabies is 2 months but varies from just over 1 week to up to 6 months and is shorter the higher the viral dose and/or if the site of inoculation is close to the CNS and/or the viral dose high. Clinical rabies infection in cats, like dogs, is divided into two general categories: Furious and paralytic. A prodromal phase can also occur before the furious stage, but it is often subclinical. Prodromal clinical signs, if they occur, include vague neurologic and behavioral changes, irritation at the site of viral inoculation (even if the wound has healed), fever, and increased agitation lasting for 1–2 days. As the disease progresses, about 90% of affected cats manifest the furious type of disease, which lasts up to 7 days and is due to an encephalitis. Affected cats show exaggerated emotional responses, becoming particularly aggressive toward humans as well as other animals and inanimate objects. Affected cats may aimlessly run or pace continuously until they collapse and act disorientated. In contrast to dogs, cats with rabies frequently manifest increased vocalization and a change in the pitch of voice. Other signs of cranial nerve and forebrain involvement can be seen including absent/reduced palpebral, corneal and pupillary reflexes, strabismus, dropped jaw, hypersalivation, seizures, twitching, and tremors. Most affected cats die within a few days. In cats that survive this first phase, clinical signs progress to paralytic disease. Affected cats manifest ataxia, flaccid ascending paraparesis, which often involves the site of inoculation,

incoordination, paralysis, coma, and death from respiratory arrest.

Differential Diagnosis

Kittens and cats infected with and shedding rabies may not manifest clinical signs, at least during the early stages of infection. (Any cat with unexplainable neurologic and/or behavioral changes should be considered suspect for rabies, especially if unvaccinated in an endemic country.) Neoplasia, spinal or head trauma, and poisoning or toxicity are important differential diagnoses for feline rabies. In the United States, the use of killed and recombinant rabies vaccines in cats has eliminated vaccine-induced signs of rabies.

Diagnosis

No specific changes are characteristic of rabies infection on hematology, serum biochemistry, or CSF analysis. Serum tests to detect anti-rabies virus antibodies in infected animals are often negative. Direct IFA staining or immunohistochemistry of nervous tissue collected at necropsy is the most common and gold-standard method of confirming rabies infection in both dogs and cats (Figure 21.2.27). Reverse transcriptase (RT)-PCR is a sensitive and specific test that can provide fast (within hours) results when neural tissues and/or saliva are submitted for testing. However, attempts to make antemortem diagnoses of rabies in animals are not recommended, and a negative RT-PCR test performed on saliva cannot be used to rule out rabies.

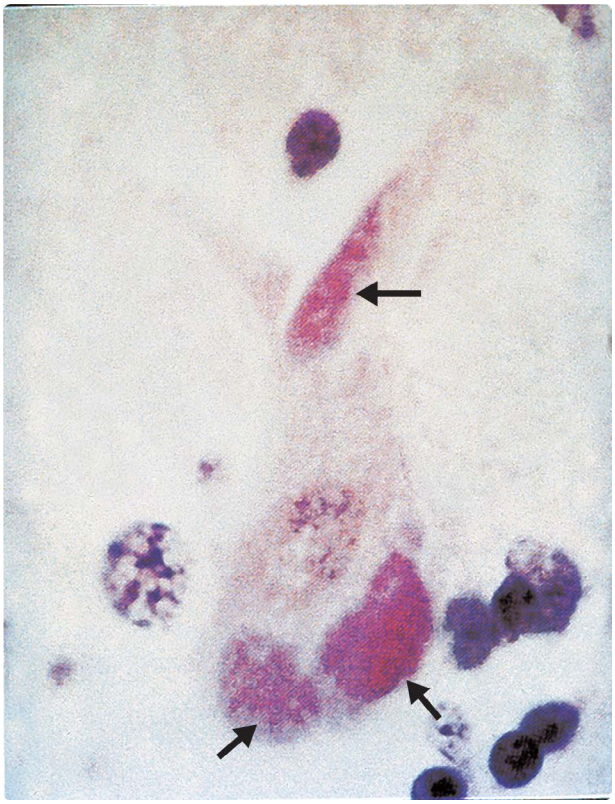


FIGURE 21.2.27 Rabies causes characteristic microscopic Negri bodies (arrows) in the brains of affected animals. (*From Kassira JP (1997). (ed.)* Images in Clinical Medicine. *Selections from the* New England Journal of Medicine*, with permission.*)

Management

Treatment/Prognosis

The zoonotic threat posed by rabies virus infection in cats justifies strict isolation and quarantine of cats suspected of or known to be infected. Treatment should not be attempted due to zoonotic potential. The prognosis for recovery from the clinical infection is grave, and euthanasia is recommended.

Prevention

Killed (adjuvanted) virus vaccines (1 year and 3 years) and a feline recombinant (adjuvant-free) rabies vaccine are available for use in cats. Current standards for vaccination of cats against rabies are outlined in Table 21.2.1. Where feline rabies vaccine is mandated by law, the first dose of vaccine can be given as early as 3 months of age. A second dose, administered 1 year following the date of the initial rabies vaccine, is required. Today, there is considerable variation among states and countries as to the frequency of booster vaccinations in adult cats. It is recommended that rabies vaccinations should be administered as low as possible on the right hindlimb, so that if a sarcoma develops subsequent to vaccination, there is a history of the type of vaccine used at the site. Vaccination intervals range from 1 to 3 years depending on the specific product used. While rare, there have been cases of rabies in vaccinated animals when vaccinations have been allowed to lapse.

Public Health Implications

As with dogs, any human exposed to the saliva of a cat suspected of having rabies should be considered exposed, and immediate isolation and treatment should be instituted. Treatment of a bite wound in a person caused by any domestic or feral cat must be treated aggressively by washing thoroughly as soon after the injury as possible. Irrigation of the wound with large quantities of a 20% aqueous soap solution or quaternary ammonium solution (e.g., benzalkonium chloride) is recommended. Humans who receive unprovoked bite wounds from feral or free-roaming cats have the highest risk of exposure. In endemic countries, approach stray cats with caution and appropriate protective equipment, even if they appear healthy. In addition to local wound treatment, these individuals are justifiably treated according to standard postexposure prophylaxis. Rabies virus is fragile and quickly inactivated outside the host and susceptible to routine disinfectants. Once saliva and/or tissue has dried, it is no longer deemed infectious.

FUNGAL INFECTIONS

FELINE CRYPTOCOCCOSIS

Definition/Overview

Cryptococcosis is an important noncontagious fungal disease of cats worldwide, and infection is usually via inhalation of environmental basidiospores. Infection is usually in the nasal cavity, although CNS signs can occur if infection breaks through the cribriform plate; pulmonary infections are rare. Dermatologic infections with ulcerative cutaneous lesions can also occur, as can disseminated infections, which are associated with clinical signs, including lethargy, cachexia, meningoencephalomyelitis, uveitis, chorioretinitis, osteomyelitis and polyarthritis, systemic lymphadenitis, or multiorgan involvement, including renal infection.

Etiology

Cryptococcus spp. are encapsulated, and most feline infections are due to *C. neoformans* and *C. gatii* species complexes. *C. neoformans* is usually associated with avian feces, particularly pigeon, but has also been isolated from decaying vegetation. Asymptomatic colonization of the respiratory tract is the most usual outcome of environmental exposure.

Pathophysiology

Cryptococcus is not a contagious disease. Infection comes from a contaminated environment. The cryptococcal capsule contains protective factors that can inhibit phagocytosis, so infection can be disseminated via infected macrophages and neutrophils. There is debate in the published literature regarding the possible role of immunosuppression in clinical infection. The incubation period varies from months to years, and fungal factors, such as infective burden, genotype, and virulence factors, as well as the host immune response, determine the outcome of exposure. Once established in the nasal cavity or lung, hematogenous and host cell–cell spread can occur to the lymph nodes, eye, skin, and CNS.

Clinical Presentation

Cats with nasal cryptococcosis usually present with a chronic unilateral nasal discharge (serous, mucopurulent, or hemorrhagic), often accompanied by unilateral or bilateral swelling that can be followed by ulcerative nasofacial lesions (see Figures 21.2.28–21.2.30). Submandibular lymph nodes are usually enlarged. Nasopharyngeal granulomas can sometimes protrude from the nostrils, causing stertor, dyspnea, and open-mouth breathing. Otitis media and vestibular signs can also develop as a consequence. Blindness can result from ocular infection, and if the cribriform plate is breached, intracranial neurologic signs (e.g., seizures), including blindness from optic neuritis and/or chorioretinitis, can ensue (Figure 21.2.31; see also Figure 19.25).

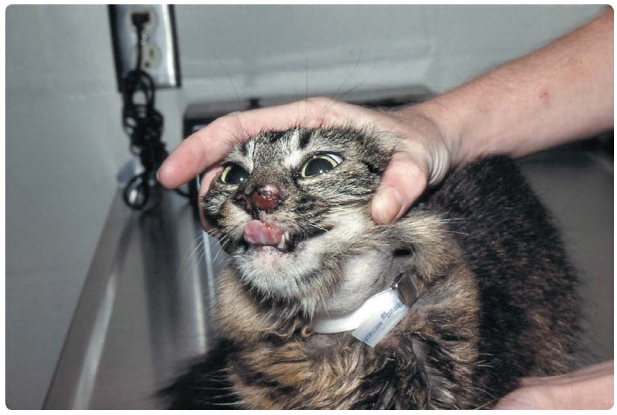


FIGURE 21.2.28 Cryptococcal granulomas involving the tongue and nares of this Domestic Shorthair cat. (*Courtesy of M. Schaer.*)



FIGURE 21.2.29 Several cryptococcal granulomas on the face of a cat. (*Courtesy of M. Schaer.*)



FIGURE 21.2.30 A solitary cryptococcal granuloma involving the nasal cavity and growing outward through the nasal bone of this 17-year-old diabetic cat. (*Courtesy of M. Schaer.*)

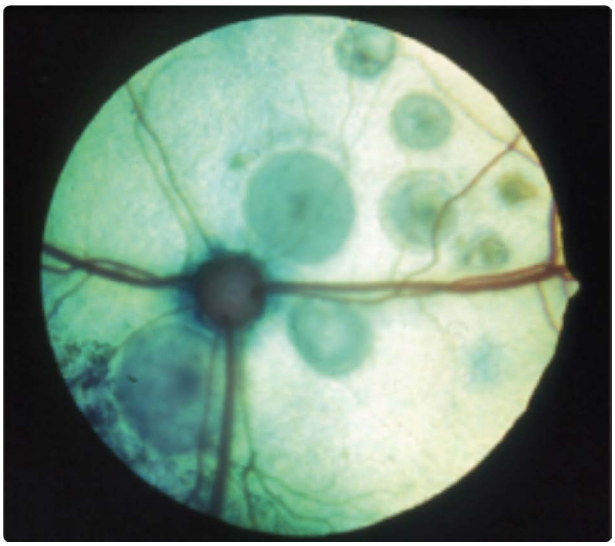


FIGURE 21.2.31 A funduscopic view showing cryptococcal chorioretinitis in a cat. (*Courtesy of D. Brooks*.)

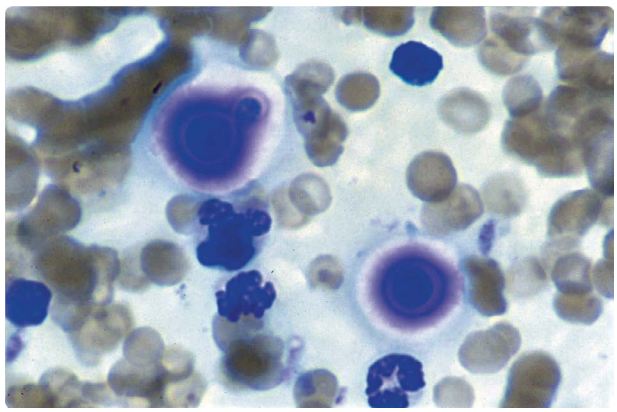


FIGURE 21.2.32 A cytology specimen stained with new methylene blue showing *Cryptococcus neoformans* spores. Note the thick capsule and the daughter spore. (*Courtesy of M. Schaer*.)

Dermatologic infection presents as single or multiple ulcerated or nonulcerated cutaneous masses (atypical presentation). Hematogenous spread can lead to multiorgan involvement, including lymphadenitis and polyarthritis. Systemic fungal dissemination and chronic infection can contribute to cachexia and depression.

Differential Diagnosis

Cryptococcal rhinitis can cause similar signs to infections with FHV-1, FCV, *C. felis*, *B. bronchiseptica*, *M. felis*, or *Aspergillus* spp.; neoplasia (e.g., nasal lymphoma), foreign bodies (e.g., plant awns), and oronasal fistulae should also be considered. Ocular and CNS signs could also be caused by neoplasia (e.g., lymphoma, meningioma), toxoplasmosis, FIP, or bacterial meningitis. The differential diagnosis for the cutaneous form in cats includes other deep mycoses, mycobacteriosis, nocardiosis, neoplasia (e.g., squamous cell carcinoma) herpetic dermatitis, and eosinophilic granuloma complex.

Diagnosis

Direct organism visualization via cytologic examination of tissue aspirates (such as directly from nasal masses), infected body fluids, or impression smears of cutaneous lesions or biopsies, stained with Romanowsky-type stains (Wright, Giemsa, Diff-Quik®) is often performed first. This usually reveals pink to violet round or budding extracellular *Cryptococcus* organisms with thick, unstained capsules (see Figure 21.2.32). Histopathology can also be performed on biopsy specimens. Cryptococcal culture can be performed after incubation for 10 days. Diagnostic imaging, including radiography and advanced imaging (CT and MRI) when appropriate, should be performed for further evaluation of clinical signs.

The latex cryptococcal antigen agglutination test (LCAT) to detect capsular antigen in serum, CSF, or urine is the diagnostic test of choice and, if possible, should be performed early in the diagnostic workup. It is both sensitive and specific, meaning that false-positive and negative results are uncommon.

Management

Published prospective controlled studies do not exist for the treatment of cryptococcal infections. Sinonasal disease is often treated with a combination of debulking therapy followed by prolonged courses of azole therapy (itraconazole 50–100 mg per cat p.o. q,24 h., fluconazole 50 mg per cat p.o. q.24 h., or ketoconazole 10 mg/kg p.o. q.12 h.), sometimes in combination with amphotericin B. Regular (1- to 2-month) liver enzyme testing should be performed for possible azole-related hepatotoxicity, and treatment should continue until the LCAT titer is zero. A four- to fivefold reduction in LCAT titer indicates an adequate response. LCAT titers should be repeated every 3–6 months thereafter so that recrudescent infections can be diagnosed early. Amphotericin B is the most efficacious anticryptococcal drug and can be administered as amphotericin deoxycholate (0.25–0.5 mg/kg per cat of 5 mg/mL stock solution diluted in 350 mL of 0.45% NaCl with 2.5% dextrose SC 2 or 3 times weekly to a cumulative dose of 10–15 mg/kg; nephrotoxicity can occur) or as liposomal amphotericin B (1–1.5 mg/kg IV q.48 h. to a cumulative dose of 12–15 mg/kg; administer as a 1–2 mg/mL solution in 5% dextrose by IV infusion over 1–2 hours; this is less nephrotoxic than amphotericin B deoxycholate, but azotemia can occur). Monotherapy with 5-flucytosine should not be used because of the potential for drug resistance to develop, but it is synergistic with amphotericin B (25–50 mg/kg p.o. q.6 h.). The combination of flucytosine and amphotericin B is recommended for feline CNS infections or cats that fail azole therapy. Fluconazole can be substituted for 5-flucytosine in CNS infections if 5-flucytosine is unaffordable, as it can penetrate the blood–brain barrier.

Localized cutaneous disease can often be treated successfully with fluconazole (10 mg/kg p.o. q.12 h.)

until lesions are completely resolved and cryptococcal LCAT titer reduces to zero. As with sinonasal or CNS infections, a four- to fivefold reduction in LCAT titer indicates an adequate response, and LCAT titers should be repeated every 3–6 months thereafter so that recrudescent infections can be diagnosed early. Surgical excision of any nodules can also be considered.

Prevention

Avoidance of exposure to environmental sources can usually be achieved by indoor only housing; however, cases have occurred in indoor only cats in endemic areas.

Public Health Implications

Infection is acquired from direct exposure to contaminated environmental sources such as avian feces and rotting vegetation. Since there is no aerosolization of cryptococcal organisms from infected tissues, infection is not transmitted between animals or from infected animals to people.

FELINE ASPERGILLOSIS

See also Chapter 6.

Definition/Overview

Although aspergillosis does occur in the cat, the incidence of infection is far less than that in the dog. There are two anatomic forms of upper respiratory tract aspergillosis in cats, and both commence in the nasal cavity: Sinonasal aspergillosis (causing local signs of chronic nasal infection) and more commonly (65% cases) invasive sino-orbital aspergillosis (with signs of orbital and local soft tissue swelling). This is in contrast with the dog, in which 99% of cases are noninvasive and sinonasal. Disseminated aspergillosis is typically associated with immunosuppression, and while it has been reported in the cat, it is rare. Invasive focal (non-upper respiratory tract) infections have also been the subject of rare feline case reports.

Etiology

Aspergillosis is caused by several species of fungus of the genus *Aspergillus*, which occurs in rotting vegetation, moldy hay, and sewage. Animals become infected through inhalation of airborne spores. *A. fumigatus* and *A. niger* are most commonly associated with sinonasal aspergillosis (SNA), while *A. felis* and *A. udagawae* are the most common isolate responsible for sino-orbital aspergillosis (SOA).

Pathophysiology

Colonization is usually prevented by a local immune response to inhaled spores involving mucociliary clearance, macrophages, and dendritic cells that recognize specific fungal epitopes. In cats where this immune response is suboptimal, the spores adhere to and invade the respiratory epithelium, destroying surrounding cells and avoiding phagocytosis. Infection usually occurs in young to middle-aged cats, those with previous viral upper respiratory tract infections, and brachycephalic breeds, such as Himalayans. Association with damage to the normal mucosal barrier as a consequence of nasal trauma, foreign bodies, and neoplasia has also been reported. SNA progresses to SOA via development of direct naso-orbital communication due to bone lysis.

Clinical Presentation

Cats with upper respiratory tract aspergillosis can present with sneezing, stertor, unilateral or bilateral serous to mucopurulent nasal discharge, mild ipsilateral mandibular lymphadenopathy, and clinical signs relating to periorbital involvement, such as exophthalmos and third eyelid protrusion. Epistaxis, pyrexia, and/or a discharging sinus or soft tissue mass involving the nasal bone or frontal sinus are less commonly seen.

Differential Diagnosis

Differential diagnoses include viral upper respiratory disease (FHV-1 and/or FCV), nasal cryptococcosis or other fungal infection (e.g., sporotrichosis, phaeohyphomycosis), nasal neoplasia (e.g., lymphoma, squamous cell carcinoma), nasal foreign body, penetrating bite wound, tooth root abscess, oronasal fistula, trauma to the nasal cavity or frontal sinus, or congenital abnormalities such as choanal atresia or palatine defects.

Diagnosis

Diagnostic tools include serology, radiography, advanced imaging (CT and/or MRI), rhinosinuscopy, cytology, histology, fungal culture, and molecular identification. Identification of fungal hyphae on cytology or histologic examination of biopsy specimens or sinonasal fungal plaques can confirm aspergillosis. Ventrodorsal radiography with the animal's mouth open usually reveals major lysis of the turbinates and increased radiolucency. CT has become the imaging technique of choice for sinonasal aspergillosis because it shows clearly the destruction of the turbinates, increased soft tissue attenuation in the nasal cavity, and fluid or soft tissue accumulation in the frontal and sphenoid sinuses; signs are usually bilateral. MRI is preferred for assessment of intracranial soft tissue. In sino-orbital aspergillosis, a ventromedial orbital mass with dorsolateral displacement of the globe and lytic lesions in the paranasal bones are also visualized. The cribriform plate should be inspected for integrity before topical antifungal treatment is considered. Nasopharyngoscopy, rhinoscopy, and/or sinuscopy usually reveals white to greenish gray colonies, which are typical of nasal aspergillosis. Hematology is unremarkable, and a stress or inflammatory leukogram with eosinophilia can be found; mild-to-severe hyperglobulinemia on serum biochemistry is relatively common. For species identification, PCR is required.

Antibody detection assays can be useful as supportive tests but are not confirmatory for diagnosis.

Management/Prognosis

Before treatment commences, the fungal isolate and its susceptibility should be identified, and the integrity of the cribriform plate should be determined on CT examination. Endoscopy and saline irrigation should be used to débride fungal plaques from the nasal cavity and frontal sinuses. Sinus trephination may be required. Pretreatment assessment of renal and liver function should be undertaken because of the hepatotoxic and nephrotoxic nature of the systemic therapies used.

For noninvasive sinonasal infections (and intact cribriform plate), topical 1-hour intranasal infusions with 1% clotrimazole or enilconazole solution can be administered under general anesthesia. Antifungal creams, as used in dogs, are not usually recommended as they are more likely to cause postprocedure airway obstruction. The head should be tilted to ensure drainage of the infusion at the end of the procedure. Systemic antifungal agents can be considered depending on case severity. Repeat treatments are commonly required to resolve infection (ideally cessation of clinical signs and imaging abnormalities (endoscopy +/– repeat CT).

For invasive sino-orbital infections (paranasal soft tissue infiltration and orbital involvement and/or interruption of the cribriform plate), systemic antifungal therapy using itraconazole (10 mg/kg p.o. q.24 h. with food; hepatotoxicity can occur), or posaconazole (2.5–3.75 mg/kg q.12 h. with food; hepatotoxicity can occur), perhaps combined with terbinafine or amphotericin B (deoxycholate (0.25–0.5 mg/kg per cat of 5 mg/mL stock solution diluted in 350 mL of 0.45% NaCl with 2.5% dextrose SC 2 or 3 times weekly to a cumulative dose of 10–15 mg/kg or liposomal (1–1.5 mg/kg IV q.48 h. to a cumulative dose of 12–15 mg/kg; administer as a 1–2 mg/mL solution in 5% dextrose by IV infusion over 1–2 hours; this is less nephrotoxic than amphotericin B deoxycholate, but azotemia can occur). *Aspergillus* spp. are intrinsically resistant to fluconazole therapy. At least 6 months of therapy is often required, and reinfections or relapses can occur. Treatment should be continued for at least 1 month beyond cessation of clinical signs. No benefit of surgical excision of granulomas over medical treatment alone in SOA has been demonstrated.

The prognosis for feline SNA is generally favorable with intensive treatment, while SOA has a poor prognosis, although there are only a handful of published case reports.

FELINE DERMATOPHYTOSIS

See also Chapter 18.

Definition/Overview

This is the most common fungal infection in the cat and presents primarily as a superficial skin disease. It presents with scaling to regular areas of circular alopecia with occasional erythematous margin around a healed center ("ringworm"). The majority of cases are caused by *Microsporum canis* and transmitted by direct contact.

SYSTEMIC MYCOSES

Definition/Overview

The systemic (or deep) mycoses are those infections in dogs and cats caused by *Blastomyces dermatitidis* (blastomycosis), *Coccidioides immitis* (coccidioidomycosis), *Cryptococcus neoformans* (cryptococcosis), and *Histoplasma capsulatum* (histoplasmosis). Each of the organisms listed can be isolated from soil within specific geographic regions throughout the world. Despite the mapping of endemic areas within the United States, the frequency with which pets travel throughout the country suggests that both dogs and, less commonly, cats can be presented with clinical disease outside of defined endemic areas. Since humans and animals share the environment in which soil contamination exists, it is not unusual to see the prevalence of animal infections correspond to the prevalence of human infections.

Etiology

The respiratory tract is the primary route of exposure among susceptible cats. Given the ubiquitous nature of the organisms in soil, it is obvious that many more animals will be exposed than will become clinically ill.

Pathophysiology

In susceptible animals, primary infection generally begins in the lung once the organism reaches the terminal airways. From there, dissemination to multiple organs is possible. In the clinical setting, it is the particular organ or organ systems infected that are responsible for the clinical signs. It is still unclear why some animals, subsequent to exposure, develop severe disseminated disease, while others remain healthy. It has been suggested that disseminated disease is a consequence of exposure in immunocompromised animals. Although antibody does develop in response to infection, it is not protective. Recovery from mycotic disease is attributed to cell-mediated immunity.

Clinical Presentation

In the few reported cases of systemic mycosis in cats, there appears to be no age, breed, or sex predilection to infection. In most cases, clinical signs include weight loss, decreased appetite, and lethargy. Since the respiratory tract is the portal of entry, clinical signs of pneumonia, including cough and dyspnea, are reported. Systemic signs include diarrhea, lameness, abdominal effusion, skin lesions, renal or hepatic failure, and ocular disease, but the signs vary depending on the particular organism involved.

TABLE 21.2.3 Summary of the major clinical signs and recommended biopsy sites for systemic mycotic infections in cats

	Feline	
Mycotic infection	**Presenting signs**	**Recommended biopsy site**
Histoplasmosis	– Dyspnea, tachypnea, possible abnormal lung sounds – Enlarged lymph nodes – Splenomegaly, hepatomegaly	– Bone marrow aspiration/biopsy – Fine-needle aspiration of lung and/or lymph node
Cryptococcosis	– Cryptococcosis is the most common systemic mycotic infection in cats – *Upper respiratory signs predominate:* Sneezing with mucoid nasal discharge not responsive to antimicrobials – A polypoid mass may be visible at the external nares/nasal bridge – Mandibular lymphadenomegaly – Subcutaneous papules or nodules	– Cytologic examination of FNAs from masses, exudate from the nose and skin stained with new methylene blue or Gram stain is preferred over Wright and India ink
Blastomycosis	– Uncommon in cats – When present, signs are similar to dogs – Dyspnea, weight loss, draining skin lesions, and visual impairment are most commonly reported	– Fine-needle aspiration of enlarged lymph nodes and other affected body sites – Cytopathology of skin lesions or exudate (conventional stains may be used)
Coccidioidomycosis	– Similar to the dog – Skin lesions without evidence of a bone lesion are most common – Respiratory signs are rare	– Skin biopsy involving tissue affected with micro abscesses – Multiple biopsies may be required – Attempting to culture *C. immitis* in practice is not recommended

Differential Diagnosis

The list of differential diagnoses for clinical signs associated with any of the systemic mycoses is extensive, depending on the primary organ system(s) involved. However, cachexia associated with neoplasia is one of the most important differentials to consider. Pneumonia, sepsis, enteritis, hepatic insufficiency, and polyarthritis are among the other differentials that apply.

Diagnosis

Bone marrow and other tissues are important sources for obtaining samples for a cytologic diagnosis (Figure 21.2.32). In dogs and cats with overt clinical signs and external manifestations of disease, it is practical, in the clinical setting, to identify the specific organism involved. The predominant clinical findings and the preferred tissue for identification of organisms are summarized in Table 21.2.3.

Thoracic radiographs are indicated in any dog or cat suspected of having a systemic mycotic infection. A diffuse, miliary to nodular interstitial pulmonary infiltrate is a common clinical finding, particularly in animals with signs of respiratory disease (Figure 21.2.33). The most common sites of biopsy for cytologic evaluation and diagnosis for each of the major systemic mycoses are summarized in Table 21.2.3.

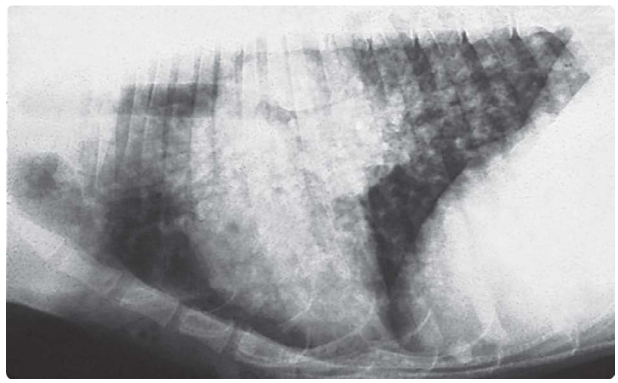


FIGURE 21.2.33 Lateral radiograph of a 2-year-old dog with a diffuse interstitial lung pattern characteristic of mycotic pneumonia.

Management

Treatment/Prognosis

The treatment protocols for cats infected with each of the four systemic mycoses described in this section are summarized in Table 21.2.4. However, the cost associated with treatment and the severity of clinical signs associated with the infection may ultimately determine the prognosis.

Prevention

There is currently no vaccine available for any of the systemic fungal infections. Given the ubiquitous nature of the organisms in soil, preventing exposure is extremely difficult in endemic areas. Chemical decontamination of the soil with formaldehyde solution is possible, but this is impractical for treating large areas.

Public Health Implications

Despite the fact that both humans and animals can be infected with each of the organisms discussed in this section, there is no known transmission from dogs or cats to humans or other animals. None of the systemic

TABLE 21.2.4 Recommended and alternative treatment protocols for systemic mycotic infections in cats

Mycotic infection	Feline
Histoplasmosis	Itraconazole (10 mg/kg p.o. q.12 h. for 4–6 months) (oral solution is recommended) **Alternatives** – Fluconazole (2.5–5.0 mg/kg p.o. q.12–24 h. for 4–6 months) or – Amphotericin B (deoxycholate) (0.25–0.5 mg/kg IV only administered on alternate days until a cumulative dose of 4–8 mg/kg is achieved)
Cryptococcosis	Itraconazole (10–20 mg/kg p.o. q.24 h. for at least 6 and up to 18 months) **Alternatives** – Fluconazole (2.5–5.0 mg/kg p.o. q.12–24 h. for 6–10 months) or – Flucytosine (75 mg/kg p.o. q.12 h. for 1–9 months) plus amphotericin B (deoxycholate) (0.1–0.5 mg/kg IV only administered on alternate days until a cumulative dose of 4–8 mg/kg is achieved) – (Recommended for patients with CNS involvement) Note: Amphotericin B is the only drug that is fungicidal
Blastomycosis	Itraconazole (5 mg/kg p.o. q.12 h. for 2 months or at least until 1 month following resolution of signs) **Alternative** – Amphotericin B (deoxycholate) (0.1–0.5 mg/kg IV only administered on alternate days until a cumulative dose of 4–8 mg/kg is achieved)
Coccidioidomycosis	Ketoconazole (50 mg [total] p.o. q.12 h.; expect to treat for up to 12 months) **Alternative** – Itraconazole (25–50 mg [total] p.o. q.12–24 h. for 8–12 months)

mycoses discussed in this section are considered zoonotic diseases.

PARASITIC INFECTIONS

PULMONARY PARASITES – FELINE LUNGWORM

Chapter 6 also covers this area and other infectious agents.

Definition/Overview

Lungworms are emerging parasites of the lower respiratory tract of cats. Several nematode species of importance are being increasingly recognized as a cause of respiratory signs, particularly in younger cats. Prevalence rates very and are linked to the cat's lifestyle and ecological factors. Wild cats are important hosts of some species.

Etiology

Aelurostrongylus abstrusus is the most important and most prevalent feline lungworm worldwide. Others of importance are *Troglostrongylus brevior* (especially in Mediterranean/Balkan countries and the Middle East) and *Capillaria aerophila* (syn. *Eucoleus aerophilus*, worldwide distribution), and mixed lungworm infestations are increasingly reported. *A. abstrusus* and *T. brevior* have indirect life cycles involving mollusks (slugs or snails) as intermediate hosts. Mollusks are penetrated by larvae hatched from eggs laid in the cat's respiratory tract, which are coughed up and swallowed and then excreted in their feces. The infective larvae are then shed in mucus from the mollusk. *T. brevior* may also be vertically transmitted, causing severe disease in kittens. *Capillaria aerophila* has a direct cycle, and eggs laid in the cat's respiratory tract are coughed up and swallowed and then excreted in their feces; earthworms can act as paratenic hosts. Cats become lungworm infected by ingesting intermediate or paratenic hosts containing larvae, which then migrate from the intestinal tract to the lungs where they mature into adults.

Cats of any age can be infected, but it is more prevalent in younger cats of less than 4 years and in cats with outdoor access.

Pathophysiology

Eggs, larvae, and adults accumulate in the alveoli, bronchioles, and arteries, inducing granulomatous or mixed inflammation. Bacterial complications such as mucopurulent bronchopneumonia or pyothorax can occur. In severe disease, pulmonary hypertension and right-sided heart disease can result.

Clinical Presentation

The severity of clinical signs depends on the lungworm species and numbers as well as the cat's immune response to infection. Respiratory signs can be absent, mild, or severe. They include nasal discharge, sneezing, coughing, tachypnea, dyspnea, diffuse bronchopneumonia, pyothorax, or pneumothorax. Kittens/younger cats and cats with mixed infestations generally develop more severe disease. *A. abstrusus* and *T. brevior* are more pathogenic. Asymptomatic carriage of *C. aerophila* is common. Lungworm is reported as a cause of anesthesia-associated death in cats.

Differential Diagnosis

These include common conditions of the lower respiratory tract such as feline bronchial disease and feline asthma. Other differentials include pneumonia, fungal disease, toxoplasmosis, feline infectious peritonitis, and neoplasia.

Diagnosis

The Baermann method, based on larval migration, detects the live larvae of *A. abstrusus* and *T. brevior*, while flotation is used to detect *C. aerophila* eggs, but both these methods are insensitive and require trained personnel to identify species. Ideally, fecal samples should be collected over 3 days. PCR assays now exist for diagnosis in feces, and pharyngeal swab PCR shows promise for *A. abstrusus* and *T. brevior* diagnosis. Thoracic imaging provides information on severity of disease, but changes are nonspecific, including interstitial, alveolar, and/or bronchial abnormalities. Although lungworm may be visible in bronchoalveolar lavage samples, anesthesia required for this procedure is a risk in cats with lungworm infection.

Management

Treatment/Prognosis

Even in cats showing severe clinical signs, widespread radiographic changes, and/or pulmonary hypertension, suitable treatment is usually very effective, although supportive care may be required with oxygen and thoracocentesis (pyothorax).

Several anthelminthic products are effective in eradicating infection, although studies published vary in lungworm species evaluated and labeled uses vary. Agents effective for *A. abstrusus* include oral fenbendazole, spot-on moxidectin 1%, and spot-on emodepside 2.1%. The latter has been shown to be effective via two repeated doses of emodepside spot-on applied with a 2-week interval. Spot-on eprinomectin 0.4% is also effective for *A. abstrusus*. Fewer studies have been done on the response of *T. brevior* and *C. aerophila* to treatment, but spot-on products containing emodepside, eprinomectin, or moxidectin appear to be effective. The Baermann test should be repeated after treatment to confirm cessation of larvae shedding.

Prevention

No vaccine is available for the prevention of lungworm in cats. Avoiding outdoor access reduces hunting behavior and the risk for predation of intermediate or paratenic hosts, although this may not be possible in many cats that need outdoor access for behavioral needs.

Spot-on moxidectin 1% and eprinomectin 0.4% can prevent *A. abstrusus* and *T. brevior* infections.

Public Health Implications

Capillaria aerophila has zoonotic potential as it infects many mammalian species, including humans, in which it occasionally causes respiratory disease.

GASTROINTESTINAL PARASITES

The scope of this subject is too extensive to cover in the current chapter and they are discussed in Chapter 9. The two most common gastrointestinal parasites of clinical concern will be discussed briefly here: Feline tritrichomonas and giardiasis.

FELINE TRITRICHOMONAS

Tritrichomonas is protozoan parasite causing predominantly pungent large intestinal diarrhea (mucous, hematochezia) usually in young cats from multicat households. Presence of perianal swelling and fecal incontinence raises suspicion. Not all infections are associated with clinical signs. Transmission is via the fecal–oral route.

Diagnosis in the presence of clinical signs is based on detection of motile trophozoites in wet mount preparations or by PCR from feces (sample collection by insertion of a fecal loop into the rectum may be more reliable than colonic washes).

Treatment is either supportive as infections are often self-limiting, but this can take months, or consideration of ronidazole (30 mg/kg per day p.o. for 14 days), an unlicensed product that carries the risk of neurotoxicity. Relapses occur in up to 25% of cases. Addition of a probiotic to treatment has shown some promise. Ideally, affected cats are isolated, and strict hygiene with regular litter tray cleaning, using routine disinfectants, is advised. It is not considered to be a zoonosis.

GIARDIASIS

Giardia is a protozoan parasite causing typically small intestinal diarrhea (although large intestinal characteristics such as occasional mucus and fresh blood can be seen) and weight loss in young cats (< 1 year old) from multicat households. Many infections are subclinical, so cause and effect can be hard to prove.

Initial treatment consists of fenbendazole (50 mg/kg p.o. s.i.d. 5–7 days) and environmental management. Giardia cysts are highly infectious and resistant in the environment, so only a small number are needed to cause infection or re-infection. Regular high temperature washing of food and water bowls, removal of feces, and quaternary ammonium compounds with a 1-minute contact time to clean contaminated surfaces is important. Alternatively, metronidazole (25 mg/kg p.o. s.i.d. for 5 days; higher doses are associated with neurotoxicity). In cases of repeated episodes in a multicat environment, treatment of all in-contact cats should be considered.

There is no current evidence of transmission from cats to humans, but due to potential risk, normal hygiene measures are advised.

POLYSYSTEMIC INFECTIONS

FELINE TOXOPLASMOSIS

Definition/Overview

Feline toxoplasmosis is caused by infection with the obligate intracellular coccidian parasite *Toxoplasma gondii*. Several genotypes exist worldwide. Around 35% of cats are seropositive for *T. gondii* antibodies, with higher percentages reported in Australia (52%) and Africa (51%) and lower percentages in Asia (27%). The organism is capable of infecting virtually all species of warm-blooded animals, including humans, although cats are the only definitive hosts for the parasite.

Etiology

Infection of cats or kittens from infected queens occurs via ingestion of cysts, transplacentally, or transmammary. While infection via ingestion of sporulated oocysts in cat feces is possible, this is thought to be rare because of fastidious elimination habits in cats. Cats with outdoor access are especially at risk of exposure subsequent to hunting and ingesting *T. gondii* cysts in the tissues of intermediate hosts or mechanical vectors such as cockroaches and rodents; indoor-only cats can also have access to intermediate hosts as well as via raw meat feeding.

Pathophysiology

As the cat is the definitive host of *T. gondii*, it is the only species where the parasite undergoes the enteroepithelial cycle, where infection in intestinal cells undergoes asexual and sexual phases to produce oocysts, which are passed in the feces. After primary infection, cats shed unsporulated oocysts in the feces for up to 3 weeks (usually 1–2 weeks) before the immune response stops oocyst shedding. Oocysts sporulate and become infective in 1–5 days, and the resulting oocysts remain viable for up to 18 months in suitable environmental temperature and humidity conditions before being ingested by warm-blooded intermediate hosts. Repeat oocyst shedding after the primary infection cycle in cats is rare, even in immunosuppressed cats. Clinical abnormalities associated with the enteroepithelial cycle are uncommon, but self-limiting small bowel diarrhea has been reported in some cats.

In the cat and all other mammals, the extraepithelial cycle occurs. After contact with cat feces containing sporulated oocysts, or ingestion of bradyzoite cysts in infected tissues, sporozoites penetrate the intestinal wall and develop into an actively replicating phase (tachyzoites), which spread via the blood and lymphatic circulation to localize infected tissues. As the host immune system responds, parasitic replication slows, and bradyzoites are then formed in tissue cysts and remain in the host for life. The extraepithelial cycle does not result in oocyst production.

Clinical illness subsequent to the ingestion of tissue cysts or oocysts or reactivation of latent infection is uncommon in cats. The reason that some cats develop significant clinical disease while many others do not is likely due to parasite virulence factors and the immune response of the host. Immunosuppression due to high-dose corticosteroid and cyclosporine therapy and FIV infection has been associated with recrudescent *T. gondii* infection. Additionally, naïve *T. gondii* infection in cats receiving immunosuppressive therapy, such as cyclosporine, can sometimes be fatal due to disseminated toxoplasmosis.

Clinical Presentation

Clinical signs of extraepithelial toxoplasmosis, if present, can include neurological signs (ataxia, seizures, encephalitis [Figure 21.2.34]), muscle pain (sometimes myocarditis), pulmonary disease (dyspnea, cough), ocular inflammation (uveitis, chorioretinitis, glaucoma, and retinal detachment have been reported (see Figure 19.24), hepatitis (occasionally with icterus), pancreatitis, dermatitis (nodules, panniculitis), and fever. In kittens, pulmonary and hepatic disease tends to be most life threatening. Transplacental infection can cause abortion and stillbirths.

Differential Diagnosis

For cats with neurological signs, consider FIP, FeLV, FIV, and neoplasia as differential diagnoses, while for those with respiratory signs, consider bacterial pneumonia/pyothorax, mycobacterial disease, lungworm, and heart disease. Inflammatory ocular disease can occur with FIP, FeLV, FIV, and mycobacterial disease. Among kittens, sudden death may be reported, so feline panleukopenia virus infection should be considered. FeLV and FIV testing is indicated.

Diagnosis

Hematologic and biochemical changes reported in cats with *T. gondii* disease are nonspecific but can include mild



FIGURE 21.2.34 This 4-year-old Domestic Shorthair cat has diffuse *Toxoplasma* encephalitis. The cat was euthanized, and the diagnosis confirmed on necropsy. (*Courtesy of M. Schaer.*)

anemia, leukocytosis, eosinophilia, and polyclonal hyperglobulinemia. Depending on the degree of hepatitis present, liver enzymes and serum bilirubin may be increased. Creatine kinase is elevated with myositis. Radiographic evidence of pneumonia or thoracic or abdominal effusions may be present, and ultrasonography may show changes with pancreatitis or hepatitis. Sampling may demonstrate evidence of tachyzoites on bronchoalveolar lavages or fine-needle aspiration of the lung (if accessible and safe to perform) or other affected sites (e.g., dermal nodules, bile, CSF) or effusions and provides a definitive diagnosis. PCR assays for *T. gondii* can also be performed on these samples, and positive results provide supporting evidence for a diagnosis of toxoplasmosis.

Since infected cats harbor *T. gondii* tissue cysts for life, measurement of serum anti-*T. gondii* antibodies is not always helpful for diagnosis. Anti-*T. gondii* IgM antibodies are associated with recent or recrudescent extraepithelial infection (from 2 until 16 weeks after infection), and anti-*T. gondii* IgG antibodies generally indicate infection of at least 10 days' duration, but neither of these antibody measurements correlate with active disease. In the absence of demonstration of tachyzoites on sampling, and in the presence of clinical signs consistent with toxoplasmosis, a tentative antemortem diagnosis can be based on a combination of: (1) An IgM titer higher than 1:64; (2) a fourfold or greater increase in IgG titer; and (3) positive response to treatment for toxoplasmosis.

Routine fecal examination of cats suspected of having toxoplasmosis is not helpful in diagnosis, as most cats are no longer shedding oocysts by the time clinical signs of extraepithelial infection occur. Following primary infection, cats usually shed *T. gondii* oocysts for only 1–2 weeks, and repeat oocyst shedding is rare. Additionally, microscopically *T. gondii* oocysts are indistinguishable from *Hammondia hammondi* oocysts, necessitating PCR to differentiate.

Management

Treatment/Prognosis

Cats with extraepithelial toxoplasmosis can be treated with clindamycin (10–15 mg/kg p.o. q.12 h. for 4 weeks) or trimethoprim/sulfa combination antimicrobial drugs (15 mg/kg p.o. q.12 h. for 4 weeks). Clinical improvement is expected within 7 days following onset of therapy. If clinical response does not occur with one drug within 7 days, therapy with the other drug can be tried. Cats with clinical uveitis associated with toxoplasmosis may be treated with topical (e.g., 1% prednisolone acetate) or systemic corticosteroids in combination with a topical mydriatic to prevent secondary lens luxation and glaucoma. Cats with hepatic, CNS, or pulmonary disease, and those with concurrent FeLV or FIV, carry a poorer prognosis with treatment. Complete resolution of signs might not occur in neurologic infections after clinical resolution.

Prevention

Treatment does not eliminate extraepithelial *T. gondii* infection, and reactivated infection is always possible. No vaccine is commercially available. Preventing kittens and cats from hunting (including ingesting transport hosts such as cockroaches) and feeding only commercially prepared cat food, without raw meat supplements, is a highly effective means of preventing infection. Freezing meat kills cysts too. Assessing the toxoplasma status of cats before starting cyclosporine therapy can be helpful, as if the cat is seronegative, then the earlier mentioned preventative measures can be taken to reduce the possibility of *T. gondii* infection when immunosuppressive treatment is started. Some have suggested giving clindamycin to cats for 3–4 weeks before starting cyclosporine, but the efficacy of this has not been confirmed.

Public Health Implications

Since the cat is a definitive host for *T. gondii* and is capable of excreting oocysts in feces during the enteroepithelial phase of infection, the cat represents a potential threat to human health, although oocyst excretion typically only occurs during 1–2 weeks over the cat's lifetime and is usually asymptomatic. Excreted oocysts are not infectious until they have undergone sporulation (approximately 48 hours at room temperature), so quick clearing of litter trays should help prevent human contact with sporulated oocysts during feces removal from trays. Because of fastidious grooming habits, cats are unlikely to harbor infective oocysts on their hair coat. Thus, the cat is a rare source of direct infection to people. Oocysts are resistant to disinfectants, and boiling water is superior to liquid disinfectants. Steam cleaning can be used to decontaminate hard, impervious surfaces.

Cat owners who are regarded as being at risk of infection, such as immunocompromised individuals or seronegative pregnant women, with *T. gondii* can take basic precautions to avoid exposure. If possible, at-risk individuals should not have access to litter pans; however, cleaning litter boxes at least every 24 hours will minimize the chance of exposure to sporulated oocysts, as outlined previously, and gloves should be worn. Since sporulated oocysts can survive in the environment for up to 18 months or more, avoiding locations where cats are likely to defecate and/or wearing gloves while working in soil can minimize the risk of exposure to humans, although cats do tend to bury their feces. Most human infections are acquired by eating undercooked meat containing tissue cysts, and the prevalence of protective antibody titers against *T. gondii* is high in people who eat meat. Washing fruit and vegetables that could be contaminated by soil is also important. Human infection can result in mild self-limiting malaise, fever, and lymphadenopathy and is commonly misdiagnosed. Primary infection during pregnancy can result in clinical toxoplasmosis in the fetus, with stillbirths, CNS, and ocular disease.

NOTE

1. For all of the drugs mentioned in this section, it is advised that the dosage recommendations by manufacturers in your country be followed, as they will vary due to each country's licensing requirements.

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CHAPTER

22

Immunologic Disorders

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INTRODUCTION

The immune system interfaces with virtually all other body systems and consequently almost all diseases have an immunologic aspect. For example, the immune system will respond appropriately to the presence of infectious or neoplastic disease, or the existence of a chronic disease state may lead to secondary immunosuppression. More importantly, there is a wide range of diseases that have an immunopathological basis, and these are the focus of this chapter. In order to fully understand these primary immunologic disorders, a solid working knowledge of the immune system is required. This chapter will briefly overview current knowledge of the immune response and immunopathology, and then discuss the four major categories of immune-mediated disease: (1) Allergic disease; (2) autoimmune disease; (3) primary immunodeficiency disease; and (4) immune system neoplasia. Many of the key diseases within these groups are discussed in the individual systems-based chapters of this book. These will be cross-referenced from this chapter, and only selected immunologic disorders not covered elsewhere will be presented here.

THE IMMUNE RESPONSE

The immune system may be fundamentally considered in terms of innate and adaptive immunity. Innate immunity encompasses the more primitive, nonspecific defense mechanisms of the body, while adaptive immunity is antigen-specific, considerably more potent, and encompasses the phenomenon of immunologic memory. It is now known that activity within the innate immune system directs the nature of the subsequent adaptive response. The key cell that links these two systems is the dendritic antigen presenting cell (APC).

Innate Immunity

The innate immune system is most dominant at the mucocutaneous barriers of the body, which are the front line of exposure to pathogens. The microanatomic aspects of these barriers themselves are considered part of the innate immune system and are represented by structures such as:

- The thick, keratinized epidermis of the skin, which is coated by antimicrobial secretions of the sebaceous and sweat glands (**Figure 22.1**).
- The mucociliary escalator of the lower respiratory tract.
- The peristaltic motion of the intestinal tract, coupled with the rapid turnover of enterocytes and secretion of a wide range of enzymatic and antimicrobial substances.

Similarly, the natural microflora of many of these surfaces provides powerful competitive exclusion to pathogens and may also be considered an innate protective feature.

These barrier functions are supported by the soluble and cellular constituents of the innate immune system. The former include secreted immunologic molecules such as components of the alternative complement pathway, antimicrobial peptides such as the "defensins," selected proinflammatory cytokines (such as interleukin [IL]-1, IL-6, and tumor necrosis factor [TNF]-α), and polyreactive IgA and IgM. The cellular components of the innate immune system include nonspecific phagocytic cells (neutrophils and macrophages), the natural killer (NK) cells, which undertake cytotoxic destruction of target cells (e.g., virally infected cells or tumor

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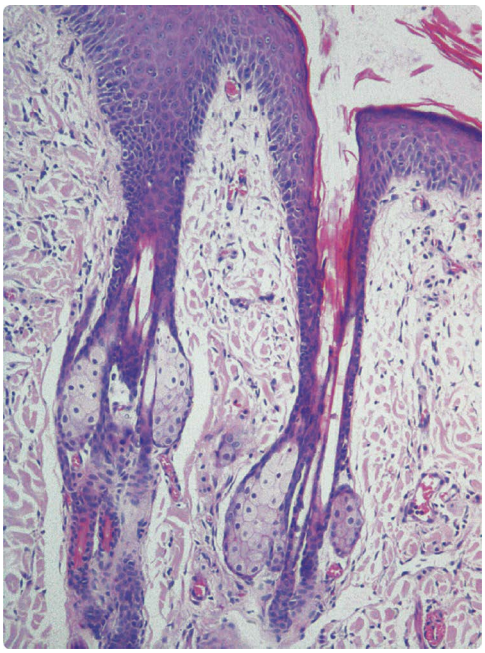


FIGURE 22.1 Section of skin from a cat displaying features of the innate immune system, including the keratinized epidermal barrier, sebaceous gland secretions, and resident leukocytes within the epidermis and superficial dermis.

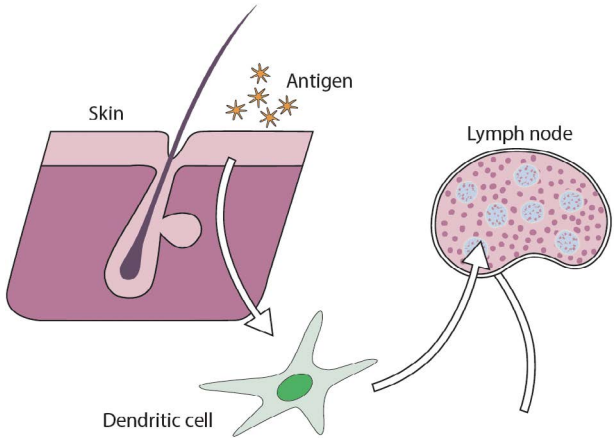


FIGURE 22.2 The dendritic cell is the key link between the innate and adaptive immune systems. In this example, percutaneously absorbed antigen is taken up by an epidermal Langerhans cell and translocated to regional lymphoid tissue via the dermal lymphatic drainage.

cells) in a less specific fashion than T lymphocytes, and the specialized subset of T lymphocytes that express an antigen-specific T-cell receptor (TCR) comprised of a γ and δ chain (γδ TCR).

These components of innate immunity work together to provide immediate protection following exposure to a potential pathogen. Although a relatively less effective means of immune defense, the innate immune system is crucial for the provision of this protective cover until the adaptive response is activated, mobilized, and recruited to the site of pathogen exposure.

The Dendritic Cell—Link between Innate and Adaptive Immunity

The dendritic APC provides the link between innate and adaptive immunity. Dendritic cells are widely distributed throughout the tissues of the body, and are particularly prominent at the mucocutaneous barriers. Some of the best characterized dendritic cells are those of the skin, and these include the epidermal Langerhans cell and the dermal dendritic cells. The primary role of the dendritic cell is the capture of foreign antigen as it penetrates these barriers, the "processing" of this antigen to a form which can stimulate adaptive immunity, and the translocation of antigen from the peripheral point of exposure to the regional draining lymphoid tissue for induction of the adaptive immune response (Figure 22.2).

The initial encounter between foreign antigen and dendritic cell involves a series of dendritic cell receptor molecules termed "pattern recognition receptors" (PRRs) or "Toll-like receptors" (TLRs). These PRRs are expressed either on the surface membrane of the dendritic cell or within the cytoplasm. They interact with ligands that are derived from foreign antigen (e.g., pathogenic microorganisms) or damaged body cells. These ligands are termed "pathogen-associated molecular patterns" (PAMPs) or "microbe-associated molecular patterns" and include structural antigens expressed on the surface of microbes (e.g., lipopolysaccharide) or their internal constituents (e.g., portions of microbial DNA). Ligands derived from altered tissue cells are referred to as "damage- associated molecular patterns." The interaction between PRR and PAMP permits the foreign antigen to be internalized into the cytoplasm of the dendritic cell where it may enter one of two distinct intracellular antigen processing pathways. The first of these pathways involves the enzymatic degradation of the antigen within a cytoplasmic membrane-enclosed compartment. Within this compartment, the complex antigenic structure is degraded into small peptide constituents (of the order of 25 amino acids in length), which become associated with molecules that line the inner surface of the compartment. These are the class II molecules of the major histocompatibility complex (MHC), which are pivotal to the generation of the immune response. Following this "processing" event, the combination of MHC class II and peptide becomes re-expressed on the surface of the dendritic cell, such that the dendritic cell is now "presenting" the antigen–MHC complex (thus the terminology "antigen-presenting cell").

The second intracellular antigen-processing pathway involves degradation of antigen within a distinct cytoplasmic compartment known as the proteasome. Within the proteasome, slightly smaller peptide fragments (10 amino acids in length) are generated, which are then translocated into the cytoplasmic Golgi apparatus where they become associated with class I molecules of the MHC. These complexes of class I MHC and antigenic peptide are also then expressed on the surface of the dendritic cell.

Which of these intracellular processing pathways is activated is determined by the nature of the foreign antigen and, therefore, which of the dendritic cell PRRs become engaged. Broadly speaking, the majority of antigens that are derived from outside of the body (exogenous antigens) and require phagocytosis or pinocytosis enter the MHC class II expression pathway. In contrast, antigens that are derived from within tissue cells (endogenous antigens [e.g., viral antigens synthesized in the cytoplasm from viral genetic material within the cell] or tumor antigens expressed by a tissue cell) are processed by the class I pathway. These pathways are not mutually exclusive, so it is possible for an antigen to be processed by both routes ("cross-presentation").

The antigen-processing procedure involves not only expression of MHC–peptide on the surface of the dendritic cell, but the upregulation of other (co-stimulatory) molecules on the dendritic cell surface and the secretion of soluble intercellular messengers (cytokines) by the activated APC (Figure 22.3). Again, the nature of these co-stimulatory molecules and the type of cytokines are directed by the nature of the inciting antigen and the intracellular signaling pathways triggered when that antigen binds to particular dendritic cell PRRs. All of these outcomes of antigen processing (e.g., presentation by MHC I or II, the nature of co-stimulatory molecules and cytokines) will in turn determine the type of adaptive immune response that is made to the antigen. Thus, the dendritic cell truly is the link between innate and adaptive immunity and the key factor determining the quality of the adaptive immune response.

All of the events described above occur within the dendritic APC, but the second major role of this cell is in translocation of antigen from the site of exposure (e.g., at a mucocutaneous surface) to the regional draining lymphoid tissue. This procedure involves the antigen-laden dendritic cell entering the tissue lymphatics where it travels to the lymph node and enters the T-cell area (paracortex) of the node.

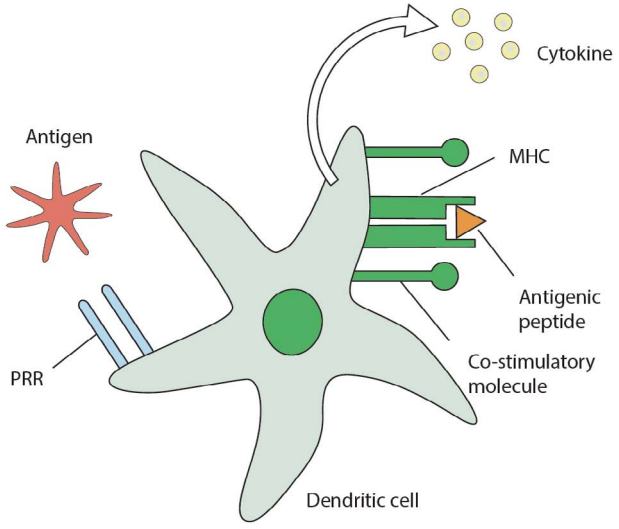


FIGURE 22.3 The APC (dendritic cell) engages foreign antigen via surface PRRs. The antigen is internalized, processed, and re-presented on the surface of the cell associated with a class II MHC molecule. The dendritic cell also upregulates the expression of co-stimulatory molecules and secretes co-stimulatory cytokines.

The Adaptive Immune Response

Once the antigen-laden dendritic cell arrives in the lymph node paracortex it remains relatively stationary, while numerous T lymphocytes approach it to "test out" whether their TCRs are designed to be able to bind to the combination of antigenic peptide and MHC expressed by the APC. These T cells express a receptor comprised of an α and β chain, the antigen-binding capacity of which has been predetermined by gene rearrangements within the cell. The T- and B-cell populations of the body between them bear an enormous range of receptor specificities (the receptor "repertoire"), which are designed to be able to interact with any foreign antigen that may ever be encountered by that individual. In order to maximize the potential for any one T or B cell to encounter the antigen that they are 'pre-programmed' to recognize, the lymphoid cells of the body continually recirculate through a complex pathway involving the tissues, lymphatics, and vascular circulation ("immune surveillance"). The recirculating T cells within the lymph node paracortex may or may not be relevant to a particular antigen expressed by any one dendritic cell at any time. *In-vivo* video microscopy of labeled T cells and dendritic cells has shown that an APC within the paracortex might be expected to be approached by up to 500 different T cells each hour.

Possibly the most amazing feature of the immune response is that such interactions between APCs and T cells do occur and result in generation of the adaptive immune response. For antigens that have never before been encountered by the individual, the "naïve" T cell that associates with the APC is not yet committed to generating an adaptive immune response of any particular type. Again, it is the dendritic cell that now determines the nature of this adaptive response by the way in which it signals the naïve T cell.

Dendritic cells expressing antigenic peptide primarily associated with MHC class II are most likely to stimulate that subset of T cells bearing the CD4 ('cluster of differentiation' molecule number 4) molecule (T helper [Th] cells), whereas class I-peptide expression is more likely to activate the CD8-expressing T-cell subset (T cytotoxic [Tc] cells). There are a number of key functional subpopulations of $CD4^+$ T cells and which of these is preferentially activated by activation of the naïve $CD4^+$ T cell precursor by the dendritic cell determines the functional nature of the ensuing adaptive immune response.

Signaling of the naïve $CD4^+$ T cell, involving release of APC-derived cytokines such as IL-12, IL-18, and IL-27 and activation through the T-cell intracellular signaling pathway STAT 4, results in differentiation of the naïve cell into a mature Th1 cell. The Th1 cell is defined functionally by production of the cytokines IL-2 and interferon (IFN)-γ and by the initiation of an adaptive immune response dominated by cell-mediated immunity

(CMI). CMI involves the activation of cytotoxic CD8+ T cells and NK cells for destruction of virally infected or neoplastic target cells, or the activation of macrophages to permit destruction of an intracellular pathogen such as *Leishmania*, *Salmonella*, or *Mycobacterium*. The Th1-driven immune response features only limited antibody production of those IgG subclasses that might be involved in opsonization or antibody-dependent cell-mediated cytotoxicity. Consequently, the antigens that induce this form of immune response are largely exogenous pathogens of the type listed above (Figure 22.4).

By contrast, signaling of the naïve CD4+ T cell, involving release of APC-derived cytokines such as IL-4 and activation through the T-cell intracellular signaling pathway STAT 6, results in differentiation of the naïve cell into a mature Th2 cell. The Th2 cell is defined functionally by production of the cytokines IL-4, IL-5, IL-6, IL-9, and IL-13 and by the initiation of an adaptive immune response dominated by humoral (antibody-mediated) immunity. Such antibody responses (involving production of alternative IgG subclasses to those above, IgA and IgE) might be required in adaptive immune responses driven by the presence of pathogens such as yeasts, *Escherichia coli*, or helminth parasites (Figure 22.4).

Activation of the naïve CD4+ T cell via the STAT 3 pathway and APC-derived IL-6, IL-23, or transforming growth factor (TGF)-β results in differentiation into a Th17 cell. Th17 cells are defined by their production of IL-17 and have a key role in the defense against bacterial and fungal infections.

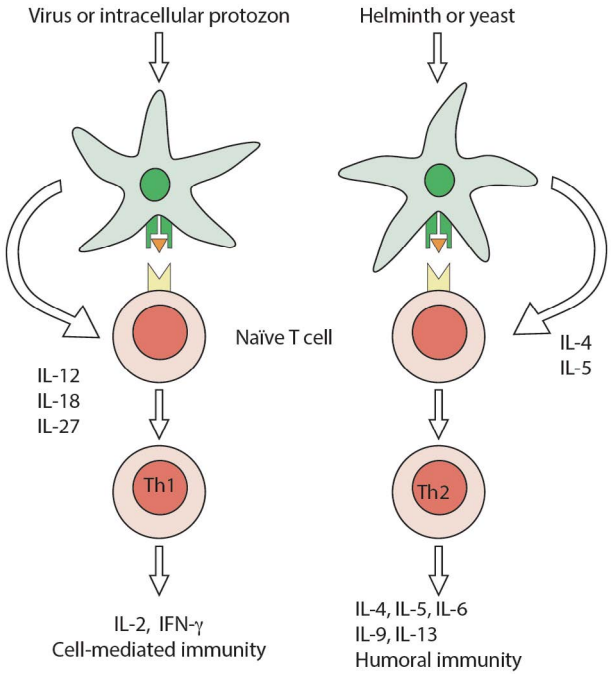


FIGURE 22.4 Processed antigen is presented by the dendritic cell to naïve CD4+ T lymphocytes. The nature of the inciting antigen determines the type of stimulatory signal provided by the dendritic cell and thus the pathway of differentiation of the T cell. Differentiation towards Th1 promotes a cell-mediated effector immune response, whereas the Th2 subpopulation induces a humoral effector response.

Although less well understood, the dendritic cell–T cell encounter is also likely to control the differentiation of the subsets of CD4+ T cells that are involved in suppression (or "downregulation"') of the immune response. The major suppressive populations include the CD4+CD25+ "natural suppressor cells," which are constitutively present in the body, the CD4+ IL-10 producing "induced suppressor cells" (T regulatory cells [Tregs]), which are induced following antigen exposure, and the Th3 cells that are important in the regulation of mucosal immune responses and defined by the production of TGF-β.

The activation of T cells by interaction with APCs involves not only determination of the qualitative nature of the adaptive immune response, but the expansion of antigen-relevant clones of T cells via the process of clonal proliferation. This generates large numbers of antigen-specific T cells that mediate the effector immune response. At least some of these T cells are required for activation of antigen-specific B lymphocytes, which will undertake the humoral immune response.

B-cell activation proceeds in a different fashion to that described for T cells. B cells within the lymphoid tissue reside in primary follicles. Antigen-specific B cells similarly require a combination of activation signals. The first of these comes from the antigen itself, which is recognized by the B-cell receptor (BCR) or surface membrane immunoglobulin. The naïve B cell expresses the combination of IgD and IgM receptor molecules of identical, genetically determined, antigen specificity. The BCR recognizes a large, conformational determinant of antigen (rather than an MHC-associated peptide fragment). This antigenic determinant may be present in soluble form in the B cell environment or may be physically delivered on the surface of an APC. Again, only those B cells bearing antigen-relevant BCRs will be able to recognize antigen, and continual B-cell recirculation is important to maximize the chance of this occurrence. For the majority of (T-dependent) antigens, B-cell activation requires T-cell help. It is now known that following Th cell activation (as described above), some of these cells migrate from the paracortex into the margins of primary follicles, where they encounter B cells carrying receptors for the same stimulating antigen (Figure 22.5).

Following BCR–antigen recognition, the B cell internalizes these surface molecules into a cytoplasmic compartment where there is antigen processing and association with MHC class II molecules as described for the dendritic cell. The B cell also presents these MHC–antigen complexes on its surface membrane. T-cell help for B-cell activation takes the form of:

- TCR binding MHC–peptide on the B-cell surface.
- The interaction of other co-stimulatory molecules on the surface of each cell.
- The release of co-stimulatory cytokines from the T cell (e.g., IL-4, IL-5), which bind cytokine receptors on the B-cell surface (Figure 22.6).

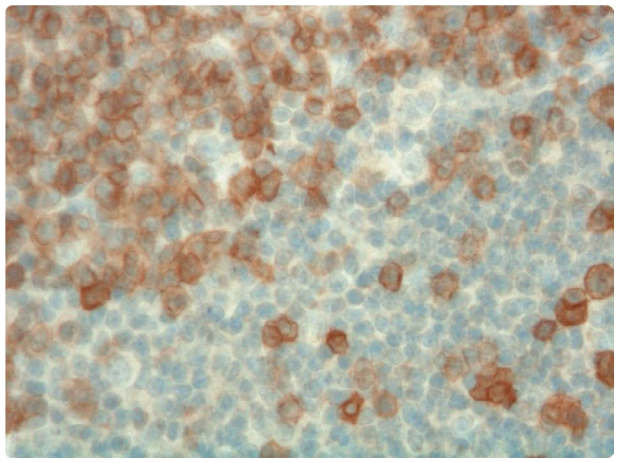


FIGURE 22.5 Canine lymph node labeled to show expression of the T-cell marker CD3. The image includes the junction between paracortex and a primary lymphoid follicle. Scattered T cells are found within the follicular (B cell) area. These helper cells will provide co-stimulation for antigen-activated B cells and generation of a secondary lymphoid follicle.

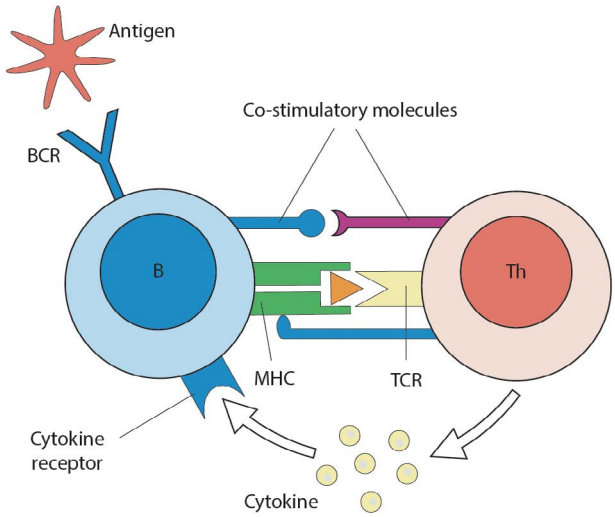


FIGURE 22.6 Provision of T-cell help for activation of a B cell. The B lymphocyte recognizes intact antigen through surface immunoglobulin (the B-cell receptor). The B cell internalizes the antigen, processes it, and re-presents a peptide fragment of antigen associated with an MHC class II molecule. The T helper cell physically interacts with the B cell through the TCR and engagement of co-stimulatory molecules expressed on the surface of each cell. In addition, the T cell releases co-stimulatory cytokine that binds cytokine receptor on the target B cell.

B-cell activation also results in clonal proliferation, which in the case of a B cell is shown by the formation of a secondary follicle with a blastic germinal center and surrounding mantle zone of small lymphocytes. Additionally, the stimulated B cells undergo the "immunoglobulin class switch," which involves genetic recombination to permit expression of a single immunoglobulin class (generally IgG, IgA, or IgE). The type of immunoglobulin is determined by the type of Th cell (Th1 versus Th2) and in turn by the nature of the stimulating antigen (see above). For example, an intestinal helminth parasite is most likely to stimulate Th2 activation and IgE class switching within the mesenteric lymph node. The end stage of B-cell activation is transformation of that B cell into a plasma cell, which can actively secrete immunoglobulin of the predetermined class and antigen specificity.

Having expanded antigen-specific T- and B-cell populations within the regional lymphoid tissue, the next (effector) phase of the immune response necessitates these cells leaving the node within efferent lymph, which eventually drains into the vascular circulation. The antigen-specific lymphocytes circulate in the blood until they encounter modified endothelial cells bearing molecules ("vascular addressins") that bind to ligands on the circulating cells ("homing receptors") and enable the circulating lymphocytes to be arrested in their flow and to diapedese between endothelia into the tissue containing the inciting antigen. Having attained this position, these lymphocytes of the adaptive immune system are now able to reinforce the innate immunity that has, to date, dealt with the initiating pathogen. The nature of this effector immune response is determined by the nature of the pathogen and those aspects of the immunologic armory that are best able to eliminate it. For example, the cutaneous immune response to *Leishmania* would best be served by the action of Th1 lymphocytes producing IFN-γ, which may stimulate parasitized macrophages and allow them to destroy the pathogen that was replicating within their cytoplasm. Concurrently, the activation of IgG-secreting plasma cells would provide antigen-specific antibody that might bind and neutralize free amastigotes that were released from ruptured parasitized cells. In this instance, a Th2 response with dominant humoral immunity would not be protective, which is exactly the situation that arises in susceptible dogs that succumb to the infection.

The final stage of the adaptive immune response involves suppression of the response when it is no longer required (i.e., when antigen is eliminated). Such suppression is an active event, and primarily involves the range of Tregs described above. Through either physical contact or inhibitory cytokine production, or both, suppressor cells are able to inhibit the function or physically remove (by induction of apoptosis) the effector populations. The antigen-stimulated cells are never entirely removed, as for each immune response that is made, a residual population of long-lived memory T and B lymphocytes persists, generally for the lifetime of the individual.

IMMUNOPATHOGENIC MECHANISMS

Despite the wide array of antigens that might potentially be encountered by an individual (e.g., infectious agents, allergens, tissue alloantigens, autoantigens, tumor antigens), the immune system generally responds to stimulation by using one or more of a series of well-defined immunopathogenic mechanisms. These were defined many years ago by Gell and Coombs as types I to IV hypersensitivity, and this classification still provides a

useful framework for consideration of immune effector function. These are best considered as "immunopathogenic mechanisms" rather than "hypersensitivity mechanisms" because while they do form the basis for allergic (hypersensitivity) disease, the same mechanisms are involved in other immune-mediated diseases (e.g., autoimmune disease) and in beneficial immune responses to foreign antigens (for which reason they probably evolved initially).

Type I (Immediate) Hypersensitivity

Type I hypersensitivity follows exposure to antigens that selectively trigger Th2 lymphocytes and the production of IgE antibodies. These antibodies bind specific receptor molecules on the surface of basophils and tissue mast cells, and when the sensitized individual is re-exposed to antigen there is binding and cross-linking of these cell-bound IgE molecules. This results in rapid (within 15–20 minutes, thus "immediate" hypersensitivity) mast cell or basophil degranulation, with the release of a wide range of proinflammatory mediators that lead to the well-recognized clinical effects of such reactions, which may be localized or generalized (anaphylactic) (Figures 22.7 and 22.8). These effects include:

- Vasodilation with tissue edema and egress of plasma protein and leukocytes.
- Bronchoconstriction via contraction of smooth muscle.
- Cutaneous pruritus caused by interaction with neurologic pathways.

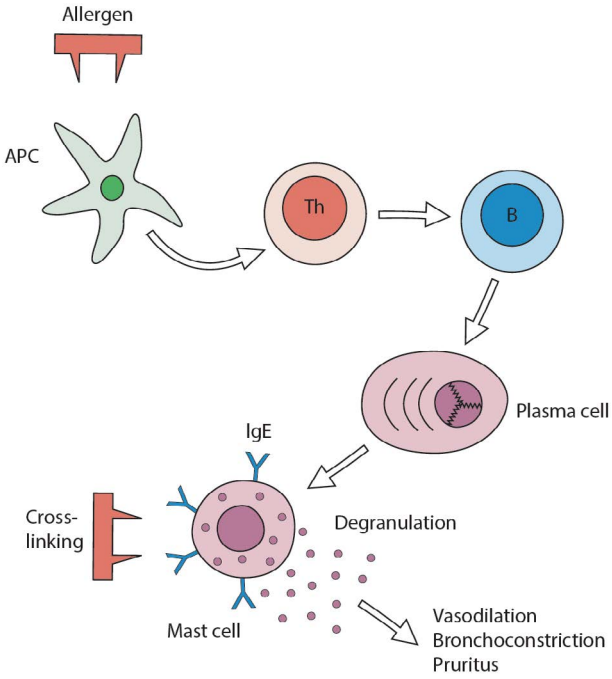


FIGURE 22.7 The type I hypersensitivity reaction. Presentation of allergen by dendritic cells results in stimulation of Th2 immunity, with the generation of allergen-specific IgE antibodies that coat mucocutaneous mast cells. On re-exposure to allergen, there is mast cell degranulation, which mediates the classical clinical features of this reaction.

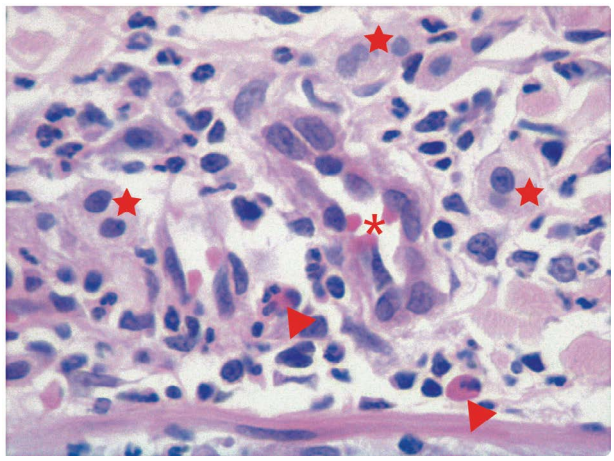


FIGURE 22.8 Skin biopsy from a 5-year-old Domestic Shorthair cat with pruritus and miliary dermatitis. The histopathologic features are characteristic of a type I hypersensitivity reaction. There is a mixed inflammatory infiltration surrounding the superficial dermal vessel (asterisk), which includes small clusters of mast cells (stars) and eosinophils (arrowheads).

The type I reaction probably evolved to provide protective immunity in the case of intestinal helminth parasitism, but it is now most widely recognized as the mechanism underlying the range of allergic diseases of the skin, conjunctivae, respiratory tract, and gastrointestinal tract of the dog and cat.

Type II (Antibody-Mediated) Hypersensitivity

In this reaction, the individual is sensitized to produce antibody that attaches to the surface of a target cell and subsequently activates the classical pathway of the complement system. The deposition of complement molecules onto the target cell surface leads to destruction of that target via either formation of the membrane attack complex of complement with osmotic lysis of the cell or phagocytosis of the immunoglobulin and complement opsonized target (Figure 22.9a, b). The classical target cell for this type of reaction is the erythrocyte, and type II hypersensitivity is the immunopathogenic mechanism that underlies diseases such as immune-mediated hemolytic anemia (IMHA) or blood transfusion reactions. Also included in this category are disorders involving the interaction of antibody with receptor molecules, classically causing either receptor blockade (e.g., antibody to the neuromuscular acetylcholine receptor [AChR] in myasthenia gravis) or receptor activation (e.g., stimulation of the thyroid stimulating hormone receptor by antibody in human Grave's disease).

Type III (Immune Complex) Hypersensitivity

This immunopathogenic mechanism has two distinct subtypes defined by the relative proportions of antigen and antibody involved in the reaction. In antibody

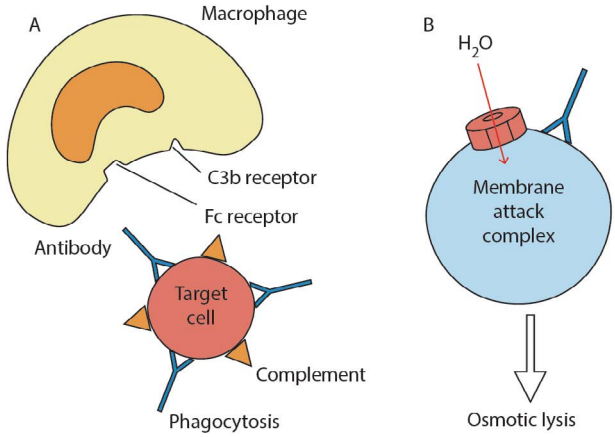


FIGURE 22.9 The type II hypersensitivity reaction. Immunologic sensitization leads to production of antibody that coats a target cell and activates complement deposition via the classical pathway. **(a)** The target cell is thus opsonized for phagocytosis by a macrophage bearing Fc and C3b receptors. **(b)** Alternatively, the membrane attack complex of complement inserts through the cell membrane, creating an ionic imbalance and resulting in a net influx of water into the target cell cytoplasm with subsequent lysis of the target.

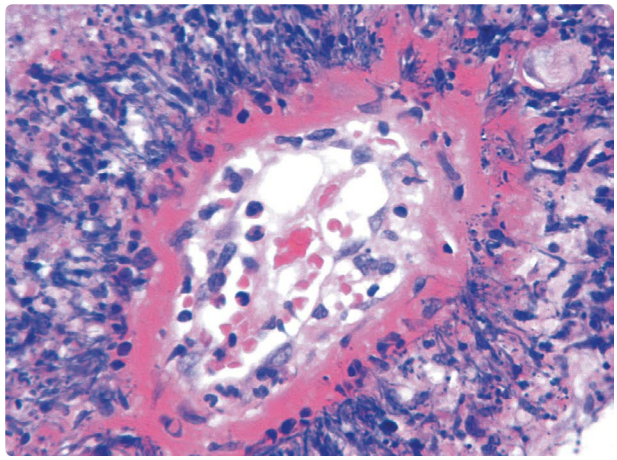


FIGURE 22.10 Cutaneous vasculitis in a dog. This is one of multiple affected dermal blood vessels in biopsy samples taken from ulcerative lesions on the flanks and scrotum of an 11-year-old dog. There is deposition of fibrin in the remains of the wall of this vessel, together with numerous apoptotic neutrophils within the wall and within the surrounding dermal collagen. The cause of this presumptive type III hypersensitivity reaction was not ascertained.

excess type III hypersensitivity, the individual is sensitized to mount a marked antibody response to antigen. On re-exposure to that antigen, the high concentrations of antibody that may be found at the site of antigen entry immediately bind to the antigen at the site of exposure.

The antigen–antibody interaction results in local formation of insoluble immune complexes, with subsequent activation of complement and production of inflammatory mediators and local recruitment of inflammatory cells. The classical example of such a reaction is the human 'Arthus reaction' involving exposure to inhaled antigens (of an occupational nature), with the development of pulmonary disease post exposure in a sensitized individual. Such reactions are rarely documented in the dog and cat.

In antigen excess type III hypersensitivity there are higher concentrations of antigen than antibody, resulting in the formation of small, soluble immune complexes that circulate in the bloodstream. Depending on the nature of the antigen and antibody involved and vascular factors (e.g., endothelial damage, turbulent flow), these complexes may become lodged in the walls of small capillaries in predilection sites such as the renal glomerulus, synovium, uveal tract, and cutaneous basement membrane zone. The ensuing local inflammation (vasculitis) may lead to thrombosis and ischemic necrosis of the tissue supplied by the vessel (Figure 22.10). This form of type III reaction is not uncommon in dogs and cats and, although the inciting antigens are rarely identified, they are often presumed to be of infectious origin and such type III reactions to be post-infectious immune sequelae. A classical example of such a reaction is immune complex glomerulonephritis secondary to *Leishmania* or *Borrelia* infection in the dog (Figure 22.11). Such reactions are also likely to have a role in diseases such as cutaneous lupus erythematosus (CLE), immune-mediated polyarthritis, and immune-mediated uveitis.

Type IV (Delayed) Hypersensitivity

This hypersensitivity reaction involves cellular rather than humoral immunopathologic mechanisms. The response to local tissue re-exposure to antigen in a sensitized individual is the activation of memory T cells, with the recruitment of mononuclear cells (chiefly macrophages, $CD4^+$, and $CD8^+$ T cells) into the site of antigenic exposure via activation of endothelia that permits this site-specific migration. Local tissue damage is mediated

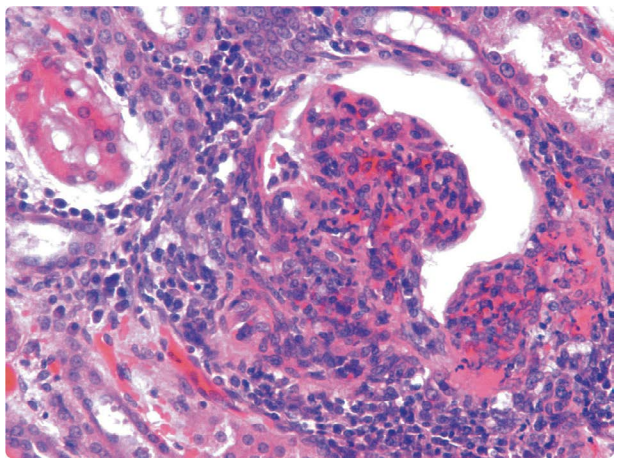


FIGURE 22.11 Section of kidney from a dog with leishmaniasis. There is mononuclear cell infiltration of the interstitium, with distortion and inflammation of the glomerular tuft. Arterial vessels in this section had clear evidence of leukocytoclastic vasculitis. The pathogenesis of these lesions likely involves the deposition of immune complexes containing IgG antibody and *Leishmania* antigen.

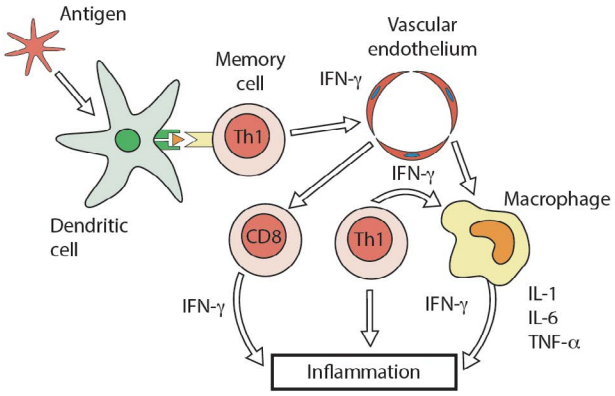


FIGURE 22.12 In type IV hypersensitivity, re-exposure to the sensitizing antigen leads to local activation of memory Th1 cells. These secrete IFN-γ, which activates vascular endothelium and permits recruitment of further T cells (Th1 and $CD8^+$) and macrophages. These in turn secrete further cytokines, which mediate the local inflammatory reaction.

by the infiltrating cells and the cytokines that they produce (Figure 22.12). The activation of T-cell memory and recruitment of mononuclear cells takes some time to occur (classically 72 hours), leading to the description of this reaction as "delayed type hypersensitivity." This type of immunopathologic mechanism is the classical manifestation of a protective Th1 response to a range of tissue pathogens, but when used inappropriately, it forms the basis of the contact hypersensitivity reaction or autoimmune reactions involving cellular infiltration (e.g., immune-mediated polyarthritis, lymphocytic thyroiditis, granulomatous meningoencephalitis).

IMMUNE-MEDIATED DISEASES

Immune-mediated diseases arise when the range of immunologic mechanisms described above are activated inappropriately to produce tissue pathology and clinical signs. This is clearly the case in the range of allergic diseases where there is an inappropriate and excessive immune response (involving combinations of type I and IV reactions) to allergens (e.g., aeroallergens, arthropod-derived allergens) to which a clinically normal individual might be exposed but fail to respond. The allergic diseases are of immense clinical significance in both human and veterinary medicine, and consequently are widely researched and relatively well characterized in terms of their immunopathogenesis.

ALLERGIC DISEASES

There are clear genetic predispositions to the development of allergy in human families and breeds and pedigrees of dog, yet the genetic basis of allergy is not well characterized. Several genome-wide association studies searching for single nucleotide polymorphisms in genes that might be associated with canine atopic dermatitis have produced conflicting data. Whatever the genetic basis, it is clear that some individuals (human and canine) have a predisposition to make high IgE responses to ubiquitous environmental allergens. Such individuals also have reduced effectiveness of immunoregulation, and the allergic state correlates with lack of induced regulatory T cell function (e.g., IL-10-producing Tregs). In addition to genetic and immunologic factors, there are clear environmental influences over the development of allergic disease. This may be as simple as environmental exposure, and reduction of exposure levels to causative allergens is one part of the clinical management of such disorders. In human medicine, much research has focused on the "hygiene hypothesis," which links the high incidence of juvenile allergy and autoimmune disease to lack of exposure to infectious microbes and intestinal parasites in early childhood. Such exposure to infectious agents, particularly those present at the intestinal mucosa, is critical for generating Tregs.

AUTOIMMUNE DISEASES

The second major group of immune-mediated disorders are the autoimmune diseases. These too involve an inappropriate and excessive induction of type II, type III, or type IV hypersensitivity to self-antigens (autoantigens) in the presence of reduced effectiveness of natural Tregs, which would normally prevent such reactions. Clinically normal humans and animals (including dogs) harbor, as part of their lymphocyte repertoire, T and B cells bearing receptors able to recognize self-antigens. These autoreactive cells are normally kept in check by a range of immunoregulatory mechanisms, including:

- Deletion of autoreactive T cells as part of intrathymic development or within the body tissues after thymic emigration.
- Exposure to autoantigen but failure to activate (anergy).
- Failure to expose to autoantigen by lack of antigen presentation or physical sequestration of antigen (immunologic ignorance).
- The activity of natural Tregs.
- Failing to provide autoreactive B cells with T-cell help.

When these control mechanisms fail (leading to loss of immunologic tolerance to autoantigens), an autoimmune reaction with tissue pathology and clinical signs may arise.

As for allergic disease, there is a clear genetic predisposition to autoimmunity in dogs, but such predispositions (for allergic or autoimmune disease) are not well-recognized in feline medicine. The strongest genetic linkages are with specific allotypic variants of the genes encoding MHC molecules. Associations with class II MHC gene haplotypes are now described for a range of canine autoimmune diseases, including rheumatoid arthritis, IMHA, lymphocytic thyroiditis, hypoadrenocorticism, necrotizing meningoencephalitis, diabetes mellitus, and breed-associated chronic hepatitis.

While it was once considered that autoimmunity involved a spontaneously arising immunologic defect in a genetically predisposed individual, there is now recognition that autoimmune diseases have many defined predisposing and trigger factors. Predisposing factors include age (autoimmunity is generally a phenomenon of middle to old age), gender, and lifestyle (e.g., stress, exercise, diet). A recent study has shown that neutered dogs are more likely to die from immune-mediated diseases. Trigger factors are largely environmental and include exposure to drugs, vaccines, and infectious agents. In fact, most autoimmune disease is now considered to be a post-infectious phenomenon and in humans, the active infection may precede onset of the autoimmune disease by months or years. Finally, other chronic disease states (particularly neoplasia or chronic inflammatory disease) may sufficiently disturb immune homeostasis to result in secondary autoimmunity.

This growing concept of recognized trigger factors for autoimmune disease has reshaped the way in which we think about these disorders in companion animal medicine. One example of this changing trend has been the impact of molecular diagnostic methodology for the range of arthropod-transmitted infectious agents that are generally unculturable and may remain cryptic within an infected animal ("stealth pathogens"). The use of molecular diagnostics increasingly allows us to attribute "idiopathic" disease to an infectious agent, and modify management protocols accordingly.

PRIMARY IMMUNODEFICIENCY DISORDERS

The third category of immune-mediated diseases includes the primary immunodeficiency disorders. Instead of being an inappropriate excess of immunity (as in allergy or autoimmunity) this is the reverse scenario, which means that there is an inability to mount a protective immune response due to a congenital, inherited genetic mutation in a gene encoding a key immunologic molecule. Such defects may occur at different levels of immunologic development and consequently lead to clinical disease of varying severity. For example, some defects mean that the animal fails to develop adequate T and B lymphocytes (e.g., X-linked severe combined immunodeficiency; X-SCID), with severely impaired immunity and death during early life. By contrast, a more subtle immunodeficiency (e.g., selective IgA deficiency) may not lead to clinical disease or produce only mild changes. A wide range of primary immunodeficiency disorders is documented in humans and for many the precise genetic mutation is known. A similarly wide range of disorders is suggested to have an immunodeficiency basis in numerous breeds of dog, but only a few of these have been defined at the molecular level. Thus, many of this group of canine diseases should only be considered putative immunodeficiencies at this time. Of note is the fascinating dichotomy between cat and dog in this regard; primary immunodeficiency is extremely rare in the cat, with only a handful of reported cases.

IMMUNE SYSTEM NEOPLASIA

The final group of immunologic disorders comprises those of immune system neoplasia. Although not classically an "immune-mediated" pathology, these tumors are clear manifestations of an abnormal immune system and can impair the remaining immune function of an animal, thus leading to immunocompromise. These disorders include lymphoma, lymphoid leukemia, plasmacytoma, and multiple myeloma, and arguably might also include neoplasia affecting adjunct immune cells such as dendritic cells (the range of histiocytic neoplasia) and mast cells. There are many gaps in our knowledge of the factors that underlie the development of this range of tumors. In cats, retroviral infection has a role, although these diseases still occur in geographical areas with a low prevalence of feline leukemia virus infection or where vaccination and testing programs have reduced the prevalence of infection. There are some well-documented genetic associations for canine lymphoma (e.g., Boxer) and histiocytic neoplasia (e.g., Bernese Mountain Dog, Flat-coated Retriever) and limited epidemiological studies have suggested a role for various environmental carcinogens (e.g., cigarette smoke and feline lymphoma, pesticides and radiation for canine lymphoma).

Although these disorders may be considered as individual entities, there is some linkage between them, as they are all manifestations of disturbed immune system homeostasis. It is possible for more than one type of immunologic abnormality to exist in any one patient at any one time, and a number of such associations are recognized, including:

- Thymoma and myasthenia gravis
- IgA deficiency and autoimmunity
- Inflammatory bowel disease and immune-mediated thrombocytopenia (IMTP) or IMHA
- Lymphoma or leukemia and IMHA

Similarly, different types of autoimmune disease may be recognized concurrently (e.g., combinations of IMHA, IMTP, and immune-mediated neutropenia; IMNP) or may present as multisystemic autoimmune disease (e.g., systemic lupus erythematosus, SLE).

LABORATORY DIAGNOSIS OF IMMUNE-MEDIATED DISEASE

Allergic Disease

Key to the diagnosis and management of allergic disease is identification of the causative allergen. This may be addressed through obtaining a detailed exposure history or by determining whether there is clinical improvement following dietary trial, parasiticidal treatment, or following removal of the animal from the normal environment. For aeroallergens and arthropod-derived allergens (e.g., flea saliva), the generally accepted "gold standard" diagnostic procedure remains the

intradermal test, and some experimental studies have described efficacy of patch testing for demonstration of late-phase responses. Intradermal or percutaneous challenge has not proven reproducible for the diagnosis of food allergy. The use of serologic testing has increased, and many specialists now use these tests in parallel with traditional methodology.

Serologic tests are designed to demonstrate the presence of circulating allergen-specific IgE and/or IgG antibodies. Such tests are almost all based on the ELISA, but vary in the technology used for immunoglobulin detection. Most involve coating test allergens onto the plastic wells of the plate and subsequent incubation with patient serum and then an enzyme-linked detecting reagent (Figure 22.13). The most novel detection technology involves the application of a recombinant version of the IgE Fc receptor molecule. Serologic testing can be informative, but it does not necessarily correlate with intradermal test results, which measure cutaneous mast cell-bound IgE (rather than free antibody in the circulation).

At the research level (but not clinically available), tests such as *in-vitro* mast cell degranulation, blood lymphocyte allergen stimulation (with measurement of cytokine gene transcription), and western blotting for fine definition of the serologic response, have been employed.

Autoimmune Disease

The aim of immunodiagnostic testing in autoimmunity is to confirm an autoimmune pathogenesis by demonstrating circulating or cell- or tissue-bound antibody (and/or complement) relevant to the clinical presentation of the animal. Although a number of autoimmune diseases involve cell-mediated immunopathogenesis, it is not possible at present routinely to investigate these aspects of clinical disease. The key to logical application of these tests is to become familiar with the purpose and limitations of each. For example, there is little rationale in selecting a Coombs test to support the diagnosis of a dog with putative immune-mediated polyarthritis unless that animal is concurrently anemic.

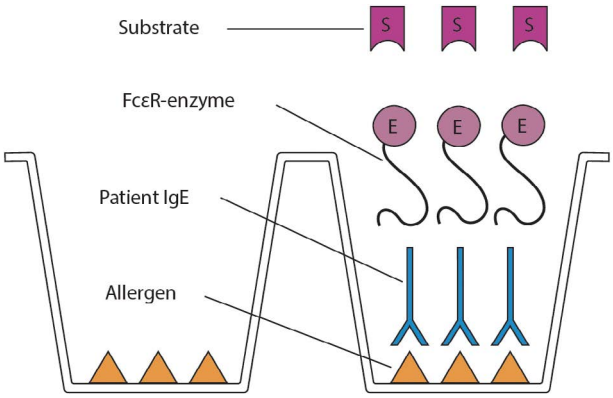


FIGURE 22.13 Serologic testing for allergen-specific IgE antibody. The wells of a microtitration plate are coated with allergen and subsequently incubated with patient serum. Serum allergen-specific IgE binds to the target and this interaction is visualized by the detection reagent (recombinant Fce receptor conjugated to alkaline phosphatase) and enzyme substrate.

Coombs Test

The most widely available immunodiagnostic test for autoimmunity is the Coombs test. This is indicated to support the diagnosis of IMHA in an animal with appropriate clinical and hematologic features. The aim of the test is to demonstrate the presence of IgG/IgM/complement C3b on the surface of patient erythrocytes as presumptive evidence that these immunoreactants are involved in the hemolytic reaction (Figure 22.14). There are numerous reasons for false-positive and false-negative Coombs tests, but the most common reason for the latter is that a complete test has not been performed. Many commercial laboratories offer a simple Coombs test using only a polyvalent Coombs reagent, with minimal titration at a single incubation temperature. A full Coombs test (which is more likely to provide a positive result) should use a combination of polyvalent and specific antisera (for IgG, IgM, and complement C3) that are fully titrated in a microtiter system at both 4°C and 37°C. An alternative approach to diagnosis using flow cytometry to detect red cell-bound antibodies is not widely available.

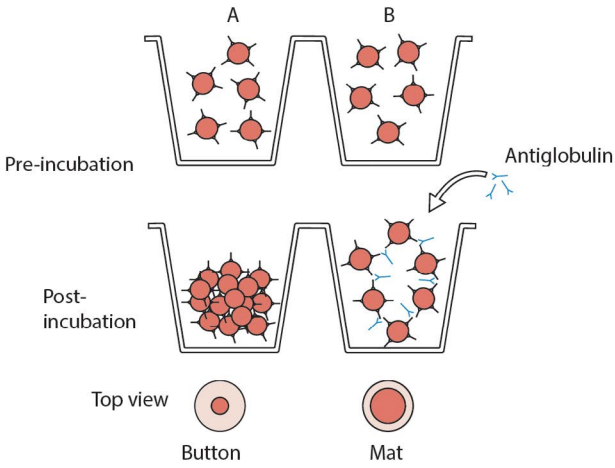


FIGURE 22.14 Coombs test. Wells A and B of a microtiter plate contain a suspension of washed erythrocytes from an animal with IMHA. The patient red cells are coated with antibody *in vivo*. An antiglobulin reagent (e.g., one of polyvalent canine Coombs reagent, anti-dog IgG, anti-dog IgM, or anti-dog complement C3) is added to well B only. After a period of incubation, the wells are examined for gross evidence of agglutination. In well B, the antiglobulin has cross-linked Ig molecules on the patient erythrocytes to form a lattice-like structure that appears as a diffuse mat of red cells that covers the base of the well (agglutination). In well A, no antiglobulin has been added, so the erythrocytes settle to the base of the well by gravity, forming a tight "button" of packed red cells. In a complete Coombs test, the different antiglobulin reagents would be fully titrated and the test performed in duplicate at both 4°C and 37°C.

Antiplatelet and Antineutrophil Antibody Detection

The detection of antiplatelet antibody in IMTP or antineutrophil antibody in IMNP is rarely available outside of specialist laboratories. A range of approaches to the detection of platelet-bound Ig has been attempted including immunofluorescence, ELISA-based, and radioimmunoassay-based tests. The most sensitive modality has proven to be flow cytometric detection using fluorochrome-labeled antibodies, but this is not widely available. Older test methodologies, such as the platelet factor 3 test and megakaryocyte immunofluorescence, can no longer be recommended. One limitation of direct testing for platelet-bound Ig is the fact that thrombocytopenic animals are often so markedly thrombocytopenic that it is difficult to harvest sufficient cells for analysis. IMNP has only recently been well-documented as a disease and although flow cytometric testing is feasible, availability is limited.

Serum Antinuclear Antibody Detection

The detection of serum antinuclear antibody (ANA) is widely available. The most commonly employed test involves the layering of diluted patient serum onto substrates of nucleated cells grown in monolayers on a sectored microscope slide. ANA bound to the nucleus is subsequently detected by use of an anti-IgG reagent coupled to a fluorochrome or enzyme (Figures 22.15 and 22.16). The test is read by microscopic examination for the pattern of nuclear labeling and determination of the titer. Classically, the ANA test is used to support the diagnosis of SLE, but it may also be present in animals with other autoimmune diseases. The key to interpretation is the titer, as many clinically normal animals and animals with chronic inflammatory, infectious, or neoplastic disease may have low-titered ANA as a reflection of cell turnover.

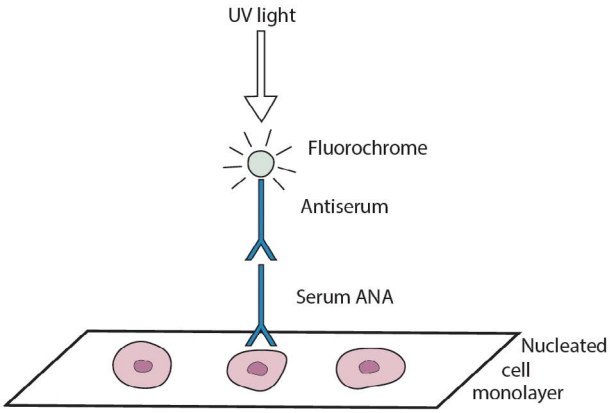


FIGURE 22.15 The antinuclear antibody (ANA) assay. Serial dilutions of patient serum are incubated with a source of nucleated cells to permit any ANA to bind to target antigens. Binding is visualized by subsequent incubation with an antiserum coupled to either a fluorochrome (for examination under UV light) or an enzyme (for reaction with substrate for light microscopic examination).

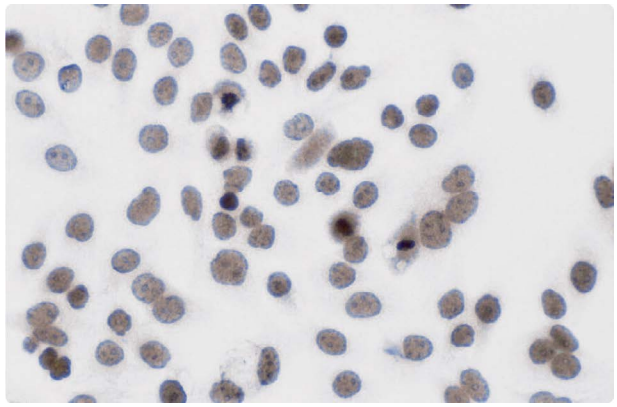


FIGURE 22.16 Positive ANA reaction as shown by immunoperoxidase labeling of nuclei within the target cell line.

Rheumatoid Factor Tests

Serum or synovial fluid rheumatoid factor (RF) may be tested in order to support a diagnosis of immune-mediated polyarthritis. Ideally, both RF and ANA would be requested in such patients as either autoantibody may be present, despite the fact that RF is classically reported to be associated with erosive rheumatoid arthritis. RF is an IgM (or rarely IgA) autoantibody with specificity for an IgG molecule that in turn is bound to an undefined antigen (Figure 22.17). RF may have a role in the pathogenesis of polyarthritis, and is thought to be formed in the synovium and leak into the circulating blood. RF may be detected by ELISA, in which target IgG is coated to the wells of a microtitration tray, or via the Rose Waller test in which the target IgG is affixed to the surface of erythrocytes and the RF causes cross-linking of target IgG and therefore agglutination of these cells.

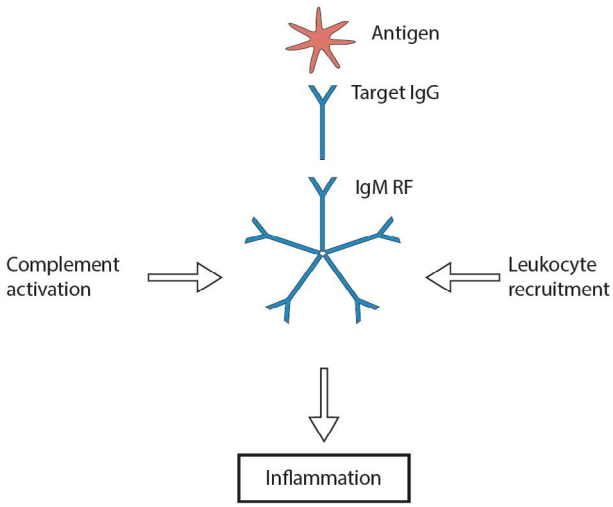


FIGURE 22.17 Rheumatoid factor (RF). An undefined synovial antigen is complexed with an IgG antibody, which in turn forms the target for the IgM RF. Binding of RF leads to activation of the classical pathway of complement and subsequent recruitment of leukocytes. RF may thus have a role in the pathogenesis of polyarthritis in addition to being a useful serologic marker of disease.

Other Autoantibody Tests

Other commonly used autoantibody tests include those for thyroglobulin autoantibodies in dogs with hypothyroidism attributed to lymphocytic thyroiditis, and for AChR autoantibodies in dogs with putative myasthenia gravis. Thyroglobulin autoantibody testing is widely available, but only one laboratory internationally offers the AChR autoantibody test.

Immunohistochemistry

For some autoimmune diseases (e.g., autoimmune skin disease, immune complex glomerulonephritis), immunohistochemistry or immunofluorescence testing has been employed in order to demonstrate the presence of immunoglobulin and/or complement within lesional tissue (Figure 22.18). Such testing is not particularly sensitive, but it can be helpful in supporting a diagnosis where histopathology is equivocal.

Immunodeficiency Disease

The diagnosis of immunodeficiency disease is one of the great frustrations of clinical veterinary medicine. At the research level, it has proven possible to assess the competence of all aspects of the immune system (i.e., immunoglobulin, complement, phagocytic cell and lymphocyte function, cytokine production), but such testing is not available commercially. Consequently, the diagnosis of primary immunodeficiency largely relies on simple measures of immune system assessment (e.g., hematology, serum protein electrophoresis, lymphoid tissue histopathology) together with characterization of any secondary infection. The only readily available immunodiagnostic test is determination of serum immunoglobulin concentration by single radial immunodiffusion (SRID)

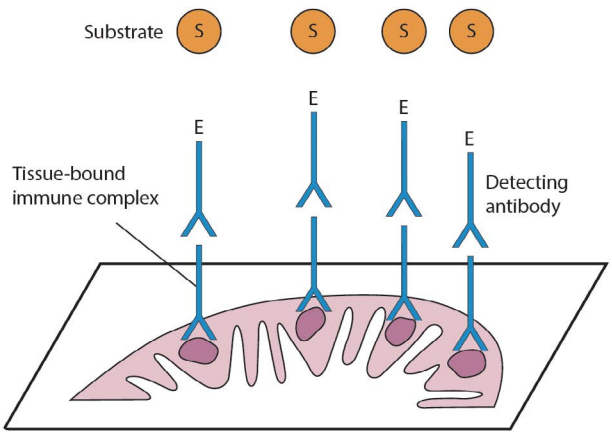


FIGURE 22.18 Immunohistochemistry. The microscope slide displays a section of kidney with suspected immune complexes localized to the glomerular capillaries. The immunoglobulin component of these complexes is detected by overlaying the section with an enzyme-linked antiserum (e.g., anti-dog IgG). On application of the appropriate substrate, there is a color change at the site of antibody binding, confirming the presence of immune complex.

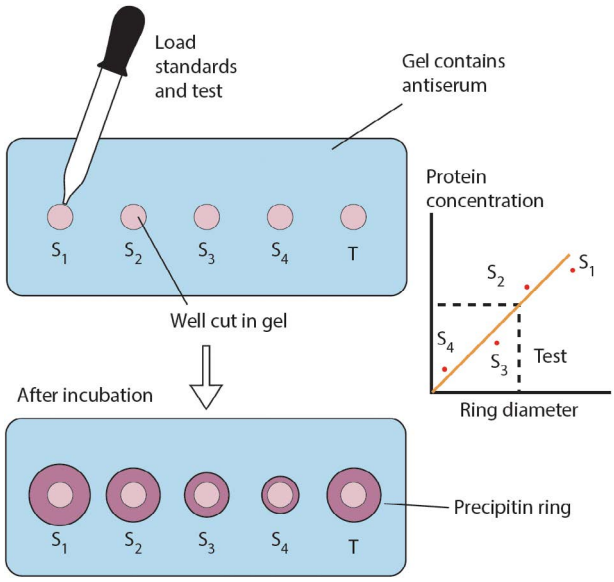


FIGURE 22.19 Single radial immunodiffusion. This test is used to determine the concentration of immunoglobulin in patient serum. An agarose gel is poured within which is mixed an antiserum (e.g., anti-dog IgG). Wells are cut into the gel and loaded with a precise volume of standards of known concentration and the patient sample. During an overnight incubation, IgG diffuses from the wells into the gel matrix where it encounters antiserum that precipitates the IgG. The higher the concentration of IgG, the larger the diameter of the precipitin ring obtained. A standard curve derived from the four samples of known value is used to determine the concentration in the test sample.

(Figure 22.19). For the dog, the serum concentrations of IgG, IgM, and IgA can be determined, but there are few reference ranges for animals of different age and breed. Specialist laboratories that have flow cytometry may offer blood lymphocyte phenotyping, generally to determine the relative proportions of $CD4^+$ and $CD8^+$ T cells and $CD21^+$ B cells among the circulating lymphoid population. These percentages should be related back to absolute lymphocyte number (as for a differential leukocyte count). At present there is relatively sparse information about how such changes correlate with disease, but marked decreases might be predicted in some immunodeficiency states. Finally, for a limited number of canine immunodeficiencies, molecular diagnostic tests have been developed after elucidation of the genetic mutation underlying the disease. These include tests for X-SCID, canine leukocyte adhesion deficiency (CLAD), the trapped neutrophil syndrome in Border Collies, and cyclic hematopoiesis in the gray Collie dog.

Immune System Neoplasia

The front line for diagnosis of immune system neoplasia is clinical and imaging examination, hematology and bone marrow analysis, cytology, and biopsy. In recent years there has been wide uptake of tissue immunohistochemistry for confirmation of the phenotype of round cell neoplasia. Following routine light microscopic diagnosis, most pathology laboratories are able to apply

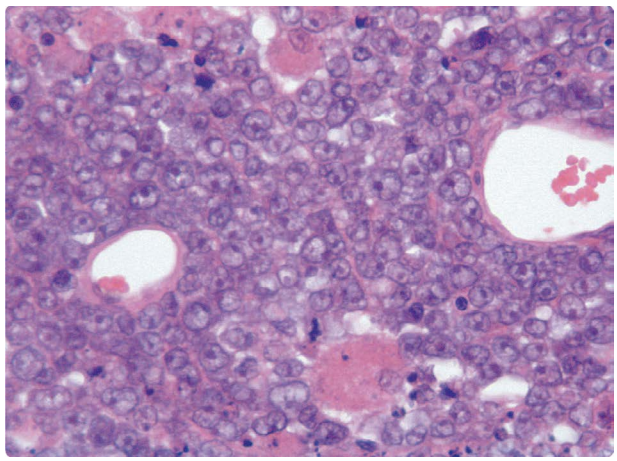


FIGURE 22.20 Lymphoma immunophenotyping. Section of skin from a dog with dermal lymphoma. The H&E-stained section reveals a closely packed population of blastic cells with a vesicular, cleaved nucleus, with central prominent nucleolus and minimal cytoplasm.

antisera in order to determine whether the neoplasm is of T cell, B cell, or histiocytic origin (Figures 22.20 and 22.21). In similar fashion, some laboratories offer immunocytochemical or flow cytometric testing of cellular suspensions derived from a fine-needle aspirate, which provides a similar (but more rapid) outcome. Flow cytometric testing has also become available for the determination of the nature of leukemia, and a range of lymphoid and myeloid markers are generally employed to phenotype such neoplastic populations. The most recent advance in this area of diagnosis has been the development of "clonality testing." This molecular test can determine whether a population of lymphoid cells is clonal (and therefore neoplastic) by examining restriction in rearrangements in TCR and BCR genes. Such testing is of particular benefit in distinguishing between a reactive and a neoplastic lymphoid infiltration (for example in the intestinal mucosa) or for monitoring the presence of residual neoplastic cells in blood or tissue throughout chemotherapy. These new diagnostic

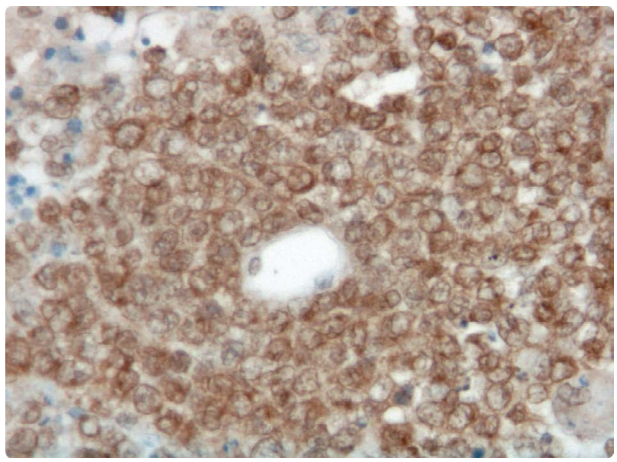


FIGURE 22.21 Immunolabeling with anti-CD79a reveals this to be a B-cell lymphoma.

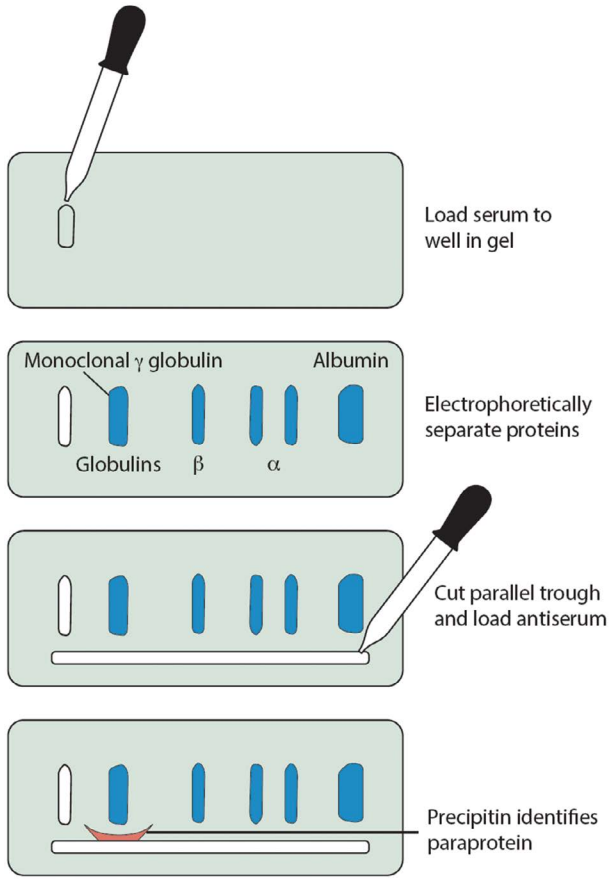


FIGURE 22.22 Immunoelectrophoresis. Serum from a patient with suspected paraproteinemia is separated electrophoretically in a gel matrix. Following this, a trough is cut into the gel parallel to the separated proteins and loaded with antiserum (e.g., anti-dog IgG-γ heavy chain). During a period of incubation, the antiserum diffuses from the trough to react specifically with the paraprotein and form an arc of precipitation. The position of this arc relative to that produced with normal serum immunoglobulin indicates that the paraprotein carries altered charge and is thus structurally altered.

approaches to tumor classification have helped to refine prognosis for canine lymphoma. Two recent studies have shown the longest median survival time (or event-free survival time) for low-grade T-cell lymphoma, the shortest survival time for high-grade T-cell lymphoma, and intermediate survival for dogs with B-cell lymphoma.

Multiple myeloma is characterized in part by serum paraproteinemia, resulting in a monoclonal gammopathy identified by serum protein electrophoresis. The immunodiagnostic workup in this disease entails more detailed analysis of this paraprotein. The traditional means of achieving this is via immunoelectrophoresis (Figure 22.22) in which the identity of the paraprotein (class of Ig) is determined together with demonstration of altered electrophoretic mobility confirming the abnormal physicochemical properties of the molecule. Similar information can be derived from immunofixation or western blotting studies, although in reality, typing of paraprotein is not routinely performed in cases satisfying the diagnostic criteria for this disease.

MAJOR IMMUNE-MEDIATED DISEASES

This section will review the major immune-mediated disorders of companion animals. Where these are described elsewhere in this book by body system, a cross-reference to the appropriate chapter will be given. Significant features of diseases that are not discussed elsewhere will be described in this chapter; however, this list is not exhaustive, and less common entities are not included.

ALLERGIC DISEASES

ATOPIC DERMATITIS

See Chapter 18.

FLEA ALLERGY DERMATITIS

See Chapter 18.

FOOD ALLERGY

See Chapter 18.

FELINE EOSINOPHILIC GRANULOMA COMPLEX

See Chapter 18.

ALLERGIC RHINITIS

See Chapter 6.

FELINE ASTHMA

See Chapter 6.

CANINE EOSINOPHILIC BRONCHOPNEUMOPATHY

See Chapter 6.

ALLERGIC CONJUNCTIVITIS

See also Chapter 19.

Definition/Overview

Allergic conjunctivitis may occur as a distinct entity or in conjunction with cutaneous allergy. The likely mechanism is type I hypersensitivity.

Clinical Presentation

The clinical features include conjunctival erythema and edema, pruritus, and ocular discharge. There may be secondary bacterial infection, and blepharitis and keratitis may also occur. Conjunctival lymphoid follicular hyperplasia may be visible grossly or on biopsy.

Diagnosis

Diagnosis may involve cytologic examination (eosinophils and mast cells may be expected) and the investigation of concurrent cutaneous hypersensitivity.

CONTACT HYPERSENSITIVITY

See Chapter 18.

AUTOIMMUNE AND IDIOPATHIC IMMUNE-MEDIATED DISEASES

IMMUNE-MEDIATED HEMOLYTIC ANEMIA AND PURE RED CELL APLASIA

See Chapter 16.

IMMUNE-MEDIATED THROMBOCYTOPENIA

See Chapter 16 and Chapter 17.

IMMUNE-MEDIATED NEUTROPENIA

See Chapter 16.

RHEUMATOID ARTHRITIS

See Chapter 15.

IMMUNE-MEDIATED POLYARTHRITIS

See Chapter 15.

PEMPHIGUS FOLIACEUS

See also Chapter 18.

Definition/Overview

Pemphigus foliaceus is the most common of the pemphigus disorders that are characterized by the formation

of autoantibody specific for the desmosomal intercellular adhesion molecules that join together the epidermal keratinocytes. Less common pemphigus variants include pemphigus vulgaris, pemphigus erythematosus, and pan-epidermal pustular pemphigus (pemphigus vegetans).

Pathophysiology

Autoantibody binding leads to physical disruption of these junctions and local activation of the complement and plasminogen–plasmin pathways. Vesicles form within the epidermis, and these contain the separated keratinocytes (acanthocytes). There is chemotactic attraction of neutrophils and/or eosinophils into these spaces to form sterile pustules.

Clinical Presentation

Classically, in pemphigus foliaceus the pustules are subcorneal in location, which is likely related to the distribution of the target autoantigen (Figure 22.23). Direct immunohistochemistry may be used to demonstrate the intercellular deposition of immunoglobulin and/or complement (Figure 22.24). Clinically, intact vesicles or pustules are rarely observed, and the predominant lesion is of crusting affecting the face, feet, and trunk.

Diagnosis

Diagnosis is by skin biopsy.

Management

Treatment involves immunosuppressive doses of oral glucocorticoid.

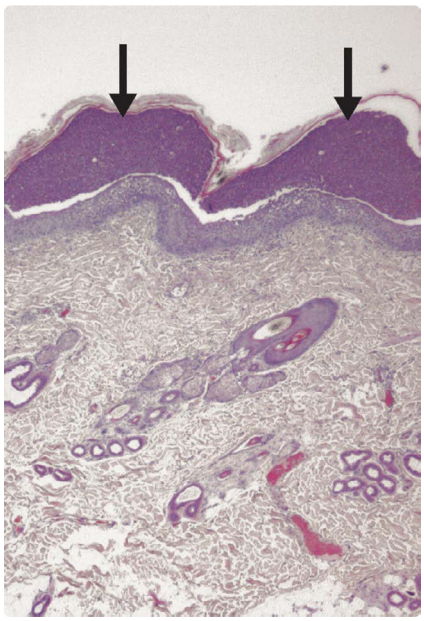


FIGURE 22.23 Skin biopsy from a 10-year-old Collie-cross dog with a generalized pustular and crusting dermatosis. There is a large, intact subcorneal pustule filled by nondegenerate neutrophils and acanthocytes (arrows). These features are consistent with pemphigus foliaceus.

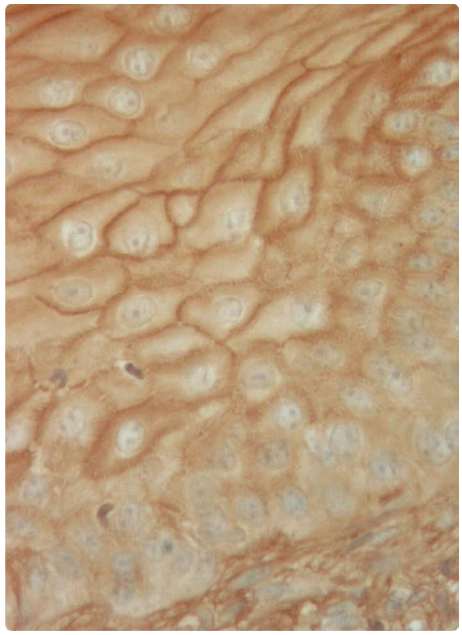


FIGURE 22.24 Skin biopsy from a 9-year-old German Shepherd Dog with pemphigus foliaceus confirmed histologically. This biopsy is labeled to detect IgG, which is present associated with the desmosomes of the mid to superficial level keratinocytes. Note there is no intercellular deposition associated with the basal cells.

BULLOUS PEMPHIGOID

Definition/Overview

Bullous pemphigoid is an autoimmune disease in which autoantibody targets structures within the hemidesmosome that anchors the basal keratinocytes into the basement membrane zone between epidermis and dermis. Bullous pemphigoid variants include epidermolysis bullosa acquisita, linear IgA bullous disease, and mucous membrane pemphigoid.

Pathophysiology

Disruption of this adhesion results in separation of the epidermis from the dermis, with formation of a cleft lined by the basal keratinocytes (uppermost) and basement membrane (lowermost). This space may become filled with fluid and/or inflammatory cells.

Clinical Presentation

Clinically, the bullous lesions are often disrupted, and the presentation is of ulceration that particularly affects the oral mucocutaneous junctions, axilla, groin, and footpads.

Diagnosis

Diagnosis is by biopsy and immunohistochemistry may be used to demonstrate the deposition of immunoglobulin/complement within the basement membrane zone.

Management

Treatment is by immunosuppression, and adjunct immunosuppression may be required in addition to oral glucocorticoid.

CUTANEOUS LUPUS ERYTHEMATOSUS

See also Chapter 18.

Definition/Overview

CLE is the name given to a group of immune-mediated skin diseases with a common pathogenesis. The prototype disorder of this group is discoid lupus erythematosus, which is now termed "nasal planum CLE." Other diseases within the CLE group include oral cavity or mucocutaneous CLE, generalized CLE, vesicular CLE of Collies and Shelties, exfoliative CLE of German Shorthaired Pointers, and lupoid onychodystrophy.

Pathophysiology

CLE has a complex pathogenesis, which in part involves infiltration of the basement membrane and epidermis by lymphocytes ("interface dermatitis") that target and destroy individual keratinocytes by induction of apoptosis (Figure 22.25). Additionally, there is deposition of immunoglobulin/complement at the basement membrane zone, although this may be an "epiphenomenon" rather than having a direct role in pathogenesis. Exposure to ultraviolet (UV) light is thought to play a role in the triggering of this disease.

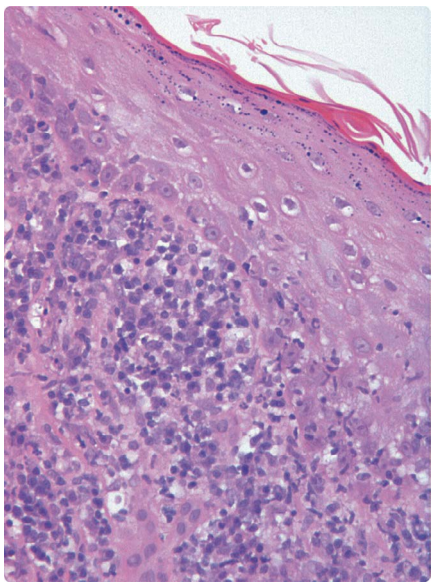


FIGURE 22.25 Skin biopsy from a 16-year-old German Shepherd Dog with depigmentation and loss of "cobblestone" pattern to the nasal planum. There is a lymphoplasmacytic interface dermatitis with prominence of the basement membrane and mild hydropic degeneration of the basal keratinocyte layer. The other key feature of "nasal planum cutaneous lupus erythematosus" not present in this field is individual keratinocyte apoptosis at higher levels.

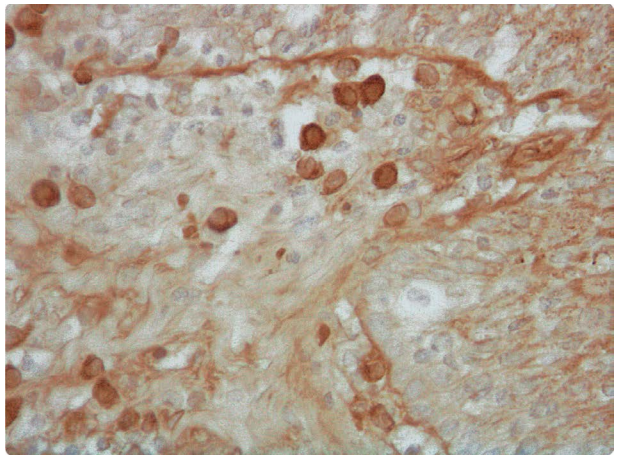


FIGURE 22.26 Skin biopsy from an 8-year-old male Norfolk Terrier with histopathologic evidence of interface dermatitis. The slide is immunolabeled to demonstrate the presence of IgG. There is a linear deposit of this immunoglobulin at the basement membrane zone between epidermis and dermis, and the cytoplasm of IgG^+ plasma cells within the dermal infiltrate is also labeled.

Diagnosis

Diagnosis is by skin biopsy, and immunohistochemistry may be used to demonstrate the local deposition of immunoreactant (Figure 22.26).

Management

A range of therapeutic options is proposed, most commonly involving the use of combination tetracycline (doxycycline) and niacinamide, topical glucocorticoid, or oral glucocorticoid at anti-inflammatory (rarely immunosuppressive) doses.

DERMATOMYOSITIS

Definition/Overview

This immune-mediated disorder primarily occurs in Collies and Shelties and is inherited as autosomally dominant with variable expression.

Pathophysiology

The pathogenesis is poorly defined, but is thought to involve immune complex deposition, as elevation in circulating immune complexes is documented before the onset of clinical signs. UV light and estrus are suggested trigger factors.

Clinical Presentation

This disease affects young dogs (under 6 months of age). They develop alopecic, erythematous, scaling, crusting, or ulcerative lesions that target the face, oral mucocutaneous junctions, pinnae, limbs, footpads, and tail tip. Concurrent muscular involvement particularly affects

facial and limb muscle groups, and these have inflammation and atrophy on biopsy and display electromyographic abnormalities. Megaesophagus may also occur. The outcome is variable; some dogs may show spontaneous resolution of disease, in others it may be cyclical, and in others progressive.

Management

Treatment options include immunosuppressive oral glucocorticoids, vitamin E, and pentoxifylline.

ERYTHEMA MULTIFORME/TOXIC EPIDERMAL NECROLYSIS

Definition/Overview

These disorders are found at each end of a spectrum of entities defined on the basis of their severity: Erythema multiforme (EM) minor, EM major, Stevens–Johnson syndrome (SJS), SJS–toxic epidermal necrolysis (TEN) overlap syndrome, and TEN.

Pathophysiology

These diseases may be triggered by drug administration or infection and involve an interface inflammatory infiltration of lymphocytes that induce cytotoxic apoptosis in small groups of keratinocytes (EM), through to full-thickness epidermal necrosis and ulceration (TEN) (**Figure 22.27**).

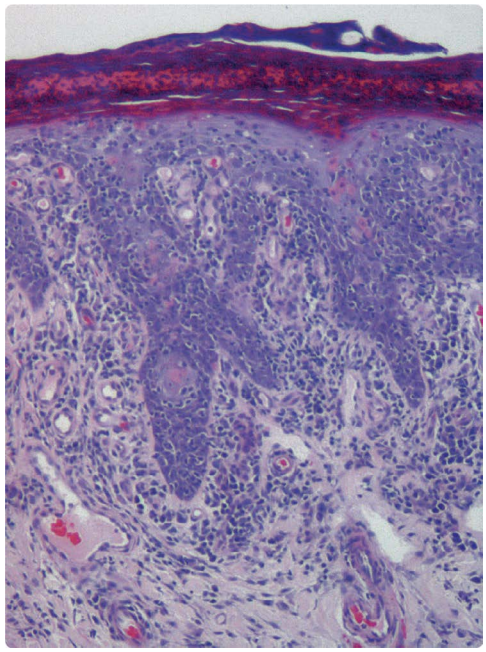


FIGURE 22.27 Skin biopsy from a 10-year-old West Highland White Terrier with severe, generalized crusting dermatosis. There is interface dermatitis with clusters of apoptotic keratinocytes within the epidermis associated with the infiltrating lymphocytes ("satellitosis"). These features are consistent with erythema multiforme.

Clinical Presentation

Lesions may be localized or generalized and affect cutaneous and/or mucocutaneous surfaces. The lesions of EM are relatively mild erythematous macules, papules, or confluent plaques, which may regress spontaneously following removal of the trigger. By contrast, TEN is a severe disease due to loss of fluid, electrolytes, and colloid from the ulcerated lesions, with high potential for secondary bacterial infection.

Management

Standard immunosuppressive glucocorticoid regimes are often ineffectual in these diseases, but IV administration of human immunoglobulin has proven beneficial.

PANNUS

Definition/Overview

Pannus (chronic superficial keratitis/keratoconjunctivitis) is a putative immune-mediated disorder of the cornea that particularly affects German Shepherd Dogs and may be triggered by UV light exposure.

Pathophysiology

There is lymphocytic infiltration, vascularization, and fibrosis of the superficial corneal stroma, which extends from the limbus.

Management

Application of topical cyclosporine has proven efficacious in management of this disease.

KERATOCONJUNCTIVITIS SICCA/ SJÖGREN'S SYNDROME

See Chapter 19.

UVEODERMATOLOGIC SYNDROME

See Chapter 18 and Chapter 19.

IDIOPATHIC UVEITIS

See Chapter 19.

LYMPHOCYTIC THYROIDITIS

See Chapter 11.

DIABETES MELLITUS

See Chapter 11.

INFLAMMATORY BOWEL DISEASE

See Chapter 9.

ANTIBIOTIC-RESPONSIVE DIARRHEA

See Chapter 9.

EXOCRINE PANCREATIC INSUFFICIENCY

See Chapter 11.

IMMUNE COMPLEX GLOMERULONEPHRITIS

See Chapter 13.

MYASTHENIA GRAVIS

See Chapter 14.

POLYMYOSITIS

See Chapter 14.

MASTICATORY MUSCLE MYOSITIS/ EXTRAOCULAR MUSCLE MYOSITIS

See Chapter 14.

GRANULOMATOUS MENINGOENCEPHALITIS

See Chapter 14 and Chapter 19.

STEROID-RESPONSIVE MENINGITIS ARTERITIS

See Chapter 14.

SYSTEMIC LUPUS ERYTHEMATOSUS

Definition/Overview

SLE is a rare disease of the dog and even less common in the cat. SLE is the prototype multisystemic autoimmune disease and is defined by strict diagnostic criteria. The simplest of these criteria are:

- The animal must show multisystemic disease involving at least two distinct body systems.
- The disease affecting these body systems must be compatible with an immune-mediated process and laboratory evidence of an immunologic pathogenesis for these changes must be obtained.
- The animal must have a high-titered serum ANA.

Although these criteria are simple, they are generally very difficult to satisfy; therefore, in many cases a diagnosis of an "SLE-overlap" syndrome (with partial fulfilment of the criteria) is made.

Pathophysiology

The most common clinicopathologic manifestations of canine SLE include IMHA, IMTP, immune complex glomerulonephritis, polyarthritis, and immune-mediated skin disease. In endemic areas, it is important to rule out arthropod-transmitted infectious disease (particularly leishmaniasis), which can mimic the clinical presentation of SLE. SLE has also been induced by drugs and may arise secondary to underlying lymphoid or myeloid neoplasia. SLE may be inherited, and early research demonstrated that it was possible to establish breeding lines in which there were dogs with serologic and clinical abnormalities of autoimmunity (but with no clear mode of inheritance).

Diagnosis

Multiple diagnostic and immunodiagnostic procedures may be required to support the diagnosis of SLE.

Management

Treatment is generally by immunosuppressive oral glucocorticoid therapy.

PRIMARY IMMUNODEFICIENCY DISEASE

IgA DEFICIENCY

Definition/Overview

Selective IgA deficiency is the most commonly reported canine immunodeficiency disorder and is most often suggested in animals that have chronic, recurrent infectious disease, most often of the mucocutaneous surfaces.

Etiology/Pathophysiology

The spectrum of infectious diseases associated with IgA deficiency includes pyoderma, demodicosis, rhinitis, bronchopneumonia, inflammatory bowel disease, and antibiotic-responsive diarrhea. IgA deficiency has

been definitively documented in the Shar Pei and in one colony of Beagle dogs. IgA deficiency has been proposed to be part of the pathogenesis in Irish Wolfhounds with chronic, recurrent rhinitis–bronchopneumonia syndrome, but although these dogs have subnormal serum IgA, the concentration of this immunoglobulin in bronchoalveolar lavage fluid is normal to elevated. IgA deficiency has been suggested to predispose to allergic disease, and there is evidence that (as for humans) there is an association with autoimmunity. Some of the IgA deficient Beagle dogs described above had serum RF, and IgA deficiency was widespread in a colony of English Cocker Spaniels in which there was also frequent occurrence of a variety of autoimmune diseases.

IgA deficiency has been proposed to underlie the multiple immunologic, infectious, and inflammatory diseases to which the German Shepherd Dog is predisposed. Although German Shepherd Dogs generally have normal serum IgA, there is increasing evidence for an inability to secrete sufficient mucosal IgA in dogs of this breed, and the IgA deficient phenotype may be particularly associated with inflammatory bowel disease and antibiotic-responsive diarrhea. Dogs have four genetic variants of IgA, and it is of note that all German Shepherd Dogs have a restricted genotype that is homozygous for a single variant.

Diagnosis

Diagnosis of IgA deficiency is not straightforward. In clinical practice the only test that is widely available is SRID for determination of serum IgA concentration. This test is insufficiently sensitive to measure the lower IgA concentrations that are found in secretions. IgA deficiency (in both man and dog) is not a simple genetic mutation in the gene encoding the α heavy chain. Instead, it is a relative immunodeficiency that in dogs is defined as serum IgA concentration persistently lower than 0.22 mg/ml. The serum concentration should be measured on at least two occasions (at least 1 week apart), as there are both day-to-day and diurnal variations in canine serum IgA concentration.

PUTATIVE IgG DEFICIENCY

Definition/Overview

Selective IgG deficiency has recently been reported to occur in young Cavalier King Charles Spaniels with pneumonia caused by *Pneumocystis carinii*. Infection with this opportunist organism is a hallmark of immunodeficiency disease, and is also the clinical presentation of a putative immunodeficiency disorder affecting Miniature Dachshunds. These latter dogs may also have subnormal concentrations of serum IgM and IgA and reduced responsiveness of blood lymphocytes to nonspecific stimulation with mitogens. In both breeds this is a relatively subtle immunodeficiency, as affected dogs appear to recover with appropriate antimicrobial therapy, although pulmonary disease may be recurrent. IgG deficiency is also the major immunologic feature of the disorder affecting Weimaraner dogs that is described below.

Diagnosis

IgG deficiency is determined by a consistently low serum concentration (below 10 mg/ml in adult dogs) of this immunoglobulin as determined by SRID.

COMPLEMENT C3 DEFICIENCY

Definition/Overview

Deficiency of the third component of complement (C3) has been reported only once, in an experimental colony of Brittanys. Affected dogs were more susceptible to infection and some developed glomerular disease.

WEIMARANER IMMUNODEFICIENCY

Definition/Overview

This complex disorder is now recognized in the Weimaraner breed internationally.

Clinical Presentation

Affected dogs are young adults (6–12 months of age) that present with chronic recurrent infections of multiple body sites, particularly mucosal and cutaneous surfaces. Another feature is the presence of hypertrophic osteodystrophy (HOD), which is more consistently a feature in affected dogs in the United States (where the disease is known as HOD of Weimaraners [Figures 22.28–22.30]). The most consistent immunologic abnormality in affected dogs is subnormal serum IgG, and in patients that are serially monitored this immunoglobulin appears never to attain its normal range.



FIGURE 22.28 This 3-month-old Weimaraner puppy had severe debilitating hypertrophic osteodystrophy that was complicated by bacterial sepsis. The dog was hospitalized in intensive care in order to receive parenteral fluid support and antibiotics.



FIGURE 22.29 Severe metaphyseal swelling.



FIGURE 22.30 The puppy also became septic and developed hemorrhagic skin bullae from which bacteria were isolated. It also had meningitis and several abscesses that were found on postmortem examination. (*Courtesy of M. Schaer.*)

Some dogs also have IgM and/or IgA deficiency and in the United States, neutrophil function defects have also been documented. The most unusual feature of this disorder is that the clinical signs appear to be triggered by vaccination and the disease often has clinical onset around the time of the 12-month booster vaccine.

Management

The prognosis for this disease is variable; some dogs spontaneously recover, others have chronic recurrent disease, and some die during the initial disease outbreak. Antiinflammatory doses of glucocorticoids appear to provide the best therapeutic outcome.

SEVERE COMBINED IMMUNODEFICIENCY

See Chapter 16.

CANINE LEUKOCYTE ADHESION DEFICIENCY

Definition/Overview

CLAD affects Irish Setters (Red and, rarely, Red and White dogs) internationally.

Pathophysiology

Affected dogs develop chronic recurrent infections of multiple body sites from a young age. This is one of the few examples of a canine immunodeficiency disorder for which the precise genetic mutation and associated pathogenesis have been determined. The gene defect means that affected dogs are unable to express the adhesion molecules CD11b and CD18 on the surface of granulocytes. Consequently, these cells are unable to interact with ligands on vascular endothelium to mediate exocytosis from blood into tissue. These dogs therefore develop severe infection of tissues (without pus formation) associated with a striking blood neutrophilia.

Diagnosis

A molecular diagnostic test is available to determine the carrier status of Irish Setters (the disease is autosomal recessive in inheritance) and with the cooperation of the breed association, this trait has been virtually eliminated. This can be regarded as one of the great success stories of veterinary immunology.

Management

As immunodeficiency disorders are untreatable (except experimentally), testing and genetic counseling offer the most practical approach to management.

CYCLIC HEMATOPOIESIS

See also Chapter 16.

Definition/Overview

Recent experimental studies (using this canine disease as a model for the human equivalent) have identified the precise genetic mutation of this disorder, which lies in the gene encoding the adaptor protein complex 3 β subunit, the effect of which is to disrupt the intracellular movement of neutrophil elastase.

Management

Gene replacement therapy has been developed in an experimental setting.

THYMIC HYPOPLASIA AND HYPOTRICHOSIS OF BIRMAN CATS

Definition/Overview

This is one of the few documented primary immunodeficiency disorders of cats, and was reported in a single litter of kittens. The association between hairlessness and thymic development is also well-recognized in particular inbred experimental strains of "nude" rats and mice, and is also likely to affect the Mexican Hairless Dog.

IMMUNE SYSTEM NEOPLASIA

LYMPHOMA

See Chapters 16, 18, and 19.

LYMPHOID LEUKEMIA

See Chapter 16.

PLASMACYTOMA

Definition/Overview

This benign plasma cell tumor is documented in both dogs and cats and generally presents as a single nodular mass arising on the face (lip), ears, and feet. The plasma cells may display considerable pleomorphism histologically (Figure 22.31), but these tumors do not recur after excision and only rarely progress to multiple myeloma.

MULTIPLE MYELOMA

Definition/Overview

Multiple myeloma is a malignant plasma cell tumor that targets the bone marrow in dogs and soft tissue (particularly liver and spleen) in cats, although a range of sites may be affected in both species (Figure 22.32).

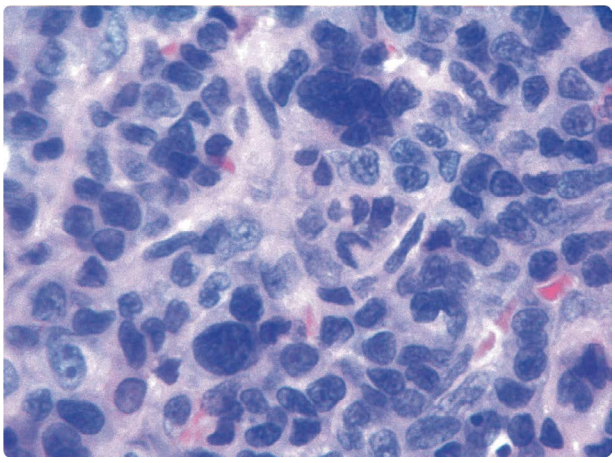


FIGURE 22.31 Section from a discrete nodular mass excised from the pinna of an 8-year-old male Dachshund. The tumor comprises a closely packed sheet of plasmacytoid cells, with scattered examples of multinucleate cells and cells with giant nuclei (both represented here). Although cytologically this appears to be an aggressive neoplasm, these are generally benign lesions that do not recur following excision.

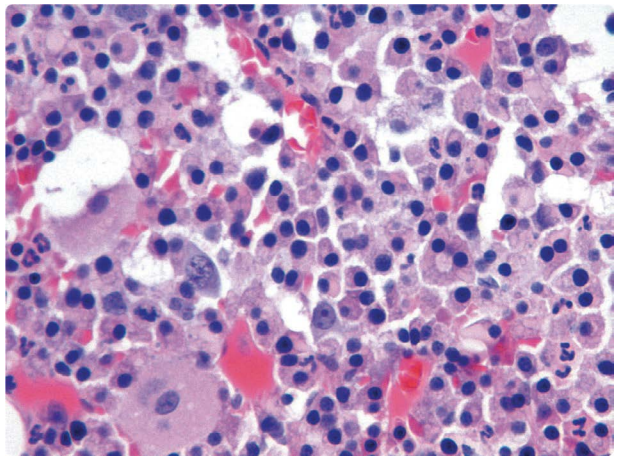


FIGURE 22.32 Bone marrow core biopsy from a 12-year-old neutered female Golden Retriever with monoclonal gammopathy identified on serum protein electrophoresis. The medullary cavity is filled by well-differentiated neoplastic plasma cells, which have virtually excluded the hemopoietic lineages in this field. The large cell at the base of the image is a megakaryocyte.

Pathophysiology

The proliferating plasma cells are associated with two distinct paraneoplastic effects. The first relates to the production of parathyroid hormone-like peptide, which leads to osteoclastic resorption of bone and the development of focal "punched-out" osteolytic lesions. The second is the characteristic secretion of a structurally abnormal immunoglobulin (paraprotein), which appears as a monoclonal gammopathy on protein electrophoresis.

These paraproteins are more commonly IgG than IgA or IgM, and rarely may take the form of free heavy or light chains that are not assembled into an immunoglobulin structure. Free light chains are of sufficiently low molecular weight to pass through the glomerular filter and be present in urine as "Bence–Jones protein." IgA and IgM paraproteins may be associated with serum hyperviscosity and a range of secondary effects related to this.

Diagnosis

Diagnosis of multiple myeloma relies on identification of characteristic clinical and radiographic features and the presence of monoclonal gammopathy. Further immunodiagnostic investigation of this gammopathy is discussed above. Important differentials for monoclonal gammopathy include particular infectious diseases such as ehrlichiosis and leishmaniasis in the dog and feline infectious peritonitis virus infection in the cat. A range of tests may be applied to the identification of Bence Jones proteinuria.

Management

Chemotherapeutic protocols are described for management of this disease.

HISTIOCYTIC NEOPLASIA

See also Chapter 18.

Definition/Overview

A spectrum of histiocytic neoplasia is documented in the dog, and it has a particular predilection for Bernese Mountain Dogs and Flat-coated Retrievers.

Pathophysiology

Immunohistochemical studies have defined this group of tumors as being of dendritic cell origin. The disorders range from the benign and spontaneously regressive histiocytoma of young dogs through to the reactive disorders (cutaneous and systemic histiocytosis) and the malignancies (localized and disseminated histiocytic sarcoma) (**Figure 22.33**).

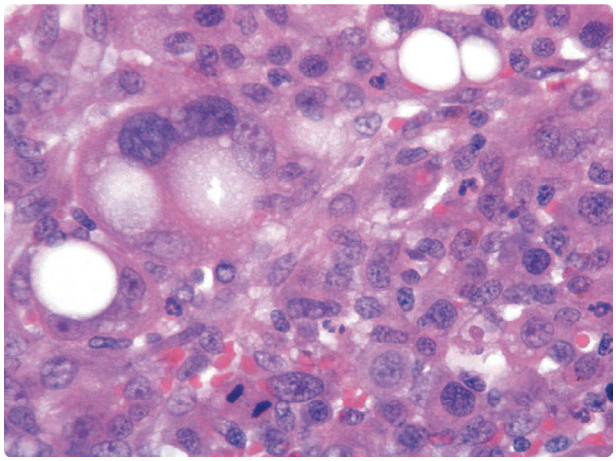


FIGURE 22.33 Section from a pulmonary mass taken at necropsy from a 6-year-old neutered female Bernese Mountain Dog. The mass comprises a sheet of highly pleomorphic histiocytic cells with abundant eosinophilic to mildly vacuolated cytoplasm and a round, pale nucleus with chromatin clumps. There are both multinucleate cells and cells with giant nuclei present. A mitotic figure is present at the lower edge of the image. The sternal lymph nodes of this dog were also infiltrated.

Diagnosis

Diagnosis is by biopsy, and immunohistochemical confirmation is now widely applied.

MAST CELL TUMOR

See Chapter 16 and Chapter 18.

RECOMMENDED FURTHER READINGS

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SECTION

V

ELEMENTS OF THERAPY



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CHAPTER 23

Fluid Therapy

Leonel Londoño

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INTRODUCTION

Intravenous (IV) fluid therapy is routinely prescribed to dogs and cats secondary to a wide range of clinical scenarios. These include but are not limited to hypovolemia secondary to hemorrhage or gastrointestinal/renal fluid loss and distributive shock due to sepsis or other noninfectious causes of systemic inflammation, such as pancreatitis or severe burns. Fluid therapy is also indicated for endocrine disorders such as diabetic ketoacidosis and Addisonian crisis and for diuresis for acute toxin ingestion and perioperative hemodynamic optimization. Despite the recognized benefits of fluid therapy in these situations, evidence-based medicine is rarely applied, and often the fluid choice and volume of fluids administered are inappropriate. In most cases, such inadequate fluid regimens may not lead to overt harmful effects because of the inability of the kidneys and cardiovascular system to compensate for the excessive volume or supraphysiological loads of electrolytes delivered to the renal tubules. On the other hand, inadequate fluid therapy prescriptions may lead to delayed fluid resuscitation during shock states, while excessive accumulation of total body water (TBW) can lead to volume overload and tissue edema, furthering cardiovascular, respiratory, and renal dysfunction in the critically ill patient. There is a great variation of bedside determination of the optimal type, volume, and rate of fluid administration, likely due to the lack of objective diagnostic parameters that accurately identify volume deficits in dogs and cats. This chapter aims to introduce the latest trends in clinical application of fluid therapy, including stages of fluid therapy, types of fluids, development of a fluid plan, and monitoring fluid balance.

STAGES OF FLUID THERAPY

Based on the fact that most dogs and cats requiring fluid therapy have a dynamic fluid balance during the acute phase of critical illness, IV fluid therapy prescriptions are not static. They should evolve based on the cardiovascular evaluation and fluid balance of the patient. Over the past decade, a conceptual framework that defines the four stages of fluid therapy has been defined to better guide clinicians during the decision-making process of fluid prescription in patients with dynamic fluid changes. The four stages have been defined as: (1) Rescue, (2) optimization, (3) stabilization, and (4) de-escalation (**Figure 23.1**).

The rescue stage characterizes patients presenting with life-threatening conditions such as shock secondary to hypovolemia or vasodilation, leading to tissue hypoperfusion and ischemia. This stage of fluid therapy is commonly applied to patients during the first 30 minutes to the first 2 hours after presentation to the hospital, when the patient is at risk of death if aggressive fluid resuscitation does not partially or entirely restore organ perfusion. Signs of shock and hypovolemia may vary between species and physiological stages. Many texts advocate providing "shock dose" fluids to patients with signs of hypovolemic shock. The volumes quoted are usually 90 mL/kg (dog) and 60 mL/kg (cat); this actually represents the entire blood volume of the animal. Clinically, it is rarely necessary to administer this large a volume of crystalloid fluids. During the rescue stage, smaller aliquot boluses of IV replacement (isotonic) fluids, 10–20 mL/kg in the dog and 5–10 mL/kg in the cat, are indicated to restore normal perfusion parameters (normal heart rate, normotension, improved mental status). Over-resuscitation can be as harmful as

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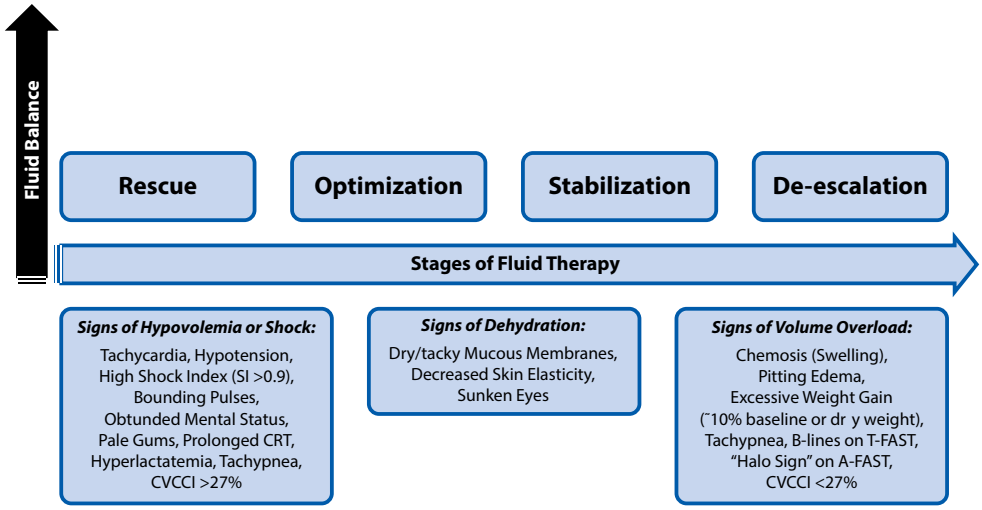


FIGURE 23.1 Stages of fluid therapy and clinical signs associated with the dynamic fluid balance of dogs and cats during hospitalization. CVCCI, Caudal Vena Cava Collapsibility Index.

under-resuscitating the patient, and goal-directed therapy can be instituted to prevent organ dysfunction from persistent ischemia due to decreased effective circulating volume.

In very specific situations, a second major strategy is low-volume resuscitation, or "hypotensive resuscitation" (to a mean arterial pressure of ~60 mmHg or a Doppler blood pressure of ~90 mmHg) in patients that are bleeding excessively until the hemorrhage is controlled. The use of hypertonic fluids such as 7.2% hypertonic saline is also indicated in such cases of severe acute hemorrhage to avoid a large volume of crystalloids being delivered that may lead to hypocoagulable states due to hypothermia and dilution of coagulation factors. During this phase, the clinician must also identify underlying causes of hypovolemia and shock, such as sepsis or septic shock, in order to effectively address the cause of the patient's critical state. While IV bolus therapy of crystalloids can be lifesaving during the rescue stage, excessive fluid therapy without early pressor support in septic patients may lead to fluid overload, organ edema, and fluid extravasation due to endothelial dysfunction.

The optimization stage of fluid therapy applies during the following 6–8 hours after the rescue phase, once the patient is no longer at imminent risk of death. During this phase, the patient requires ongoing fluid therapy to restore tissue perfusion and mitigate fluid losses due to vomiting, diarrhea, or polyuria. This phase also applies to patients presenting to the hospital with clinical signs of dehydration (Figure 23.1), in addition to having hypovolemia or shock. Fluid therapy regimens for these patients may require additional or initial boluses of fluids to improve their hemodynamic status, and fluid therapy should be aimed at restoring volume deficits, provide maintenance volume, and replace ongoing losses. There is vast heterogenicity among patients presenting with signs or without signs of dehydration despite ongoing loses, which makes fluid therapy regimens subjective and based on the clinician's best assessment of the patient. The most relevant part of the optimization phase is to have end-goals such as providing a certain volume over a certain number of hours to replace deficits and losses while avoiding liberal fluid therapy. Careful bedside monitoring of the patient with serial physical exams will help assess response to fluid therapy during this phase and prevent falling behind or exceeding fluid requirements due to the dynamic status of the patient. Normalization of hemodynamic variables such as lactate clearance, shock index (SI), and collapsibility of the caudal vena cava are also helpful for evaluation of hemodynamic optimization but are not superior to the direct observation and evaluation by the clinician.

Once the hemodynamic parameters of the patient are normalized or stable, the stabilization stage of fluid therapy is aimed at providing organ support while preventing iatrogenic complications. Such complications might include fluid overload, renal vasoconstriction, and decreased glomerular filtration rate (GFR) secondary to supraphysiological loads of chloride delivered to the renal tubular lumen, hypertension, and fluid extravasation. In this stage, clinicians should consider using maintenance or hypotonic fluids, which will decrease supraphysiological doses of electrolytes delivered with replacements (isotonic fluids). The stabilization stage may last days to weeks depending on the patient's underlying condition. This is where it becomes imperative to consider the incorporation of early enteral nutrition into the fluid plan to provide the patient with adequate nutrients during the recovery phases of critical illness. Once normal blood pressure and adequate tissue perfusion are achieved, early enteral nutrition helps deliver fluids and nutrients to the patient in a more physiological manner, while improving gastrointestinal (GI) function and supporting the immune system.

Finally, the de-escalation stage is aimed at recognizing patients who no longer require fluid support and may need fluid removal during their time in hospital. It is common practice to believe that all hospitalized

patients should be on IV fluids. Still, patients that voluntarily drink water and eat or have feeding tubes placed and are only having insensible losses may no longer require IV fluid support. Another essential concept is fluid removal in patients where fluid overload is recognized. Fluid removal may be achieved via diuretic therapy or simply by stopping fluid and allowing patients to urinate the excess circulating volume if oliguria or anuria are not developed as a consequence of fluid overload. More advanced forms of fluid removal, such as ultrafiltration with hemodialysis platforms, can be used, especially in patients with diagnosed with acute kidney injury and renal dysfunction. The goal is to achieve a neutral fluid balance, or in some cases, such as patients with pulmonary parenchymal disease (e.g. pneumonia, pulmonary contusions, or noncardiogenic pulmonary edema), a negative fluid balance may prove beneficial in their outcome. Clinicians using conservative fluid therapy and goal therapy are constantly de-escalating their patients based on their hemodynamic responses and assessment.

TYPES OF FLUIDS

Isotonic crystalloids, also called replacement fluids, are electrolyte-containing fluids with a composition similar to the extracellular fluid composition the patient. These fluids are the most common type of fluid used in veterinary medicine and are of particular importance during the rescue and optimization stages of fluid therapy. See Table 23.1 for commonly used isotonic crystalloid fluids in veterinary medicine. These fluids are considered isotonic because they have an osmolality closely resembling that of plasma (290–310 mOsm/L). Most crystalloids contain buffers such as lactate, acetate, and/or gluconate, which are useful for correcting metabolic acidosis commonly encountered in sick and critically ill patients. The only exception is 0.9% NaCl, which does not contain a buffer and is, therefore, considered an acidifying fluid. Infused crystalloids rapidly distribute into the extracellular fluid, and only a small portion (25%–30%) of the delivered volume remains in the intravascular space after the first 30 minutes post infusion. Isotonic crystalloids are theoretically used only for replacement volumes during the rescue and optimization stages in dehydrated or hypovolemic animals. Still, it is common practice to use these isotonic crystalloids as the maintenance fluid, since the kidneys can adapt and increase the excretion fraction of high doses of electrolytes delivered with these fluids. It is also more "convenient" to use a single fluid type and a single pump rather than having multiple fluid bags and several infusion pumps running simultaneously.

Large doses of chloride-rich containing fluids have recently been shown to increase the risk of acute kidney injury in people. The concentration of chloride in different types of isotonic crystalloids is shown in Table 23.1. As seen in the table, chloride concentration in a 0.9% saline solution is almost 1.5 times greater than other balanced crystalloids (154 mEq/L versus 108 mEq/L in LRS or 98 mEq/L in Plasma-Lyte 148 and Normosol-R). High chloride loads delivered to the macula densa induce renal afferent artery vasoconstriction and lead to reduced renal tissue perfusion and reduction in GFR, increasing the risk of acute kidney injury and volume overload due to fluid retention. One of the common reasons to use 0.9% NaCl is that this isotonic crystalloid is devoid of potassium, thus making it attractive for managing hyperkalemic patients. Multiple studies in cats with urethral obstructions have shown that cats receiving balanced crystalloids (LRS, Plasma-Lyte-148) had a more rapid resolution of metabolic acidosis, and potassium levels 6 hours post resuscitation trended lower when compared to cats that received 0.9% NaCl. Nowadays, the use of 0.9% NaCl is decreasing in veterinary medicine, but in certain conditions such as patients with hypochloremic metabolic alkalosis secondary to upper gastrointestinal obstructions, hypercalcemia, and mild hyponatremias, the use of saline solution may prove beneficial.

Hypotonic crystalloids, also called maintenance fluids, are fluids with lower osmolality compared to that of plasma and with lower electrolytes concentrations compared to isotonic crystalloids. These fluids have minimal concentrations of solutes to maintain body homeostasis. See Table 23.2 for commonly used hypotonic crystalloid fluids in veterinary medicine. They are

TABLE 23.1 Commonly used isotonic crystalloids in veterinary medicine with their correspondent electrolyte and buffer composition

Fluid type	Osmolality (mOsm/L)	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	Mg^{2+} (mEq/L)	Ca^{2+} (mEq/L)	Buffer (mEq/L)
0.9% NaCl	308	154	0	154	0	0	0
Lactated Ringer's solution	273	130	4	109	0	3	Lactate 28
Plasma-Lyte 148	295	140	5	98	3	0	Acetate 27 Gluconate 23
Normosol-R	295	140	5	98	3	0	Acetate-27 Gluconate 23

For Na^+, K^+, and Cl^-: 1 mEq/L = 1 mmol/L. For Ca^{2+} and Mg^{2+}: 1 mEq/L = 0.5 mmol/L.

TABLE 23.2 Commonly used hypotonic crystalloids in veterinary medicine with their correspondent electrolyte and buffer composition

Fluid type	Osmolality (mOsm/L)	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	Mg^{2+} (mEq/L)	Ca^{2+} (mEq/L)	Buffer (mEq/L)
0.45% NaCl	155	77	0	77	0	0	0
½ LRS + 2.5% Dextrose	265	65	2	55	0	1	Lactate 14
Plasma-Lyte-56	110	40	13	40	3	0	Acetate 16
Normosol-M	110	40	13	40	3	0	Acetate 16
D5W Water + 5% Dextrose	252	0	0	0	0	0	0

For the electrolytes Na^+, K^+, and Cl^-: 1 mEq/L = 1 mmol/L. For Ca^{2+} and Mg^{2+}: 1 mEq/L = 0.5 mmol/L.

made to replace the normal losses of water and electrolytes lost through respiration, urination, defecation, and other insensible losses. These insensible losses are low in sodium and high in potassium. It is essential to realize that maintenance fluids and hypotonic fluids can be dangerous to bolus or administer at high rates, as the water concentration gradient between the intravascular and intracellular compartments may lead to a rapid shift of water into the red blood cell and cause cell lysis. Dextrose is often added to maintenance fluids to supply calories to the patient and increase the osmolality of the fluid, preventing rapid shifts of water in case of an accidental rapid administration of the fluid.

The lower sodium and chloride profiles of hypotonic fluids make them ideal for providing maintenance rates of fluids to patients with cardiac and renal disease.

In patients with hypernatremia ($[Na^+]_{serum}$>160 mEq/L], the use of water + 5% dextrose (D5W) can be used to replace the free water deficit using the following calculation:

$$\text{Free Water Deficit (L)} = \left(\left\{\left[Na^+\right]_{current} / \left[Na^+\right]_{normal}\right\} - 1\right) \times \text{Body Weight (kg)} \times 0.6$$

This fluid should never be administered if electrolyte monitoring cannot be performed at minimum of every 6–8 hours to prevent rapid drops in sodium, leading to osmotic demyelination resulting in seizures, coma, and even death. The free water deficit volume can be replaced using D5W over a safe period (48 hours or longer) with caution not to decrease the plasma sodium more than 0.5–1.0 mEq/L per hour or more than 12 mEq/L over a 24-hour period. In addition to D5W, hypernatremic animals should receive an isotonic solution (same sodium concentration as the patient) to provide maintenance fluids and ongoing loss replacement. This objective can be achieved by adding a calculated volume of hypertonic saline to replacement fluids. For example, 7.2% NaCl contains 1,232 mEq/L of sodium and 1,232 mEq/L of chloride; therefore, each milliliter of this solution contains 1.232 mEq of sodium. If the patient has a sodium of 180 mEq/L, and you choose LRS as your replacement fluid ($[Na^+]$ 130 mEq/L), you will need to add 50 mEq/L of sodium, which will translate to 40.6 mL of 7.2% NaCl.

Hypertonic crystalloids are crystalloids that cause a rapid and transient osmotic shift of water from the intravascular space to the extracellular compartment, leading to a transient volume expansion. The most common hypertonic crystalloids are various saline solutions containing 3%, 5%, and 7.2% of sodium chloride in solution. Hypertonic saline use is common nowadays in emergency settings for the acute management of specific conditions such as severe hypovolemia from acute hemorrhage and increased intracranial pressure from traumatic brain injury (**Figure 23.2a, b**). Hypertonic saline decreases blood viscosity, which results in a positive rheological effect and enhances microcirculatory perfusion. Hypertonic saline also increases preload and causes a mild vasodilation that helps to increase cardiac output and coronary artery perfusion in critically ill animals. Furthermore, it has immunomodulatory effects and may increase heart contractility. The doses of hypertonic saline used in small animals range from 2 to 5 mL/kg, over 5–10 minutes. This dose can be repeated, but particular attention should be given to serum electrolyte concentrations. Hypertonic saline should not be given to animals with signs of dehydration and chronic clinical signs of water loss (vomiting, diarrhea, polyuria), especially if the patient's serum sodium concentration is unknown.

Synthetic colloids are suspensions containing large molecules (molecular weight >10,000 daltons) dissolved typically in 0.9% NaCl. Hydroxyethyl starches, dextrans, and gelatins are examples of synthetic colloids. Hydroxyethyl starches are the most commonly used synthetic colloid solutions in veterinary medicine. These large molecules do not readily filter across the vascular endothelium and remain in the intravascular space for longer periods compared to crystalloid solutions. Once these particles are filtered through the glomerulus, they are reabsorbed by the proximal tubular epithelium and cause renal tubular vacuolization, damaging this part of the nephron. The volumes of synthetic colloids administered to critically ill dogs has been correlated with the damage of the proximal tubular epithelium in proportional magnitudes. Despite the promising benefits of the use of colloids, the revision of the Starling



FIGURE 23.2 **(a)** Six-year-old mixed-breed dog receiving an IV bolus of hypertonic fluids before administration of blood products due to exsanguinating hemorrhage secondary to ballistic trauma to the abdomen. **(b)** Three-year-old Maltese dog receiving hypertonic saline as part of treatment of traumatic brain injury secondary to vehicular trauma.

forces and the effect of the endothelial glycocalyx in vascular permeability have shown that the beneficial use of colloids, synthetic or not, only applies at higher capillary pressures. Several studies have shown that colloids are not superior to crystalloids during resuscitation stages in critical illness. The 2016 surviving sepsis campaign has a strong recommendation against the use of synthetic colloid solutions for intravascular volume replacement. The use of synthetic colloid fluids has been slowly decreasing among specialty veterinary hospitals, and in the author's experience, synthetic colloids are no longer recommended for intravascular expansion and management of critically ill animals.

BLOOD PRODUCTS AND TRANSFUSIONS

Blood products and transfusion are sometimes required for the management of patients with acute and chronic conditions. The aim is to re-establish appropriate levels of circulating hemoglobin and improve oxygen delivery (DO_2) in patients with severe anemia and replace coagulation factors in patients with coagulopathies. The indications and triggers for blood transfusions are beyond the scope of this chapter. In general, patients with slow-onset anemia with decreased DO_2, will have hematocrit values <20% and have changes associated with poor tissue perfusion (tachycardia, pale mucous membranes, mental dullness or stupor, tachypnea). Patients with acute exsanguinating hemorrhage, on the other hand, may have hematocrit levels >20% while still showing signs of poor tissue perfusion, as seen in cases of hemoabdomen. The transfusion of packed red blood cells (pRBCs) is recommended in patients with anemia to prevent antigenic stimulation and decrease the risk of transfusion reactions associated with whole blood and unnecessary blood components. Ideally, all patients should be blood typed before a transfusion, and donors should also be blood typed to decrease the risk of transfusion reactions with whole blood or packed red blood cells products. In the emergency setting and in patients with critical conditions, the use of cross-matching is not absolutely required if appropriate blood typing has been performed, especially in dogs with their first blood transfusion, as they do not have pre-existing alloantibodies. Cross-matching in cats is considered more necessary due to the presence Mik cell antigens, or in dogs and cats that have received transfusion after the first 3–5 days. The use of IV fluid pumps to deliver whole blood or pRBC transfusions has been associated with red blood cell damage and lower viability of the transfused product; therefore, the use of syringe pumps in small patients (cats and dogs <10 kg) with blood filter sets is recommended. In cases involving severe exsanguinating hemorrhage or life-threatening anemias, gravity flow or pressure infusion bags can be used as an alternative form of blood product delivery (Figure 23.3a, b). The volumes of whole blood or pRBC transfusion recommended for anemia management are presented in Table 23.3. The rate of transfusion delivery will be dependent on the hemodynamic status of the patients. In patients with chronic anemias or those without evidence of impending cardiopulmonary arrest, transfusions can be delivered over 4 hours with close monitoring for the development of transfusion reactions. In patients with life-threatening anemias where



FIGURE 23.3 **(a)** A 6-year-old mixed-breed dog (same dog from **Figure 23.2a**) receiving a bolus of pRBC (15 mL/kg DEA 1.1 negative) due to exsanguinating hemorrhage secondary to ballistic trauma to the abdomen. **(b)** A 5-year-old cat receiving a unit of pRBC (30 mL type A) via syringe pump through a 170-micron filter before its fourth dialysis session due to acute kidney injury (AKI) secondary to lily toxicity.

there is no time to monitor for transfusion reactions, the rate of blood product delivery will be determined by the patient's degree of urgency. Rapid infusions can be facilitated with pressure infusion bags.

Plasma products (fresh frozen plasma, stored plasma, cryoprecipitate-poor plasma), also considered natural colloids, can be used as part of the resuscitation strategies in patients with severe bleeding in order to replace proteins and coagulation products lost in acute blood-loss conditions. The most common indication for plasma product transfusion is for the replacement of coagulation factors in cases of anticoagulant rodenticide toxicity, hepatic failure, or hereditary conditions such as hemophilia (Table 23.3). The use of plasma products for specific conditions such as pancreatitis and parvoviral enteritis is now contraindicated due to higher mortality rates observed in patients with pancreatitis treated with plasma transfusions. With these conditions, the hypercoagulable state associated with the systemic inflammatory response syndrome

TABLE 23.3 List of blood products, volumes and rates, and indications for transfusion therapies in veterinary medicine

Blood product	Dose/volume recommended	Indications
Fresh whole blood ***or*** ***Stored whole blood***	– 20 mL/kg to increase the HCT by 10% – Infusion rate of 5 mL/kg/h for stable patients	– Patients with anemia and signs of decreased DO_2 where pRBC is not available – Neonatal and pediatric patients where the required transfusion volume is low enough to not warrant waste of an entire unit of pRBC – Patients with anemia secondary to hemorrhage from coagulopathies, as fresh whole blood contains coagulation factors in addition to red and white blood cells and platelets
Packed red blood cells (pRBC)	– 15 mL/kg to increase the HCT by 10% – Infusion rate of 3–4 mL/kg/h for stable patients	– Patients with anemia and signs of decreased DO_2
Fresh frozen plasma	– 10–15 mL/kg – Infusion rate of 3–4 mL/kg/h for stable patients	– Replacement of coagulation factors – It also contains albumin, globulins, and antithrombin
Cryoprecipitate	– 1–2 mL/kg or 50 mL/10 kg	– Treatment of hemophilia A, von Willebrand disease and hypofibrinogenemia
Cryoprecipitate-poor plasma	– 1–2 mL/kg or 50 mL/10 kg	– Treatment of coagulation factors II, VII, IX, and XI deficiencies

(SIRS) may develop secondary to vascular endothelial dysfunction. Finally, the use of plasma transfusions to correct hypoalbuminemia in conditions such as protein-losing enteropathies and nephropathies are controversial, as patients receiving 18 mL/kg of fresh frozen plasma did not show an increase in serum albumin concentrations. The volume of fresh frozen plasma required to increase serum albumin concentrations by 1 g/dL may be up 40–45 mL/kg, equal to half the blood volume in dogs (90 mL/kg). Plasma products are, therefore, reserved for management of acute hemorrhage and coagulopathies because of these limitations. The indications and volumes of plasma products are presented in **Table 24.3**.

DEVELOPING A FLUID PLAN

IV fluid therapy is used to correct dehydration or volume deficits, provide maintenance of daily water balance and electrolyte needs, and replace ongoing losses such as vomiting, diarrhea, or polyuria. The type of fluid depends on the type of fluid loss suspected to be causing the volume deficit, and combination therapy is sometimes required to provide appropriate water and solute balance. Patients with signs of dehydration should have the estimated percentage of dehydration replaced over a short period (6–10 hours). Once the deficit has been calculated and the rate at which that deficit will be replaced, then a fluid therapy regimen can be created following the next steps:

- *Replacement*
  The replacement volume should be calculated by using the formula:

  $$\text{Body Weight (kg)} \times \text{Estimated Percent Dehydration (\%)} = \textbf{Deficit (L)}$$

  Then the fluid rate should be calculated using the time over which the deficit volume (in mL) will be replaced:

  $$\textbf{Deficit}\,(\text{mL})/\textbf{Time in Hours} = \textbf{Rate}\,(\text{in mL/hr})$$

  If a shock bolus has been given, this volume can be subtracted from the total deficit, and the remaining volume given over the time in hours considered appropriate for replacement. It is very difficult to accurately determine the volume deficit of sick and critically ill patients; therefore, subtracting the volume of the IV bolus is not always required, since during the rescue phases of fluid therapy patients have active ongoing losses, and re-distribution of circulating volume may affect deficit assessment. Dehydration estimates should take body habitus into consideration: Frail patients might normally have decreased skin turgor, while obese patients can have normal skin elasticity while being dehydrated.

  Subcutaneous (SQ) fluids are commonly administered in general and emergency practice. Suppose the animal is being treated with subcutaneous fluids on an outpatient basis. In that case, the aim of SQ fluid therapy should be aimed to at least replace the volume deficit of the patient (**Figure 23.4**) or provide maintenance for the next 24 hours in patients without clinical evidence of dehydration (40–60 mL/kg).



FIGURE 23.4 Prolonged skin elasticity in an 8-year-old, spayed female cat approximately 6%–8% dehydrated. The cat's weight is 4.5 kg; therefore, based on 8% dehydration, the deficit would be 0.36 L (4.5 kg × 8%; or 4.5 kg × 0.08) or 360 mL. If subcutaneous fluids were chosen as treatment for dehydration, this patient should receive between 270 and 360 mL of subcutaneous fluids to attempt rehydration.

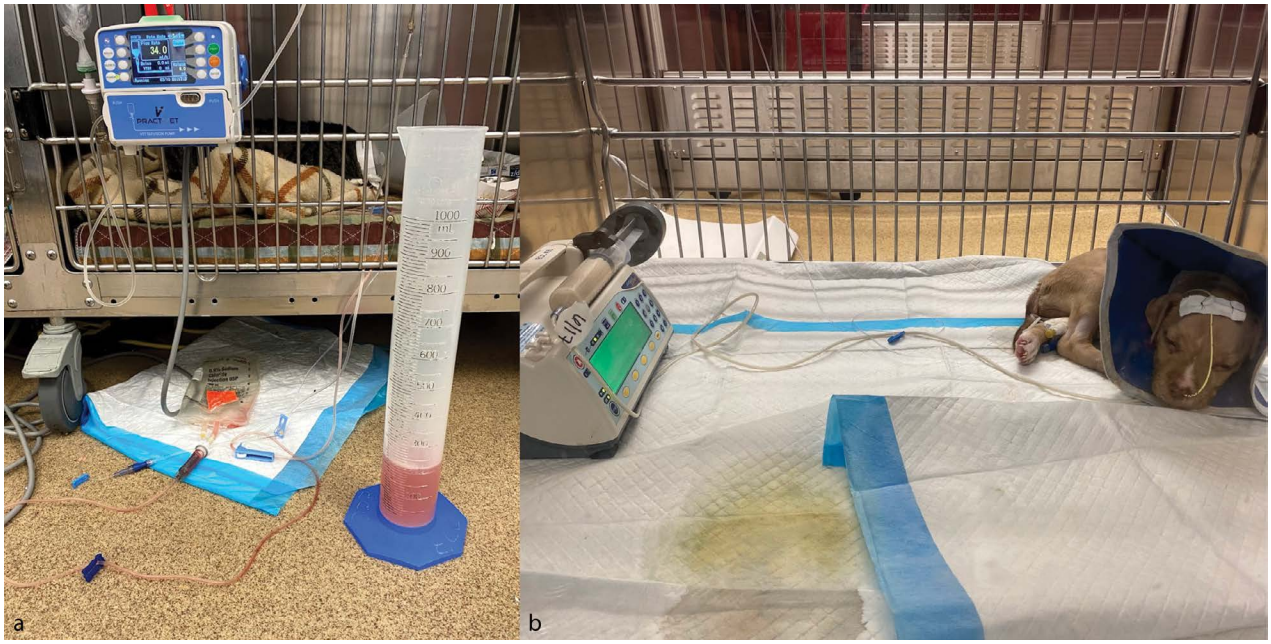


FIGURE 23.5 **(a)** Urine collection and measurement from a urinary collection system in a 2-year-old male cat with urethral obstruction secondary to feline idiopathic cystitis. **(b)** Disposable pads containing urine from a 2-month-old Pitbull puppy being treated for parvo viral enteritis and early enteral nutritional support via a nasogastric tube.

- *Ongoing losses*

  Ongoing losses can be calculated by either measuring urine output in animals with polyuric conditions and measuring or estimating the volume of diarrhea/vomitus that the animal is losing per hour in animals with gastrointestinal signs or both. Urine output can be measured via urinary catheterization, which is commonly performed in cases of urethral obstruction (Figure 23.5a, b) or during the first days of acute kidney injury. Still, urinary catheterization is not always indicated as it increases the risk of ascending infections and patient discomfort. In patients where urinary catheterization is not indicated, the measurement of urine output or GI losses can be performed via direct weighing of disposable pads. In most instances, the volume of GI losses is an educated estimate that should be accounted for in fluid regimen plans.
- *Maintenance*

  Several formulas for maintenance rates of fluids are available, and no consensus has been reached regarding which formula is best. Maintenance fluid needs are variable for each animal, with pediatric and geriatric animals requiring different volumes. Some of the formulas used include:

  1. 30 (BW in kg) + 70 = total volume (mL per 24 hours)
  2. $70 \times [BW_{kg}]^{0.75}$ = total volume (mL per 24 hours)

  This formula is considered more accurate for very small animals <2 kg (not including neonates or pediatrics) or very large animals >40 kg.

  3. 40–60 mL/kg per day (mL per 24 hours)

  This formula is mostly dictated by clinical experience where most clinicians will use 40–50 mL/kg per day for cats and geriatric animals.

It is imperative to recognize that if the replacement volume will be delivered over a short period (<24 hours), then the fluid volumes will initially include rates for:

Replacement + Ongoing losses + Maintenance

Once the replacement volume has been delivered and the patient is euvolemic and no longer shows signs of fluid deficits, the fluid rate and volume are amounts that decreased to:

Ongoing losses + Maintenance

MONITORING FLUID THERAPY AND FLUID BALANCE

In the last decade, special attention has been paid to monitoring fluid balance in hospitalized and critically ill patients, as fluid overload has been directly correlated with increased risk of mortality and development of comorbidities in people and veterinary patients. Fluid overload is defined as an increase of 10% or more from basal or ideal body weight. Liberal fluid therapy is commonly practiced in human and veterinary hospitals, with fluids rates at two to four times the maintenance rates without adequate therapeutic goals and monitoring endpoints. Not only will inappropriate fluid prescriptions increase the risk of volume overload, but lack of monitoring of fluid balance will increase the risk of fluid accumulation and edema formation. High fluid rates lead to increased central venous pressure, increased myocardial atrial stretch, and release of atrial natriuretic peptides. The consequences are endothelial

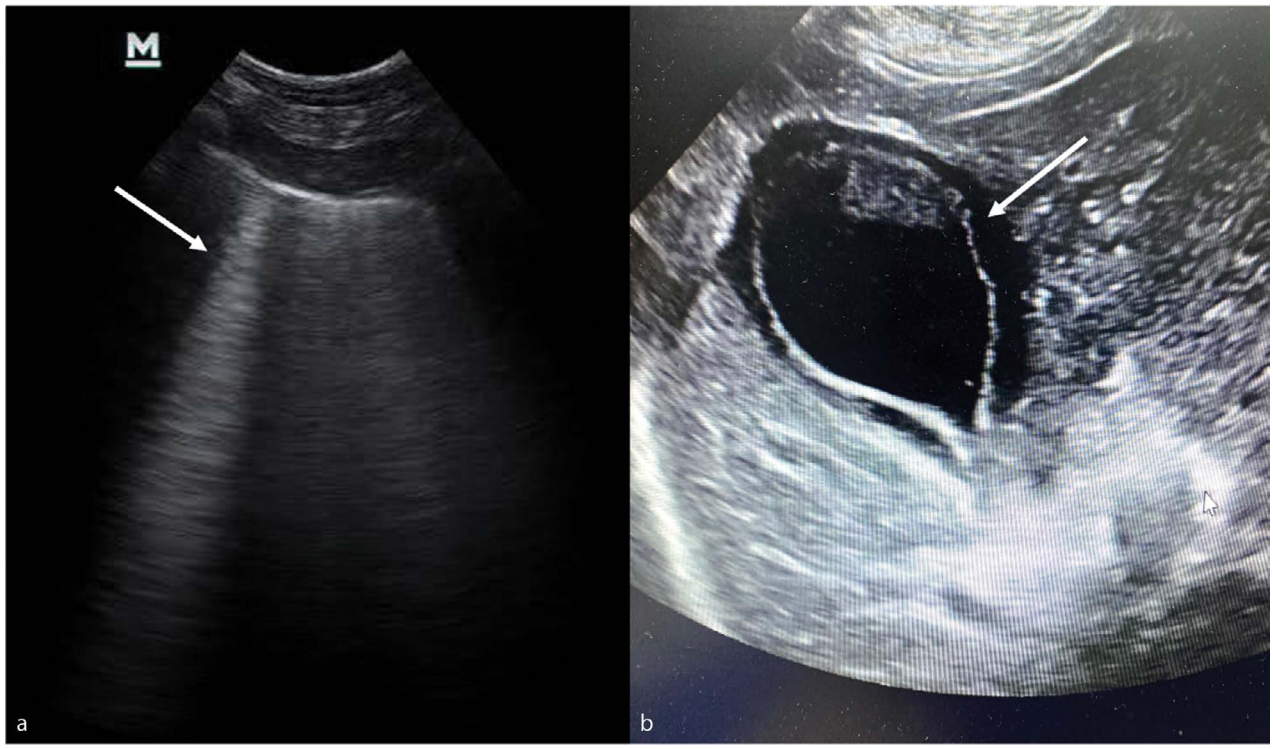


FIGURE 23.6 **(a)** Point-of-care lung ultrasound in a dog with oliguric acute kidney injury and a 7% increase in ideal body weight showing hyperechoic vertical lines (B-lines or comet-tails represented by white arrow) extending from the pleural space to the end of ultrasound field. **(b)** Abdominal point-of-care ultrasound in a dog with fluid overload, showing evidence of gallbladder wall edema represented by a hypoechoic rim or halo sign.

dysfunction, increased vascular permeability, and decreased lymphatic flow, leading to water accumulation in various organs (kidneys, heart, liver, and GI tract). Visceral edema tends to develop earlier in patients with volume overload due to rapid increases in central venous pressure, even before pitting edema is clinically evident. The percentage of fluid overload (%FO) can be calculated by the following formula:

$$\%SF = \left[\left(V_{tot}IN - V_{tot}OUT\right)/\text{basal body weight}\right] \times 100$$

$V_{tot}IN$ represents the volume of fluids that the patient has received, and $V_{tot}OUT$ represents the volume of urine and gastrointestinal losses. The development of visceral edema carries significant consequences in organ function, more specifically in the kidneys where water and electrolyte balance are tightly regulated. Renal edema secondary to volume overload results in decreased glomerular filtration rates, increased sodium and water retention, azotemia, oliguria-anuria, and worsening of volume overload. Other signs of volume overload include cardiac edema, which results in decreased systolic function, contractility, and reduction in cardiac output. Gastrointestinal edema worsens signs of vomiting, regurgitation, and diarrhea in hospitalized veterinary patients. For these and many other reasons, close monitoring of fluid balance leads to better outcomes in critically ill patients.

One of the easiest and least invasive ways of monitoring fluid balance in hospitalized patients is by frequent and consistent body weight assessment. Daily body weight measurements allow the clinician to reassess the risk of volume overload in hospitalized patients and evaluate the efficacy of fluid therapy when trying to restore fluid deficits. It is recommended to weigh the patient consistently after voiding or emptying the urinary bladder in order to prevent significant fluctuation in body weight secondary to urine retention. More advanced methods of fluid balance monitoring such as central venous pressure, pulmonary capillary pressure, and arterial pulse pressure variation are not routinely performed in veterinary patients. With the widespread use of ultrasound in veterinary hospitals, other monitoring techniques are becoming available to monitor patients for signs of volume overload. Point of care ultrasound can be used cageside to evaluate the presence of fluid accumulation in visceral organs, such as development of B-lines in the lungs or halo sign in the gallbladder (Figure 23.6a, b).

CONCLUSIONS

- Intravenous (IV) fluids should be prescribed as any other medication, with appropriate doses and dosage adjustments based on response to therapy.
- Fluid therapy is a dynamic intervention with four different stages: Rescue, optimization, stabilization, and de-escalation.

- The choice of fluids should be tailored to the patient's current physiological status. Avoiding chloride-rich solutions and synthetic colloids has become the cornerstone of fluid therapy in critically ill animals.
- Like any therapy, IV fluids can have harmful and deleterious effects. Especial attention should be paid to fluid balance and avoiding fluid overload in hospitalized patients.

RECOMMENDED FURTHER READINGS

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CHAPTER 24

Pain Management

Beatriz P. Monteiro and Bradley T. Simon

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INTRODUCTION

Pain management is an important component of animal welfare and an inspiring area of modern veterinary medicine. Advances on the knowledge of acute and chronic pain assessment and treatment in dogs and cats have occurred in the last decade supporting the practice of evidence-based pain medicine in these species.

Pain negatively affects the quality of life of dogs and cats and induces behavioral changes that affect the owner–pet bond. It causes unnecessary fear, anxiety, and stress, leading to negative mental states and causes sympathetic nervous system activation, altered food intake and metabolism. For these reasons, the management of animal pain has become a significant component of clinical practice.

OVERVIEW OF PAIN PHYSIOLOGY

According to the International Association for the Study of Pain (IASP), pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." This definition, updated in 2020, considers the following:

- Pain is a personal experience influenced by biological, psychological, and social factors.
- The multiplicity of mind–body interactions is acknowledged.
- Pain is different from nociception (nociception refers to the neural processing of noxious stimuli, whereas pain requires conscious perception, is associated with emotions and influenced by numerous internal and external factors).
- Animals are learning throughout their life's experiences, including that of pain.
- Inability to communicate does not negate the possibility that an animal is experiencing pain.

The Pain Pathway

The somatosensory system comprises the structures implicated in the processing of nociceptive information (Figure 24.1), which occurs via four main steps: Transduction, transmission, modulation, and perception. These are further described as follows.

Transduction starts with the activation of nociceptors present in the skin, muscles, joints, and viscera. Nociceptors are highly specialized structures that respond to different types of noxious or potentially tissue-damaging stimuli such as mechanical, thermal (hot and cold), and chemical stimuli. If the stimulus is of enough intensity that it reaches the threshold for an action potential, a nerve impulse is generated.

Transmission occurs when the nociceptive impulse travels from different types of primary afferent fibers (Figure 24.2) to the dorsal horn of the spinal cord. Primary afferents have a unique morphology which allows the nociceptive signal to travel in both directions within the neuron (i.e., the nociceptor can send and

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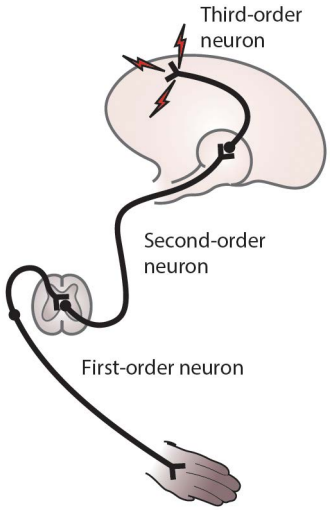


FIGURE 24.1 Simplified representation of the afferent pain pathway. (*Adapted from Tranquilli WJ, Grimm KA, Lamont LA (2000).* Pain Management for the Small Animal Practitioner. *Teton New Media, Jackson.*)

Aβ	Large myelinated and rapidly conducting fibers involved in low threshold innocuous mechanical stimulation (e.g., touch).
Aδ	Thinly myelinated and slowly conducting fibers primarily involved in nociceptive signaling (i.e., fast pain).
C	Unmyelinated and very slowly conducting fibers primarily involved in nociceptive signaling (i.e., slow pain).

FIGURE 24.2 Primary afferent fibers can be divided into three types based on their structure, diameters, and conduction velocity.

receive messages from either end). Their unique capacity to release neurotransmitters peripherally underlies the process of neurogenic inflammation. A subgroup of C fibers, "silent" nociceptors, are mechanically insensitive but can become sensitized during inflammation.

Modulation occurs at different levels of the peripheral and central nervous systems (CNS) where the nociceptive message can be amplified or inhibited depending on the nature of the neurotransmitters released and the pathway being activated. Examples of excitatory neurotransmitters include glutamate and substance P. Examples of inhibitory neurotransmitters include gamma-aminobutyric acid (GABA), noradrenaline, serotonin, and opioids, which bind to their receptors to decrease neuronal excitability.

Perception of pain occurs when the nociceptive signal is integrated in the cerebral cortex, and the stimulus is consciously perceived. Perception of noxious stimuli involves the incorporation of emotional attributes in the thalamus and cortical structures to these sensory signals. Pain perception is affected not only by the neurobiology of each individual but also by numerous variables,

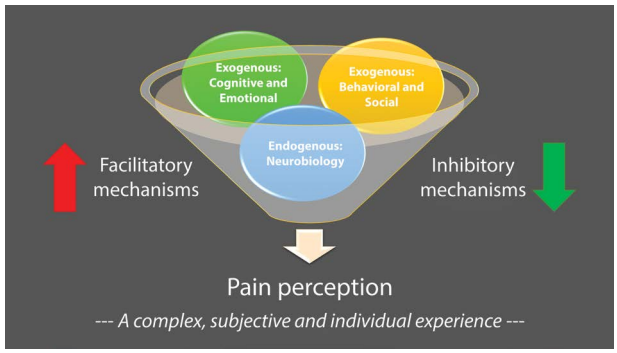


FIGURE 24.3 Factors influencing pain perception.

including past experiences, environmental and social contexts (Figure 24.3).

IMPORTANT CONCEPTS IN PAIN MEDICINE

Peripheral and Central Sensitization

Peripheral sensitization is characterized by sensitization of peripheral nociceptors (Figure 24.4). When tissue injury occurs, the release of inflammatory mediators such as prostaglandins and nerve growth factor (NGF) render peripheral nociceptors sensitized and hyperexcitable. Thus, the threshold for nociceptor activation is reduced, and the magnitude of response is increased. Activation of "silent" nociceptors and of neighboring nociceptors from undamaged healthy tissues also occurs. The persistent activation of peripheral fibers and constant input to the spinal cord contribute to the development of central sensitization.

Central sensitization is the increased responsiveness of nociceptive neurons in the CNS characterized by three main processes: Increased membrane excitability, facilitated synaptic strength, and decreased inhibitory influences (i.e., disinhibition). Neuroplasticity and neuroimmune interactions can further enhance neuronal excitability and decrease inhibitory currents. These are generally short-lived and reversible; nevertheless, they can become pathologic in the face of sustained inflammation or nerve injury.

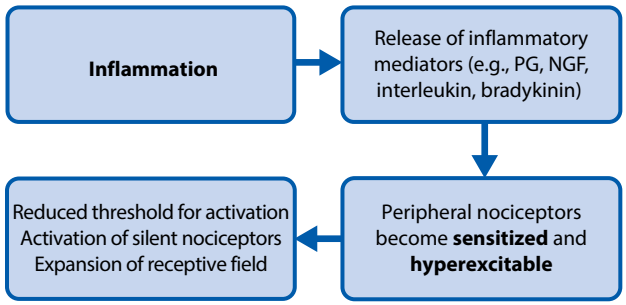


FIGURE 24.4 Schematic representation of the mechanisms involved with peripheral sensitization. NGF, nerve growth factor; PG, prostaglandins.

Hyperalgesia and Allodynia

The clinical manifestations from peripheral and central sensitization are known as hyperalgesia and allodynia. Hyperalgesia refers to increased sensitivity to pain due to a stimulus that normally provokes pain (the quality of the sensation is not altered; what changes is the severity of that sensation). Allodynia refers to pain due to a stimulus that does not normally provoke pain (the quality of the sensation is altered).

CLINICAL PAIN

Considering the complexity of the pain pathway and its enormous potential for interindividual variability, one can appreciate how the pain profile can be diverse among patients being affected by the same condition. It also explains the varied response of patients to therapeutic interventions.

Pain can be classified according to its type, duration, anatomical localization, etc. What really matters is understanding that pain is a dynamic process and that patients might have different contributions to the overall pain experience (Figure 24.5). For example, an older dog with osteosarcoma, hip dysplasia, severe periodontal disease, and cystitis has all these conditions contributing to the overall pain experience. In terms of location, there is bone pain, joint pain, orofacial pain, and visceral pain. In terms of type, there is inflammatory, neuropathic, and cancer pain. In terms of duration, most conditions are chronic, whereas the cystitis is likely acute. Regardless, the pain experience is the result from all these conditions and all the internal and external factors previously discussed (pain facilitation and pain inhibition, and cognitive, behavioral, social, and environmental components). Recognizing all these players is helpful for assessing pain and planning treatment with an evidence-based confidence.

Nociceptive pain refers to physiological pain that serves for protection (e.g., contact with a hot object, painful pinch, or chemical burn).

Inflammatory pain involves the release of inflammatory mediators which sensitize nociceptors, resulting in pain, redness, swelling, heat, and loss of function. It can be involved with adaptive (e.g., postoperative pain or acute trauma) and maladaptive (e.g., osteoarthritis [OA], cancer, gingivitis) processes. Persistent inflammation and release of substance P and NGF in the periphery can lead to neurogenic inflammation. In neurogenic inflammation, cells from the dorsal horn of the spinal cord release chemicals which fire backwards down on the nociceptors, further releasing neurotransmitters such as NGF, which then sensitizes peripheral nociceptors, reinforcing this vicious cycle (Figure 24.6).

Adaptive (acute)	Maladaptive (chronic)
Associated with potential or actual tissue damage Purpose: Avoid or minimize damage during healing Self-limiting Ex: Postoperative pain, trauma	Not associated with healing Persists beyond the expected course of the acute disease No clear end-point Can exist without a cause Ex: OA, cancer, gingivitis, etc.

FIGURE 24.5 Differences between adaptive and maladaptive pain. (*Adapted from Ref*. 31.)

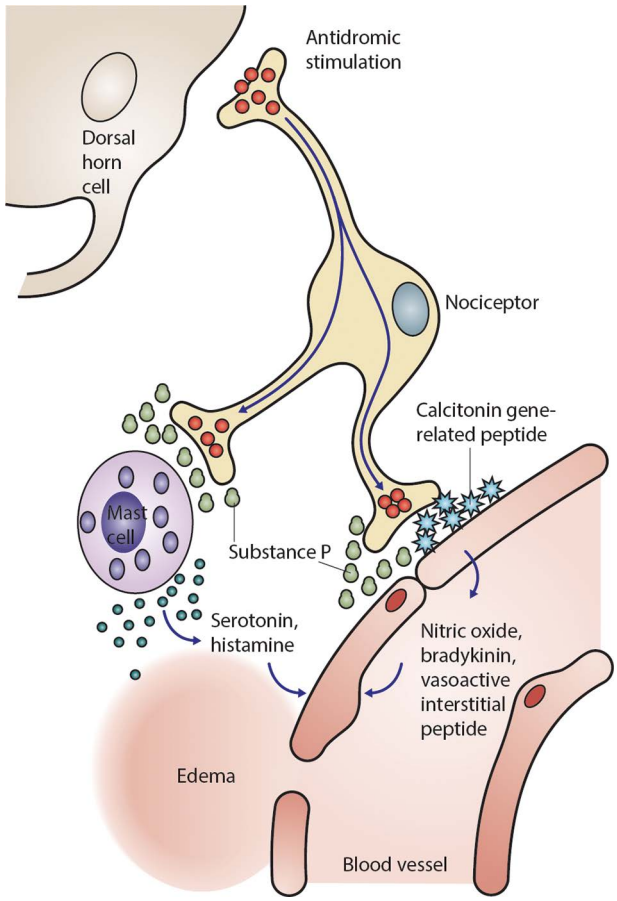


FIGURE 24.6 Neurogenic inflammation involves an antidromic firing of neurons (action potentials fire backwards down the nociceptors). Packets of chemicals located at the peripheral terminals are released. Thereafter, pain signals from peripheral nerves are heightened, and the cycle of chronic pain is continued.

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system. It is characterized by two key concepts: Inappropriate activity in nociceptive fibers and central changes in sensory processing. Examples include intervertebral disc disease (IVDD), syringomyelia, Chiari-like malformation, diabetes-induced neuropathy, OA, cancer, chronic gingivostomatitis, feline orofacial pain syndrome, persistent postsurgical pain following amputations (including tail docking in dogs and onychectomy in cats).

Cancer pain is regarded by some as a separate pain entity because of complex interactions between cancers, the somatosensory system, and the immune system (Figure 24.7). Briefly, within the tumor

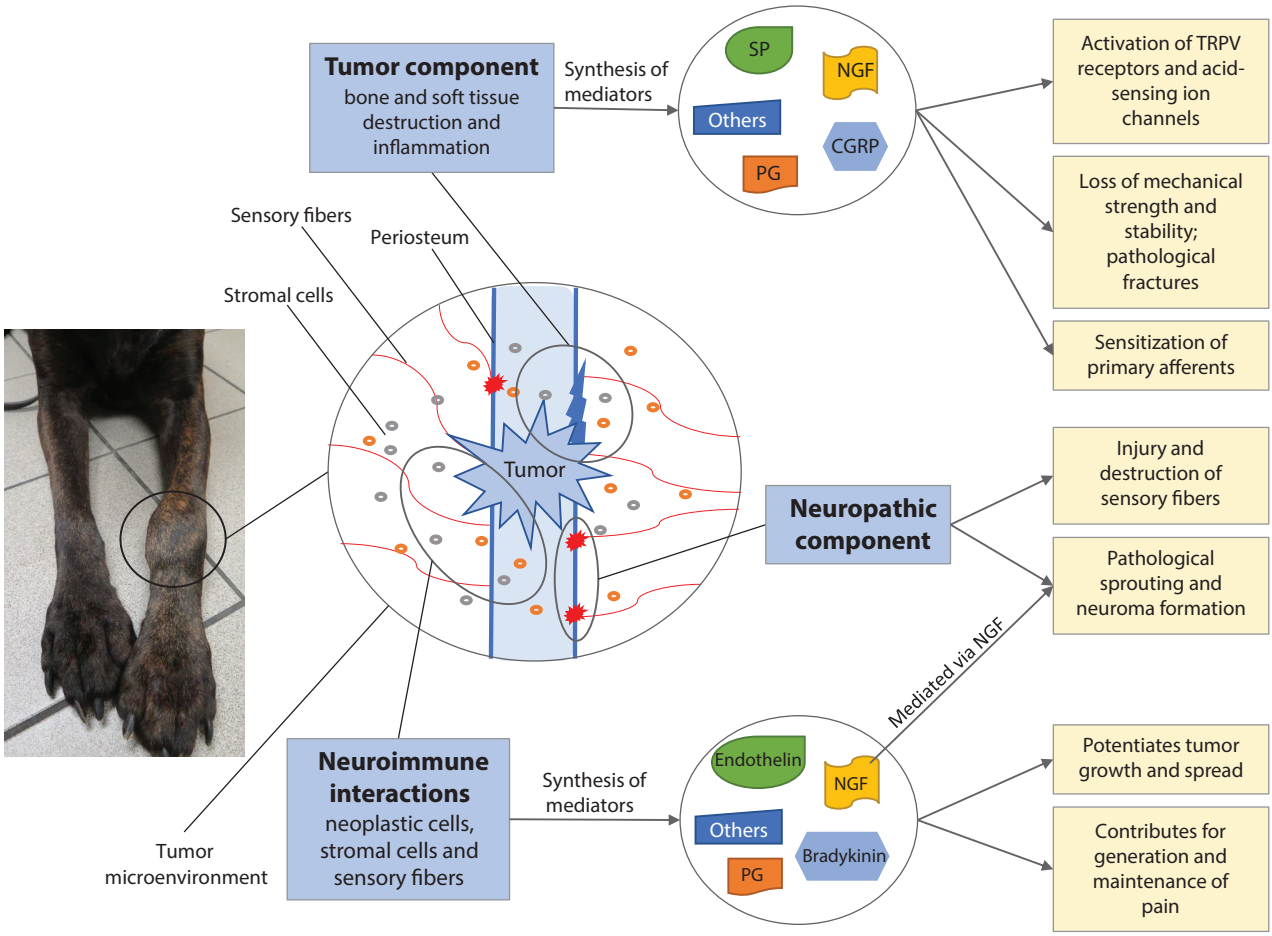


FIGURE 24.7 Cancer pain in dogs with osteosarcoma is the result of a complex interaction between the tumor, the somatosensory system, and the immune system. CGRP, calcitonin gene-related peptide; NGF, nerve growth factor; PG, prostaglandin; SP, substance P. (*Modified from Monteiro (2019).* Assessment of Chronic Pain in Companion Animals: Development and Concurrent Validation of Neurophysiological Methods *(PhD thesis; Université de Montréal).*)

microenvironment, interaction between neoplastic cells, stromal cells and sensory fibers synthetize and secrete a number of mediators resulting in sensitization of primary afferent neurons, regulation of angiogenesis, and potentiation of tumor growth and spread.

PAIN ASSESSMENT

Pain is a personal, complex, and multidimensional experience composed of sensory and emotional components. Therefore, the intrinsic challenge of veterinarians is to assess such an experience in animals. One of the main reasons for the inappropriate treatment of pain is inadequate pain assessment. Pain is now considered as the 4th vital sign, and its assessment should be incorporated into the clinical evaluation of all animal patients (Figure 24.8).

Pain assessment relies on the observation of pain-related behaviors and is aided by the use of validated pain scales. Physiological changes such as increases in heart rate and respiratory rates, pupil size and neuroendocrine assays (e.g. cortisol) are poorly specific for pain.

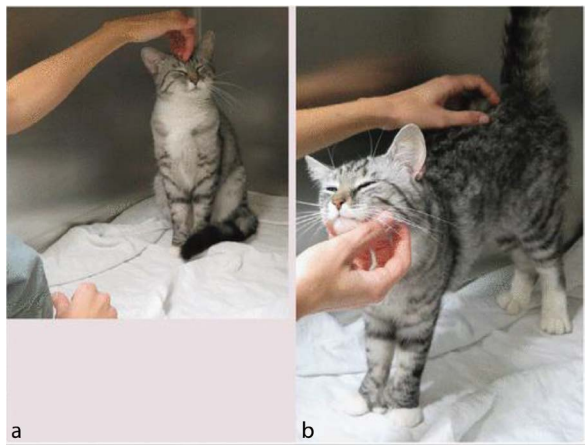


FIGURE 24.8 Pain assessment should be performed in all patients. This young female cat is evaluated for pain prior to surgery. First, she is assessed at a distance. Then, the cage door is opened, and her willingness to interact and response to palpation are performed. Having baseline pain assessment is helpful when evaluating animals postoperatively. (*Reprinted from* J Feline Med Surg *2019;21(1):25–34. Steagall and Monteiro, Acute pain in cats: Recent advances in clinical assessment. SAGE Publishing.*)

Acute Pain Assessment

For animals undergoing surgery, the veterinarian or technician should assess the animal's behavior before surgery for a baseline pain evaluation. The frequency of pain assessment following surgery will depend on the type of surgery, the condition of the animal prior to surgery, and the analgesic protocol. In studies involving dogs and cats undergoing ovariohysterectomy and receiving a multimodal analgesic protocol, including nonsteroidal anti-inflammatory drugs (NSAIDs) ± local anesthetics ± opioids, pain scores are higher than baseline from 30 minutes up until 4–6 hours after surgery. Animals that are sleeping, eating, or grooming should not be disturbed for pain assessment.

In dogs and cats with acute pain, commonly observed pain-related behaviors include:

- Decreased activity
- Decreased attention to the surroundings
- Changes in body posture (e.g., cats with abdominal pain show hunched posture; dogs with abdominal pain show praying position; Figures 24.9 and 24.10)



FIGURE 24.9 Dog with postoperative abdominal pain showing the "praying position" following ovariohysterectomy.



FIGURE 24.10 Cat with abdominal pain due to acute pancreatitis showing a hunched-up body position. The Feline Grimace Scale score for this cat was 7/10, indicating the need for administration of rescue analgesia. The scores for each action unit were as follows: 2 for ear position, 0 for orbital tightening, 2 for muzzle tension, 2 for whisker position, and 1 for head position.

- Attention to the wound; reaction to gentle palpation of the wound
- Vocalization
- Withdrawing; hiding; unwilling to interact
- Changes in facial expression
- Decreased appetite; decreased or increased grooming (cats)
- Growling; groaning; fear-motivated aggression

Chronic Pain Assessment

The assessment of chronic pain relies heavily on owner-reported changes in behavior (including home-made videos). In dogs, useful information can be generally collected from the physical exam (e.g., response to palpation, lameness, etc.). Cats tend to be more fearful in hospital settings, and less information is usually gained from physical exam.

Chronic pain manifests as a continuous flow of high, moderate, and low levels of pain. Thus, behaviors are influenced by dynamic changes in environmental and physiological demands, varying from day to day.

In dogs and cats with chronic pain, commonly observed pain-related behaviors include:

- Decreased activity and exercise intolerance
- Decreased ability to perform routine activities (e.g., cats become reluctant to jump up and down and/or use steps for doing this; cats no longer groom as they used to; dogs have difficulty in getting into the car or climbing the stairs; dogs no longer come to greet owners at the door)
- Decreased socialization towards owners and other pets
- Inappropriate/difficult elimination (e.g., cats might find it difficult to enter the litter box; dogs might have difficulty in squatting)
- Changes in demeanor (e.g., development of aggression/escape reaction when picked up or when a certain area of the body is touched)
- Sudden vocalization/agitation (e.g., cats with feline hyperesthesia syndrome might suddenly reach for their back with intense grooming behavior hair-plucking; dogs with persistent postsurgical pain after tail docking might develop spontaneous and severe pain at the stump and suddenly start chasing it vigorously)
- Difficulty rising to standing after long periods of rest

PAIN SCALES

Pain scales ensure a systematic approach to pain assessment (Figure 24.11). In most cases, acute pain scales are completed by the veterinarian or technician, whereas chronic pain scales are completed by owners. A brief description of the most validated pain scales is given here.

Acute pain scales for dogs

- *Glasgow Composite Measure Pain Scale-Short Form* (CMPS-SF): The maximum score is 24; the cutoff score for administration of rescue analgesia is ≥ 6/24 (or ≥ equal to 5/20 when mobility cannot be assessed). Available at https://www.newmetrica.com/acute-pain-measurement/.

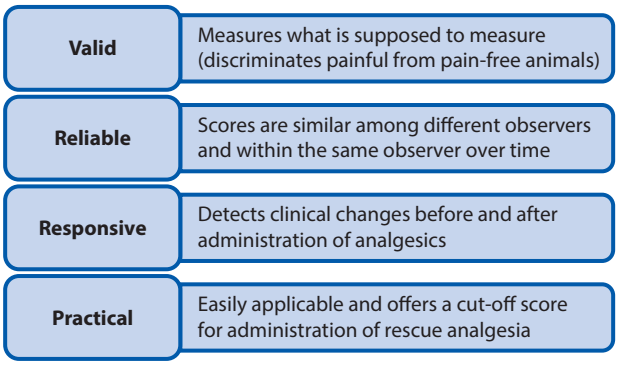


FIGURE 24.11 Using a validated pain scales means that rigorous scientific methods were undertaken to ensure that the scale is valid, reliable, responsive, and practical.

- *Melbourne Pain Scale* (MPS): The maximum score is 27; no cutoff score is available. Available in the original article (32).
- The Colorado State University Canine Acute Pain Scale has not undergone formal scientific validation. Other validated tools should be preferred until further information is available.

Acute pain scales for cats

- *Feline Grimace Scale* (FGS): Based on changes in facial expression (ear position, orbital tightening; muzzle tension; whisker position; head position) (**Figure 24.10**). The maximum score is 10; the cutoff score for administration of rescue analgesia is ≥ 4/10. The FGS has been validated for use by veterinarians, veterinary technicians, veterinary students, and cat owners. Available at www.felinegrimacescale.com.
- *UNESP–Botucatu Cat Pain Scale* (UCAPS): The maximum score is 12; the cutoff score for administration of rescue analgesia is ≥ 4/12. Available at www.animalpain.org.
- *Glasgow Composite Measure Pain Scale–Feline* (CMPS-Feline): The maximum score is 20; the cutoff score for administration of rescue analgesia is ≥ 5/20. Available at www.newmetrica.com/acute-pain-measurement/.
- The Colorado State University Feline Acute Pain Scale has undergone reliability testing. Validity is yet to be demonstrated. Other validated tools should be preferred until further information is available.

Chronic pain scales for dogs

- *Canine Brief Pain Inventory* (CBPI): Developed for use in dogs with OA and bone cancer. Evaluates pain severity and pain interference with function. Available at https://www.vet.upenn.edu/research/clinical-trials-vcic/our-services/pennchart/cbpi-tool.
- *ACVS Canine Orthopedic Index* (COI): Developed for use in dogs with OA. Evaluates stiffness, gait, function, and quality of life. Available at https://www.vet.upenn.edu/research/clinical-trials-vcic/our-services/pennchart/canine-orthopedic-index.
- *Liverpool Osteoarthritis in Dogs* (LOAD): Developed for use in dogs with OA. Evaluates general mobility and mobility at exercise. Available at https://www.galliprantvet.com/us/en/coast-tools.
- *Canine Osteoarthritis Staging Tool* (COAST): Developed as a staging tool in which the dog and the joint are assessed in steps for determining the dog's COAST stage. Available at https://www.galliprantvet.com/us/en/coast-tools.

Chronic pain scales for cats

- *Feline Musculoskeletal Pain Screening Checklist* (Feline MiPSC): Developed to increase awareness of OA in cats and as a tool for screening of cats with OA-associated pain. Available at https://journals.sagepub.com/doi/full/10.1177/1098612X20907424.
- *Feline Musculoskeletal Pain Index* (FMPI): Developed for use in cats with OA. Evaluates mobility, ability to perform daily activities, and interaction with other pets and people. Available at https://cvm.ncsu.edu/research/labs/clinical-sciences/comparative-pain-research/clinical-metrology-instruments/.
- *Client-Specific Outcome Measure* (CSOM): Developed for use in cats with OA. Three activities particular to the cat and its home are chosen and evaluated over time. Available at https://cvm.ncsu.edu/research/labs/clinical-sciences/comparative-pain-research/clinical-metrology-instruments/.

PRINCIPLES OF PAIN MANAGEMENT

Failure to recognize and adequately treat pain can result in negative physiological effects and the development of peripheral and central sensitization (**Figure 24.12**).

Oligoanalgesia refers to the inadequate treatment of acute perioperative pain. This results in postoperative impedance of routine activities, increased stress and anxiety. In humans, oligoanalgesia in patients undergoing major surgery (limb amputation, thoracotomy, mastectomy, and orthopedic procedures) can lead to the development of persistent postsurgical pain. Understanding the principles of acute and chronic pain management assist the veterinarian in developing an effective analgesic regimen and prevent oligoanalgesia.

Prior to formulating an analgesic plan, key concepts should be considered which will dictate the type, route, and frequency of administration of the analgesic drug(s)

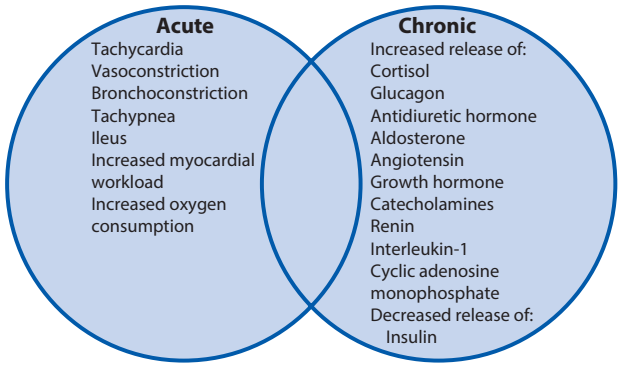


FIGURE 24.12 Acute and chronic effects of inadequately treated pain.

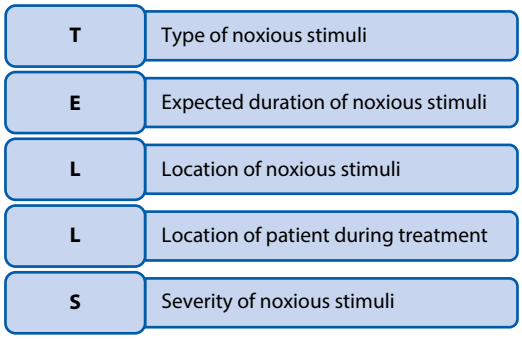


FIGURE 24.13 TELLS is an acronym used to describe the characteristics of a patient's pain and help formulate an analgesic plan (dose, frequency, type, and route of the analgesic drug).

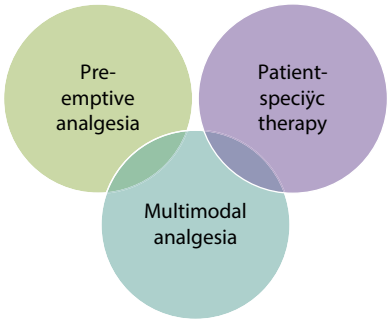


FIGURE 24.14 Fundamental principles of managing pain in dogs and cats.

(Figure 24.13). The analgesic plan should be focused around three fundamental principles (Figure 24.14). These practices involve the administration of various analgesic drugs and techniques to target multiple receptors involved in the pain pathway (i.e., mechanism-based therapy).

Pre-Emptive Analgesia

Pre-emptive analgesia involves the administration of an analgesic drug prior to surgical noxious insult (i.e., skin incision) to reduce or prevent nociceptive impulse transmission. This technique is generally more effective in reducing postoperative pain when compared to a similar dose of the same analgesic administered after the painful insult (i.e., pain pathway is already sensitized). Incorporating pre-emptive analgesic techniques in clinical practice can prevent peripheral and central sensitization, decreased intraoperative responses to noxious stimuli (i.e., increases in blood pressure, heart rate, respiratory rate, and purposeful movement), and prevent persistent postsurgical pain. It may also reduce the requirement for postoperative administration of opioids and its associated adverse effects. Clinical examples of pre-emptive analgesic techniques are described in Box 24.1.

Multimodal Analgesia

Multimodal (balanced) analgesia is the gold standard for pain control and refers to the use of two or more analgesic interventions, including pharmacological and nonpharmacological techniques with varying mechanisms of action (Figure 24.15).

Box 24.1 Techniques to employ pre-emptive analgesia in veterinary patients

- Administration of a pure μ-opioid receptor agonist as premedication prior to surgery
- Administration of coinduction agents with potential analgesic properties such as ketamine or lidocaine
- Performing local regional techniques (i.e., epidural, infiltrative line block, nerve block) with local anesthetics
- Oral administration of NSAIDs, tramadol, pregabalin, and/or gabapentin prior to surgery
- Transdermal administration of a buprenorphine or fentanyl patch 24–48 hours prior to surgery

The combination of different agents (e.g., α_2 adrenoreceptor agonists and opioids) can provide additive or synergistic analgesic effects resulting in improved perioperative comfort. It also allows for reduced doses of each individual analgesic agent, reducing the incidence and severity of adverse effects. Commonly used drugs in multimodal analgesic protocols include opioid receptor agonists, N-methyl-D-aspartate (NMDA) receptor antagonists, local anesthetics, α_2 adrenoreceptor agonists, NSAIDs, gabapentin, pregabalin, tramadol, and nonpharmaceutical adjuncts (e.g., electroacupuncture and physical rehabilitation). The combination of pre-emptive and multimodal analgesia provides the best benefit. Dosage recommendations for the most commonly used analgesics in dogs and cats are available on Table 24.1.

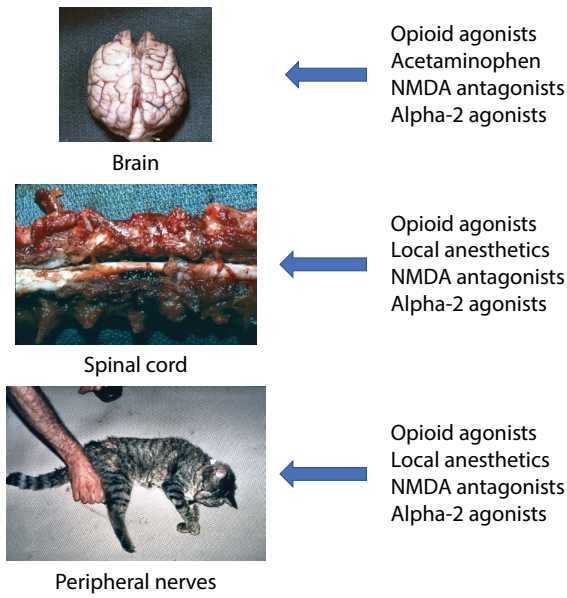


FIGURE 24.15 Multimodal (balanced) analgesia is the gold standard for pain control and refers to the use of two or more analgesic interventions, including pharmacological and nonpharmacological techniques with varying mechanisms of action. (*Courtesy of M. Schaer.*)

TABLE 24.1 Commonly used analgesic and adjuvant drugs in canine and feline pain management

	Dose	Species	Route of administration	Duration of effect	Comments
Opioids					
Morphine	0.3–1.0 mg/kg	Canine	IM, IV	3–4 hours	Caution with rapid IV administration: histamine release
	0.2–0.4 mg/kg	Feline	IM, IV	3–4 hours	
	0.2 mg/kg loading dose, then 0.1–0.5 mg/kg/hour	Canine	IV then CRI, administer bolus slowly		
	0.2 mg/kg loading dose, then 0.05–0.1 mg/kg/hour	Feline	IV then CRI, administer bolus slowly		
	0.1 mg/kg preservative free	Canine Feline	Epidural	12–24 hours	
	0.01 mg/kg preservative free	Canine Feline	Intrathecal	12–24 hours	
	0.1 mg/kg diluted to 0.5 mL/kg in sterile 0.9% saline	Canine	Intra-articular		
Meperidine	3–5 mg/kg	Canine Feline	IM, SC	1–2 hours	
Methadone	0.2–0.75 mg/kg	Canine Feline	IM, IV	2–4 hours	NMDA antagonist activity
Oxymorphone	0.05–0.2 mg/kg	Canine	IM, IV, SC	3–4 hours	Minimal histamine release
	0.03–0.1 mg/kg	Feline	IM, IV	3–4 hours	
Hydromorphone	0.05–0.2 mg/kg	Canine	IM, IV	2–4 hours	Emesis observed when administered IM Hyperthermia observed in cats
	0.025–0.1	Feline	IM, IV	2–4 hours	
Fentanyl	2–5 μg/kg initial dose, then 3–10 μg/kg/hour	Canine	IV then CRI		
	2–5 μg/kg initial dose, then 2–10 μg/kg/hour	Feline	IV then CRI		
Fentanyl patch	25 μg/hour	Canine (3–10 kg body weight)	Transdermal	1–3 days	12–24 hours to reach peak concentrations
	50 μg/hour	Canine (10–20 kg body weight)	Transdermal	1–3 days	
	75 μg/hour	Canine (20–30 kg body weight)	Transdermal	1–3 days	
	100 μg/hour	Canine (>30 kg body weight)	Transdermal	1–3 days	
	25–50 μg/hour	Feline		≤6 days	6 hours to reach peak concentrations
Remifentanil	6–20 μg/kg/h	Canine Feline	CRI		May induce hyperalgesia Ultra-short duration of action
Buprenorphine	0.01–0.04 mg/kg	Canine Feline	IM, IV, SC, OTM	4–8 hours	The IV and IM provide superior analgesia The SC route does not appear to provide adequate analgesia Inconsistent results after OTM administration

(*Continued*)

TABLE 24.1 Commonly used analgesic and adjuvant drugs in canine and feline pain management (*Continued*)

	Dose	Species	Route of administration	Duration of effect	Comments
Buprenorphine (high concentration 1.8 mg/mL)	0.24 mg/kg	Feline	SC	24 hours	Administer for up to three days
Tramadol	3–5 mg/kg	Feline	p.o.	8–12 hours	Seems to be effective in cats but not in dogs with OA
Alpha-2 agonists					
Dexmedetomidine 0.5 or 0.1 mg/ml	1–5 µg/kg	Canine	IM, IV	0.5–1.5 hours	Sedation, bradycardia, vomiting (cats) Consider lower doses when administered IV Only higher doses provide analgesia when used alone For medetomidine use twice the dosing recommendations made for dexmedetomidine
	1–10 µg/kg	Feline	IM, IV	0.5–1.5 hours	
	1 µg/kg, then 0.5–2 µg/kg/hour	Canine Feline	IV slowly over 10 minutes then CRI		
	1–5 µg/kg	Canine Feline	Epidural		
	2–5 µg/kg	Canine Feline	Intra-articular		
NMDA antagonists					
Ketamine	0.5–1 mg/kg, then 0.2–1 mg/kg/hour	Canine Feline	IV then CRI		
Amantadine	3–5 mg/kg	Canine Feline	p.o.	12–24 hours	Chronic painful conditions with a neuropathic pain component
Methadone	0.1–0.5 mg/kg	Canine Feline	IM, IV	2–4 hours	Opioid derivative
Tricyclic antidepressant					
Amitriptyline	1–4 mg/kg	Canine Feline	p.o.	12–24 hours	Chronic painful conditions Avoid combining to serotoninergic drugs
Ca^{2++} channel modulator					
Gabapentin	5–10 mg/kg	Canine Feline	p.o.	8–12 hours	Higher doses are anecdotally used Dose is limited by the amount of sedation observed
Local anesthetics					
Lidocaine (1–2%)	≤6.0 mg/kg	Canine	Perineural	1–2 hours	Onset 10–15 minutes Maximum dose: 12 mg/kg (canine), 6 mg/kg (feline)
	≤3.0 mg/kg	Feline	Perineural	1–2 hours	
	2–4 mg/kg, then 25–80 mcg/kg/minute	Canine	IV then CRI		Caution as a CRI in cats due to the cardiovascular depressant effects
	05–1 mg/kg, then 10–40 mcg/kg/minute	Feline	Slow IV then CRI		
Bupivacaine (0.25–0.5%)	≤2.0 mg/kg	Canine	Perineural	2–6 hours	Onset 20–30 minutes Maximum dose: 2 mg/kg (canine or feline)
	≤1.0 mg/kg	Feline	Perineural	2–6 hours	
Liposome encapsulated bupivacaine (13.3 mg/mL Nocita®)	0.4 mL/kg	Canine Feline	Infiltration	72 hours	Can dilute 1:1 with sterile 0.9% saline or Lactated Ringer's Solution

(*Continued*)

TABLE 24.1 Commonly used analgesic and adjuvant drugs in canine and feline pain management (*Continued*)

	Dose	Species	Route of administration	Duration of effect	Comments
Mepivacaine (1–2%)	≤6.0 mg/kg	Canine	Perineural	2–2.5 hours	
	≤3.0 mg/kg	Feline	Perineural	2–2.5 hours	
Non-steroidal anti-inflammatory drugs (NSAIDs)					
Carprofen (injectable and tablet)	4.4 mg/kg	Canine	SC or p.o.	24 hours	
Deracoxib (tablet)	1–4 mg/kg	Canine	p.o.	24 hours	
Firocoxib (tablet)	5 mg/kg	Canine	p.o.	24 hours	
Meloxicam (injectable, tablet or oral suspension)	0.2 mg/kg once followed by 0.1 mg/kg	Canine	IV, SC, p.o.	24 hours	
Meloxicam (injectable or oral suspension)	0.2–0.3 mg/kg once followed by 0.05–0.1 mg/kg	Feline	SC, p.o.	24 hours	Palatable oral suspension Lower doses (0.02–0.05 mg/kg) are used long-term in cats with chronic pain
Robenacoxib (injectable and tablet)	2 mg/kg	Canine	SC, p.o.	24 hours	
Robenacoxib (injectable and tablet)	1–2.4 mg/kg	Feline	SC, p.o.	24 hours	Lowest effective dose in long-term treatment
Cannabinoids					
CBD oil	2 mg/kg	Canine	p.o.	12 hours	
Adjunctive drugs frequently administered with analgesics					
Acepromazine	0.005–0.05 mg/kg	Canine	IM, IV, SC	8–12 hours	No intrinsic analgesic properties, but used to potentiate or prolong analgesic drugs
	0.01–0.1 mg/kg	Feline	IM, SC	8–12 hours	
Midazolam	0.1–0.2 mg/kg	Canine Feline	IV	2–4 hours	No intrinsic analgesic properties, but used to potentiate or prolong analgesic drugs
	0.25–1.0 mg/kg	Canine Feline	p.o.	12–24 hours	

Patient-Related Factors

Patient-specific therapy has gained popularity in veterinary medicine. Individual variation in drug responses can lead to unforeseen toxicity or failure to respond to therapy. For example, genetic polymorphisms of metabolizing enzymes in dogs have significant clinical implications in opioid drug metabolism, duration of effect, and oral bioavailability. As we further understand the intricacies of veterinary pharmacogenetics, there is potential to better predict dosage regimens, improve perioperative analgesia, and reduce the incidence of adverse effects. Patient-specific therapy also includes the concept that "not one size fits all," and standardized protocols should be avoided. In a broader sense, analgesics effective in cats may not provide the same degree of pain relief in dogs. As observed with the administration of oral tramadol, evidence supports its efficacy as a sole analgesic agent in cats but not in dogs. The patient's medical history, physical exam, and diagnostic results should be used to dictate and appropriate analgesic regimen. Emphasis should be placed on reviewing the patient's hepatic, renal, cardiopulmonary and neurologic status, behavior, current and predicted degree of pain, age, species, and breed. For example, an ovariohysterectomy in a geriatric canine patient with

several comorbidities may not receive the same analgesic protocol as an adolescent healthy cat undergoing the same procedure.

The duration of pain (acute versus chronic) impacts prescribing methods. Administration methods for sustained pain relief include transdermal patches (e.g., fentanyl or buprenorphine patch); sustained-release, liposomal encapsulated (Nocita™); high-concentration (Simbadol™) or oral formulations; constant rate infusions; or lumbosacral and peripheral nerve catheters. Additionally, the choice of analgesic is largely influenced by pain severity. In mild-to-moderate pain, an opioid such as buprenorphine may be effective for pain relief; however, with severe pain, a potent opioid receptor agonist such as fentanyl may be required. The site or origin of the noxious stimuli is also important, particularly when performing locoregional techniques. The administration of local anesthetics is extremely effective in treating acute and chronic pain if (1) the anesthetist can determine the noxious stimuli's site of origin and (2) is familiar with anatomy associated with locoregional anesthesia.

Hospital-Related Factors

Management of pain is also impacted by hospital-related factors (Figure 24.16). The frequency and route of analgesic administration depends on the hours of service of the hospital. If a patient needs to be discharged prematurely due to lack of overnight staff or left unattended throughout the night, practitioners need to rely on longer-lasting oral, sustained-release, or transdermal analgesic drugs, whereas in hospitals with continuous 24-hour service, constant rate infusions (CRI) or parenteral therapy might be preferred. It is also crucial that the hospital staff is available and educated for appropriate pain assessment and management. Globally, 39%–77% of veterinarians acknowledge their ability to identify pain is inadequate. This deficiency in knowledge creates a "domino effect" on to those expected to learn from them (e.g., veterinary technicians and staff members).

Hospital-related stress has important implications in pain management (Figure 24.17). It can result from noncyclic and artificial lighting, excessive noise, nonfamiliar (e.g., disinfectants, medications, humans) and animal-emitted (e.g., anal gland secretions, pheromones) scents, extremes in temperature, unfamiliar or uncomfortable housing, proximity to unfamiliar animals, interrupted sleep, fear, and pain. Alterations in the levels of dopamine, oxytocin, and endogenous opiates as observed during stress can distort the normal responses to pain masking the ability of a veterinarian to assess pain. Chronic stress also can contribute to the development of hyperalgesia and reduced efficacy of opioid analgesics. Furthermore, stress has the ability to weaken and disrupt the gastrointestinal (GI) system resulting in visceral pain. Painful patients experiencing stress often require higher analgesic doses than those that are stress-free, with the former increasing the incidence for drug-related adverse effects and complications. Strategies to reduce stress, fear, and anxiety can lead to reduction in analgesic requirements.

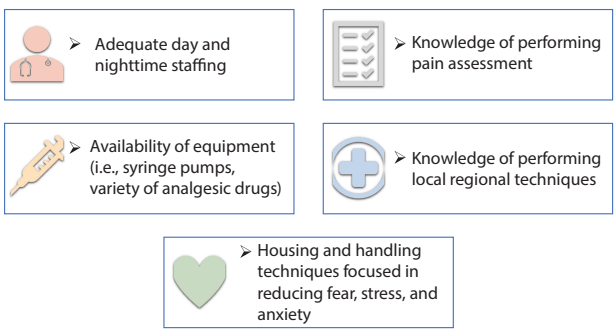


FIGURE 24.16 Hospital-related factors impacting pain management.

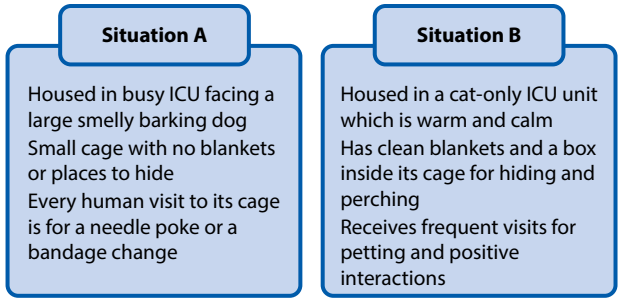


FIGURE 24.17 Stress and patient care can influence pain perception. Imagine the same cat after a fracture repair with the same analgesic protocol in situation A or B. Certainly, in situation B, the cat is more comfortable, feels safer, and is less fearful, anxious, and stressed. Pain perception is thus decreased, and the cat is more likely to be in a positive mental state contributing to its welfare during hospitalization.

LOCAL ANESTHETICS

Local anesthetics are one of the most versatile classes of drugs when treating pain and are used to treat somatic, visceral, and neuropathic pain during acute and chronic states. This versatility can be attributed to the variety of routes, formulations, and concentrations in which they can be administered. Administration by the IV (lidocaine only), epidural, intrathecal, transdermal, infiltrative, perineural, and topical routes can produce analgesia in dogs and cats. Several formulations and concentrations are available for veterinary use depending on the duration and severity of pain.

Local anesthetics prevent the nociceptive impulse from reaching the spinal cord (depolarization and propagation) via nonselective blocking of voltage-gated sodium channels located within nerve fibers. Local regional techniques in dogs and cats are discussed in detail elsewhere (see Recommended Further Readings). Lidocaine, bupivacaine, mepivacaine, or ropivacaine are most commonly used.

Adverse effects are dependent on systemic absorption and plasma concentrations. Generally, central nervous system signs are observed first (e.g., agitation, muscle twitching, seizures, and/or convulsions). Cardiovascular adverse effects may include hypotension, myocardial

depression, and arrythmias. At high plasma concentrations, unconsciousness, apnea, cardiovascular collapse, and death may occur.

Local Anesthetics at-a-Glance

Lidocaine (1% or 2% concentrations)

- The most versatile local anesthetic as it can be administered topically, intravenously, epidurally, subcutaneously, and perineurally.
- Onset 5–10 minutes, and duration is typically 1–3 hours.
- Also possesses anti-inflammatory and antiarrhythmic properties.
- Can be administered as a CRI to help prevent central sensitization and treat perioperative pain associated with orthopedic and abdominal procedures, particularly when combined with opioids and NMDA receptor antagonists.
- May cause significant reductions in cardiac output when administered as a CRI in cats. Consider using lower dosages (35–50 mcg/kg/min) in multimodal analgesic protocols and monitor blood pressure closely.
- Transdermal 5% lidocaine patches are commercially approved for humans. Pharmacokinetic studies in dogs and cats suggest highly variable absorption rates with limited adverse effects. Evidence to support their analgesic efficacy when placed over the surgical incision has yet to be confirmed. Veterinarians should not rely on 5% lidocaine patches as a sole postoperative analgesic in dogs and cats.

Mepivacaine (1% or 2% concentrations)

- Similar onset to lidocaine but with a longer duration of action of 2–4 hours.
- Less commonly used in small animal practice.
- Not recommended for intravenous administration.

Bupivacaine (0.125%–0.75% concentrations; 0.5% is the most commonly used)

- Slower onset of action of 20–30 minutes but with a longer duration of action of 6–8 hours.
- Not recommended for intravenous administration.
- More cardiotoxic than lidocaine.
- Frequently used for nerve blocks and neuraxial anesthesia.
- Available in a variety of concentrations which can allow for differential blockade (i.e., sensory anesthesia without motor blockade when using bupivacaine concentrations <0.25%).

Ropivacaine (0.25%–0.75% concentrations)

- Similar onset and duration of action when compared to bupivacaine.
- Lower potential for inducing cardiovascular and central nervous system toxicity.
- At concentrations similar to bupivacaine (0.5%), it has a reduced chance of inducing motor blockade, making it optimal when neuraxial anesthesia is recommended.
- Not recommended for intravenous administration.



FIGURE 24.18 An infiltrative local anesthetic block using Nocita™ along an incision. (*Courtesy of Irina Yankin.*)

Bupivacaine liposome injectable suspension (Nocita™ 13.3 mg/mL)

- Doses of 5.3 mg/kg in dogs and 10.6 mg/kg in cats.
- Currently approved for local infiltration into the surgical site following cranial cruciate ligament surgery in dogs and for peripheral nerve block for regional analgesia following onychectomy in cats (Note: Onychectomy is not advocated by the authors or Nocita).
- Provides up to 72 hours of analgesia.
- Onset of action generally occurs within 15–20 minutes following administration.
- Administered as an infiltrative locoregional block in a variety of surgeries at the site of surgical incision in dogs and cats during tissue closure (Figure 24.18).
- Should not be combined with other local anesthetics or hypotonic solutions as this can disrupt the liposomal particles causing systemic toxicity.
- Can administer up to 0.4 mL/kg of Nocita™. If more volume is required to cover the surgical area, combine with an equal volume of sterile 0.9% saline or lactated Ringers solution.

Eutectic mixture of local anesthetics (EMLA®) cream

- 2.5% lidocaine and 2.5% prilocaine (Figure 24.19a).
- Topical anesthetic used to desensitize mucous membranes or intact clean bare skin.
- Facilitates procedures such as intravenous catheter placement, small surgical incisions (e.g., skin cutdown to the jugular vein performed during noninvasive cardiac procedures), and thoracentesis (Figure 24.19b).

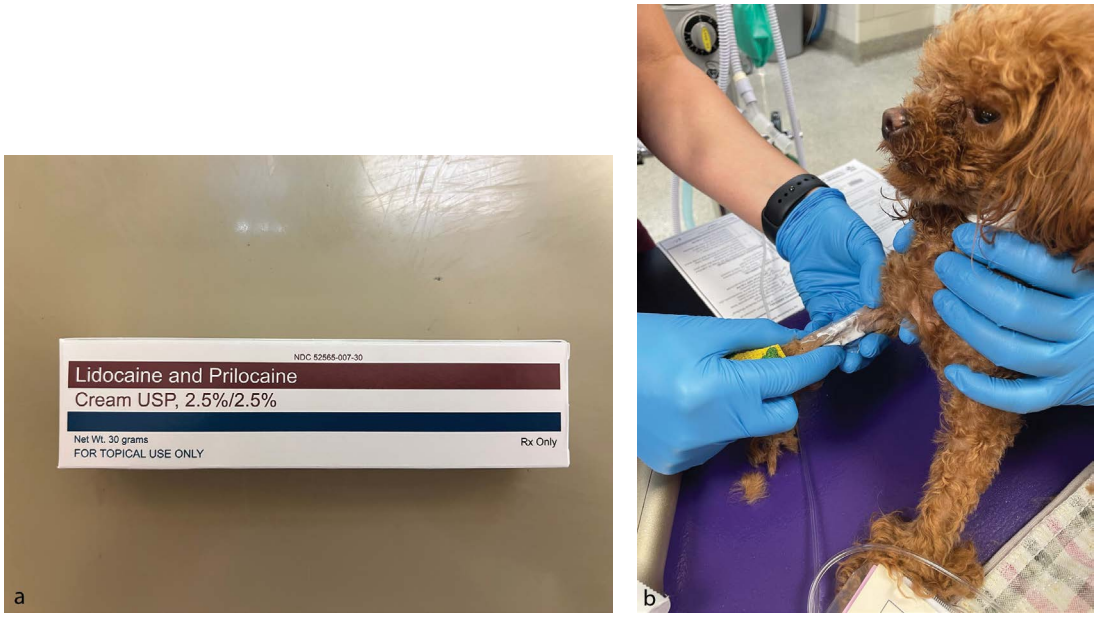


FIGURE 24.19 The eutectic mixture of local anesthetics (EMLA®) cream **(a)** is applied over the shaved skin and covered for 15–20 minutes before asepsis. Local anesthesia of the skin facilitates venous catheterization in anxious/fearful dogs and cats **(b)**.

OPIOIDS

Opioid analgesics are effective in the management of visceral, oncologic, somatic, and neuropathic pain in dogs and cats. They are reliable and efficacious analgesics, considered relatively safe, and have the benefit of reversibility. Adverse effects following opioid administration are generally mild and most often easily managed (Figure 24.20 and Table 24.2).

Opioid analgesics have been readily available for general veterinary use until recently. Recent shortages were a sequala of production quota reductions associated with the global opioid crisis, particularly with pure μ-opioid receptor agonists, set forth by the Drug Enforcement Agency. The national opioid crisis has hindered veterinarians' ability in prescribing opioids; however, it has strengthened our understanding and confidence in utilizing multimodal analgesic techniques.

Urinary retention (neuraxial morphine)	**Vomiting** (morphine and hydromorphone)	**Gastrointestinal Ileus**
Pruritis (neuraxial morphine)	**Hypoventilation**	**Hyperthermia** (hydromorphone most common)
Histamine reaction (intravenous morphine or meperidine)	**Bradycardia**	**Euphoria or dysphoria**

FIGURE 24.20 Adverse effects associated with opioid analgesics.

Opioids bind to opioid receptors in the central and peripheral nervous system, resulting in decreased release of excitatory neurotransmitters (presynaptic terminals) and hyperpolarization of neuronal membranes (postsynaptic terminals), reducing the propagation of nociceptive stimuli. There are three main types of opioid receptors responsible for analgesia: μ, κ, and δ. Pure μ-opioid receptor agonists yield a dose-dependent intensification in effect until maximum stimulation of the receptors is achieved. Partial μ-opioid receptor agonists yield a dose-dependent response that plateaus at an effect less than that observed with pure μ-opioid receptor agonists (Figure 24.21). Generally, opioids can be classified as pure μ-opioid receptor agonists, partial μ-opioid receptor agonists, or μ-mixed opioid receptor agonists/antagonists.

Opioid versatility is in part attributed to their routes of administration: Intravenous (IV), subcutaneous (SC), intramuscular (IM), sublingual, oral, intrathecal, epidural, perineural, transdermal, and intraarticular. Intravenous administration provides the most rapid onset and least variation in analgesic efficacy. Subcutaneous route is considered less painful than IM at injection; however, in cats, greater individual variations and reduced analgesic efficacy was observed with SC administration of hydromorphone or standard concentration buprenorphine (0.3 mg/mL). Vomiting is more commonly observed following hydromorphone and morphine administration via IM and SC than the IV route.

The sublingual route requires minimal restraint and administration is pain-free. It bypasses first-pass metabolism allowing for higher systemic bioavailability when compared to oral administration. Buprenorphine (0.01–0.02 mg/kg) or methadone (0.6 mg/kg) can be

TABLE 24.2 Adverse effects following opioid administration and their suggested treatment

Opioid	Adverse effect	Treatment
Hydromorphone Morphine	Vomiting	– Maropitant 1 m/kg SC or IV 30–60 minutes prior to opioid in dogs and cats – Maropitant 2–4 mg/kg p.o. 2 hours prior or 8 mg 2.5 hours prior to opioid in dogs or cats, respectively – Metoclopramide 0.2 mg/kg IM or 0.5 mg/kg SC 30–45 minutes prior to opioid in dogs – Acepromazine 0.05 mg/kg IM 15 minutes prior to opioid
Morphine	Urinary retention following epidural or spinal administration	– Gentle bladder expression – Urinary catheter placement – Bethanechol 2.5–5 mg p.o. q.8–12 h in dogs or cats – Naloxone generally is not effective for opioid induced urinary retention
	Histamine (IV administration)	– Diphenhydramine 2 mg/kg IV or p.o. q.8 h as needed – Supportive therapy as needed
	Pruritis following epidural or spinal administration	– Ondansetron 0.1–0.2 mg/kg IV q.12 h as needed
All opioids (specifically pure μ-opioid receptor agonists)	Hypoventilation	– Administer positive pressure ventilation – Naloxone reversal 0.01–0.04 mg/kg IV slowly to effect in dogs and cats – Maintain an end-tidal CO_2 of 35–45 mmHg
	Bradycardia	– Atropine 0.02–0.04 mg/kg IV in dogs and cats – Glycopyrrolate 0.01–0.02 mg/kg IV in dogs and cats
	Hyperthermia (cats)	– Naloxone reversal 0.01–0.04 mg/kg IV slowly to effect – Supportive therapy as needed
	Ileus (chronic administration)	– Reduce opioid dose and frequency – Consider multimodal analgesic therapy

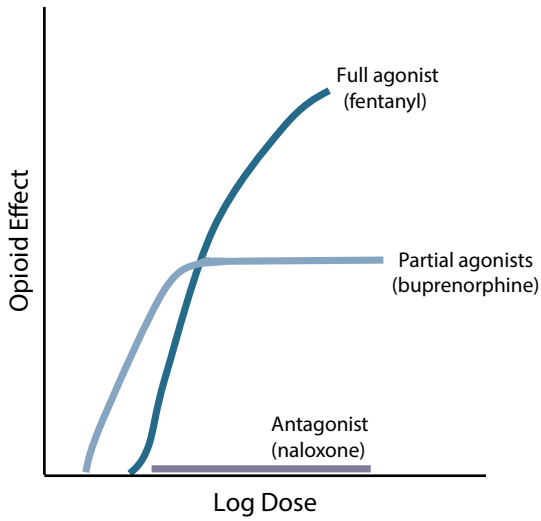


FIGURE 24.21 Dose-response curves for full and partial μ-opioid receptor agonists and a full μ-opioid receptor antagonist.

administered by the sublingual route in cats. Systemic absorption following sublingual administration is dependent on oral mucosal pH, which might be altered with infection or inflammation in cats with stomatitis and impact opioid systemic absorption. In dogs, sublingual buprenorphine provides analgesia; however, high doses are required (0.12 mg/kg), which could be cost prohibitive and result in excessive volumes, increasing the likelihood for accidental swallowing and loss through hypersalivation. Despite the sublingual route's ease of administration and practicality, it has been reported to provide less perioperative analgesia when compared to the IV and IM route in cats.

Epidural or intrathecal administration of opioids is effective in treating somatic and visceral pain without interfering with sensory or motor function or the sympathetic nervous system. Neuraxial morphine's prolonged duration of effect is attributed to long residence time in the cerebrospinal fluid and delayed systemic absorption within the vertebral canal. Urinary retention has been reported following the epidural administration of morphine in dogs but not following buprenorphine.

Opioid receptors have been identified within intra-articular and periarticular inflamed tissue following experimentally induced arthritis in dogs. Minimal adverse effects are reported via this route when administered aseptically.

Transdermal opioid patches are used for pain management in dogs and cats for up to 72–96 hours. Fentanyl patches can be incorporated into multimodal analgesic perioperative protocols, particularly when CRIs or overnight hospitalization are not available. They can also be added to chronic pain management protocols when oral analgesic and anti-inflammatory agents are not adequate. The onset of transdermal fentanyl is delayed and often requires a minimum of 12 or 24 hours of application prior to providing analgesia in cats and dogs, respectively. Significant variability in drug plasma concentrations were reported when using fentanyl patches in these species. Evidence of efficacy of transdermal buprenorphine patches in small animals are lacking.

Oral administration of opioids produces poor bioavailability (20%–60%), large individual variability, and limited analgesic efficacy in dogs. There is limited evidence to support the oral administration of opioids such as codeine, oxycodone, or hydrocodone in dogs or cats.

Opioids at-a-Glance

Pure μ-Opioid Receptor Agonists

Morphine

- Duration of analgesia 2–4 and 4–6 hours in dogs and cats, respectively, via traditional routes (e.g., IV, IM, SC).
- Onset and duration of analgesia is within 40 minutes and up to 24 hours, respectively, when administered via the epidural (0.1 mg/kg) or spinal route (0.01 mg/kg).
- May provide a greater degree of sedation than other pure μ-opioid receptor agonists due to its agonistic effects on the κ-receptor.
- Can be administered as a CRI with low incidence of hypersensitivity reactions in dogs and cats.
- Intraarticular administration (0.1 mg/kg diluted to 0.5 mL/kg in sterile 0.9% saline) can be used as part of a multimodal analgesic technique following orthopedic procedures.

Hydromorphone

- Duration of analgesia 2–6 and 4–6 hours in dogs and cats, respectively, via traditional routes.
- Age affects hydromorphone-induced antinociception; shorter duration (< 1 hour) and reduced magnitude of antinociception was recorded in cats 6 months of age when compared to 12 months.
- Contributes to opioid-induced hyperthermia in cats. Incidence is increased with intraoperative hypothermia and ketamine and inhalant anesthetics administration.

Methadone

- Duration of analgesia 3–4 and 4 hours in dogs and cats, respectively, via traditional routes.
- May serve as a weak NMDA receptor antagonist; useful in central sensitization, chronic pain, and opioid-induced hyperalgesia.
- Low incidence of vomiting and nausea.

Oxymorphone

- Duration of analgesia 2–4 and 4–6 hours in dogs and cats, respectively, via traditional routes.
- Low incidence of vomiting and nausea.
- Expense and availability have limited its use in the United States.

Meperidine (pethidine)

- Duration of analgesia 1–2 hours in dogs and cats when administered IM.
- Produces significant histamine release when administered IV.
- Anticholinergic effects resulting in increases in heart rate.

Fentanyl

- Short duration of analgesia, 1–2 hours, in dogs and cats when administered as an IV bolus.
- Recommended as a CRI.
- Caution with the accumulation of plasma fentanyl concentrations following prolonged infusions (> 3 hours).
- Induces more pronounced cardiopulmonary adverse effects when compared to other μ-opioid receptor agonists.

Remifentanil

- Short duration of analgesia (< 10 minutes) due to its metabolism via plasma cholinesterases; recommended as a CRI.
- May cause opioid-induced hyperalgesia; however, a one-time dose of a NMDA receptor antagonist immediately prior to its administration may prevent this occurrence.
- May induce profound bradycardia.

Partial μ-Opioid Receptor Agonists

Buprenorphine

- Standard formulation/concentration (0.3 mg/mL) provides up to 6–12 hours of analgesia in dogs and cats via traditional routes.
- High concentration buprenorphine (Simbadol™ 1.8 mg/mL) provides up to 24 hours of analgesia when administered SC in cats.
- Slow onset of analgesic action (30–60 minutes); provides less analgesia when compared to pure μ-opioid receptor agonists (ceiling effect).
- Sublingual and SC (excluding Simbadol™) routes produce unreliable analgesia in cats.
- Strong affinity for the μ-opioid receptor and may be difficult to displace from the μ-receptor.
- Reduced adverse effects when compared to pure μ-opioid receptor agonists.
- Has been used in conjunction with bupivacaine for perineural injections at 0.003–0.004 mg/kg. May prolong the duration of analgesia (> 24 hours) of local anesthetics following infraorbital nerve blocks in dogs.
- Epidural buprenorphine (0.005 mg/kg) provides similar duration of analgesia as morphine with less adverse effects (e.g., urinary retention).

Mixed Opioid Receptor μ-Antagonist/κ-Agonists

Butorphanol

- Evidence supports butorphanol as a very weak μ-agonist rather than a μ-opioid receptor antagonist.
- Weak analgesic and not recommended for the management of acute or chronic pain.
- Duration of analgesia 1–2 hours in dogs and cats.
- Useful as a reversal agent (0.02–0.1 mg/kg) for pure μ-opioid receptor agonists.

ALPHA-2 ADRENOCEPTOR AGONISTS

Alpha-2 adrenoceptor agonists are incorporated into multimodal analgesic protocols in acutely painful patients and in the attenuation or reversal of allodynia in patients with neuropathic or opioid-resistant pain. Dexmedetomidine and medetomidine are the most common α_2 agonists used in small animal practice. Dexmedetomidine is the dextrorotary enantiomer of the racemic mixture medetomidine and has replaced medetomidine in the United States. Dexmedetomidine (0.5 mg/mL) is approximately twice as potent as medetomidine (analgesic and sedative effects). This concentration allows clinicians to use the same injection volume as medetomidine. A 0.1 mg/mL concentration of dexmedetomidine is available for smaller patients.

High doses (e.g., 40 mcg/kg dexmedetomidine IM or sublingual) are required to provide analgesia when administered as the sole analgesic, which may lead to cardiopulmonary depression and morbidity and mortality in critically ill patients. In clinical practice, the authors administer dexmedetomidine CRI (0.5–2 mcg/kg/h) in a multimodal approach. Sedation is observed at lower plasma concentrations than those required for analgesia. Therefore, sedation in dogs and cats following the administration of dexmedetomidine or medetomidine does not correlate with analgesia.

Alpha-2 adrenoceptor agonists provide enhanced or synergistic analgesic and sedative effects when combined with opioids due to the simultaneous activation of opioid receptor subtypes and α_2 adrenoreceptors. With traditional parenteral routes, dexmedetomidine's and medetomidine's duration of analgesia is approximately 60 minutes. When opioids are unavailable, α_2 adrenoreceptor agonists can be administered with ketamine, NSAIDs, and locoregional techniques to provide adequate perioperative multimodal analgesia.

Alpha-2 adrenoceptor agonists bind to α_2 receptors located in the cerebral cortex, brain stem, and spinal cord, resulting in dose-dependent sedation, muscle relaxation, and spinal and supraspinal analgesia. The mechanism of analgesia involves (1) presynaptic and postsynaptic inhibition in the spinal cord dorsal horn, resulting in reduced membrane depolarization and enhanced hyperpolarization; (2) direct inhibition of noradrenaline release; (3) depolarization of descending noradrenergic pathways; (4) peripheral analgesic effect via inhibition of pain transmission within Aδ and C fibers; and (5) local analgesic effect via stimulation of α_2 receptors.

Dexmedetomidine can be administered via the IV, IM, SC, sublingual, perineural, and epidural routes. It is well absorbed through the oral mucosa (doses required to provide antinociception are similar to the IM route). There is limited literature regarding the neuraxial administration of dexmedetomidine and medetomidine in small animals. Epidural dexmedetomidine (4 mcg/kg) combined with bupivacaine (1 mg/kg) provided similar postoperative analgesia when compared to epidural morphine (0.1 mg/kg) and bupivacaine (1 mg/kg) in dogs undergoing orthopedic procedures; time to return to normal hindlimb motor function was delayed. Medetomidine (10 mcg/kg) may produce dose-dependent antinociception when administered epidurally in dogs for up to 90 minutes. Epidural administration of α_2 adrenoreceptor agonists may still result in dose-dependent mild-to-moderate cardiovascular changes; caution should be taken in critically ill patients. Veterinarians should also avoid contamination of multiuse nonpreservative-free vials when performing neuraxial administration. Dexmedetomidine (0.1 mcg/kg or 1 mcg/mL of local anesthetic) and medetomidine (0.01 mg/kg) have been administered with local anesthetics to prolong the latter's duration of sensory blockade (reduced systemic absorption of local anesthetics through local vasoconstriction). The authors administer dexmedetomidine with bupivacaine in thoracic limb, pelvic limb and dental nerve blocks, and intraperitoneally.

Adverse effects are dose-dependent but can be significant in compromised patients (Box 24.2). Atipamezole can be administered IV slowly (half the original volume of dexmedetomidine) or IM (equal to the original volume of dexmedetomidine) to reverse the behavioral effects associated with dexmedetomidine (0.5 mg/mL). Administration of atipamezole has not been shown to reverse the unwanted cardiovascular effects associated with dexmedetomidine in cats. Administration of atipamezole should be one-fifth the original volume of the low-concentration (0.1 mg/mL) dexmedetomidine.

Box 24.2 Adverse effects associated with α_2 adrenoreceptor agonists in dogs and cats (adverse effects are dose-dependent and exacerbated when administered with opioid analgesics)

- Sedation
- Vagal-induced bradyarrhythmias (first- and second-degree atrioventricular heart block)
- Biphasic blood pressure response (hypertension followed by hypotension)
- Hyperglycemia via suppression of insulin release
- Reduced packed cell volume
- Diuresis due to decreased antidiuretic hormone
- Mild reduction in respiratory rate (dogs greater than cats)
- Vomiting via stimulation of the chemoreceptor trigger zone in dogs and cats (up to 20% and 90% incidence, respectively)

Alpha-2 Adrenoceptor Agonists at-a-Glance

Dexmedetomidine/medetomidine

- Dose-dependent sedation and analgesia.
- Enhances the analgesic efficacy of opioids.
- May be beneficial in patients with neuropathic pain.
- Analgesia is observed at higher plasma concentrations than those producing sedation.
- Not recommended as a sole analgesic agent.

- Reversal of dexmedetomidine with atipamezole may not alleviate the negative effects on heart rate and blood pressure in cats.
- Caution with the administration of anticholinergics during the initial cardiovascular phase (bradycardia, peripheral vasoconstriction) of α_2 adrenoreceptor agonists because of significant hypertension.
- Caution in patients with significant systemic cardiovascular disease.
- Can be administered via a variety of routes (e.g., IV, IM, SC, sublingual, perineural).

N-METHYL-D-ASPARTATE (NMDA) RECEPTOR ANTAGONISTS

NMDA receptor antagonists are becoming increasingly popular for the management of pain in dogs and cats. In humans, it is incorporated into multimodal analgesic protocols when treating acute, chronic, and neuropathic pain. The NMDA receptor plays a critical role in the development of central sensitization or "wind-up" pain. The efficacy of NMDA antagonists is enhanced when administered preemptively in dogs undergoing surgery. In cats, NMDA receptor antagonists have been effective when used as an adjunct analgesic agent to treat neuropathic pain, hyperalgesia, and allodynia. Ketamine, the most common NMDA receptor antagonist used in veterinary medicine, exerts its action at several sites within the central nervous system. Its primary mode of action is via noncompetitive antagonism of NMDA receptors preventing the binding of glutamate. Other mechanisms involve opioid receptors (μ, κ, δ), nicotinic and muscarinergic receptors, monoaminergic receptors, and sodium, potassium, and calcium channels. Amantadine, an oral antiviral agent and NMDA-receptor antagonist, is used as an adjuvant for management of chronic pain in dogs and cats. However, few clinical studies evaluating its efficacy are available.

Ketamine can be administered via the IV, IM, SC, or neuraxial route; however, it is most commonly administered as a CRI due to its short analgesic duration of action. A ketamine bolus of 0.5–1 mg/kg immediately followed by a CRI of 30 or 50 mcg/kg/min results in a transient (20 minutes following discontinuation of CRI) increase in mechanical antinociception in dogs. At these doses, plasma ketamine concentrations are maintained between 100 and 200 ng/mL, which is required when administered as an analgesic agent. Adverse psychomimetic effects may occur at these doses, but the duration is short lived (< 20 minutes) following ketamine's discontinuation. Ketamine's ability in providing adequate visceral analgesia has been questioned. In dogs, a ketamine CRI of 40 mcg/kg/min following a 1 mg/kg IV bolus did not result in adequate postoperative analgesia in dogs undergoing ovariohysterectomy. However, a preemptive ketamine CRI (50 mcg/kg/min) combined with a lidocaine CRI (100 mcg/kg/min) enhanced the attenuation of central sensitization and improved perioperative analgesia in a canine ovariohysterectomy model.

Low-dose ketamine infusions have been suggested as part of multimodal analgesic CRI regimens. These low doses may enhance the degree of analgesia with reduced adverse effects (e.g., dysphoria). For example, dogs undergoing forelimb amputations administered a fentanyl and low-dose ketamine CRI intraoperatively (10 mcg/kg/min) and for 18 hours postoperatively (2 mcg/kg/min) had lower pain scores and were more active when compared to those receiving only fentanyl. When administered as a sole agent to conscious dogs, a low-dose ketamine CRI (10 mcg/kg/min following a 0.5 mg/kg IV bolus) did not produce adequate plasma concentrations to provide antinociception (<100 ng/mL). Similar results were found in cats administered a 5 or 23 mcg/kg/min CRI of ketamine. At these doses, caution when used as a sole analgesic agent.

Ketamine has also been used successfully as an adjunct agent in protocols when opioids are not readily available. In these circumstances, NSAIDS and local regional blocks are also recommended. Ketamine infusions are also effective in treating central sensitization or wind-up pain. For example, a ketamine CRI of 10 mcg/kg/min used in conjunction with several other analgesic and anti-inflammatory agents was effective in managing a feline patient which developed severe neuropathic pain due to trauma.

Ketamine

- Used for the treatment of neuropathic pain and central sensitization.
- More effective as a pre-emptive analgesic.
- Generally recommended as a CRI.
- Evidence is lacking regarding its effectiveness in managing visceral pain.
- Low-dose ketamine infusions are good alternative when used in multimodal regimens when opioids are not readily available.
- Adverse psychomotor effects may have confounding effects on some pain scales leading to erroneous administration of rescue analgesia.

Amantadine

- Limited adverse effects when administered orally at 3–5 mg/kg q.12–24 h.
- May be useful in dogs with osteoarthritic pain refractory to NSAID therapy.
- Improved owner-identified mobility and owner-perceived quality of life in cats with OA at 5 mg/kg q.24 h.
- High-dose amantadine (~14 mg/kg) and meloxicam have been used to treat chronic neuropathic pain in a dog.
- Suitable drug for at-home chronic pain management with limited abuse potential.
- Limited clinical studies evaluating its efficacy in dogs and cats and, therefore, should not be used as a sole analgesic.

Methadone

- Considered a weak NMDA-receptor antagonist.
- Has been used to treat neuropathic pain and opioid-induced hyperalgesia in humans.
- See previous section on opioids.

Magnesium

- Inhibits calcium ions entering cells by blocking NMDA receptors.
- Has been administered in humans for the treatment of central sensitization and neuropathic and postoperative pain.
- Limited evidence to support its analgesic efficacy in small animals.
- Dosages (5–15 mg/kg IV bolus administered over 15 minutes followed by a CRI of 15mg/kg/h) are extrapolated from human studies.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) AND OTHER ANTI-INFLAMMATORIES

Anti-inflammatory drugs act on different pathways of the arachidonic acid cascade (Figure 24.22). NSAIDs are the most widely used analgesics in veterinary medicine. Extensive research supports the safety and efficacy of contemporary NSAIDs for the management of acute and chronic pain in dogs and cats. They are excellent analgesics but have narrow safety margins. By inhibiting COX enzymes (COX-1 and COX-2), NSAIDs inhibit the production of prostaglandins, resulting in anti-inflammatory, analgesic, and antipyretic effects, as well as adverse-effects. Adverse effects are generally self-limiting and related to gastrointestinal signs. Provided that patient selection and monitoring are performed, most patients can be safely administered NSAIDs. Serious adverse effects usually result from inappropriate administration (e.g., higher than recommended doses, administration in close temporal association with corticosteroids or other NSAIDs, patients with unstable disease), although idiosyncratic events of acute liver toxicosis have been reported.

In acute pain management, NSAIDs should always be considered as part of a multimodal protocols ideally combined with opioids and local anesthetics. In healthy, normovolemic patients undergoing surgery, preemptive administration of NSAIDs is recommended for optimal efficacy. Provision of fluid therapy and monitoring of blood pressure are important. If significant bleeding, hypotension, or hypovolemia are risks, NSAIDs can be administered at the end of the procedure.

In chronic pain management, particularly OA, NSAIDs are the first line of analgesics used in combination with nonpharmacological analgesic strategies. As pain and dysfunction progresses, adjuvant analgesics

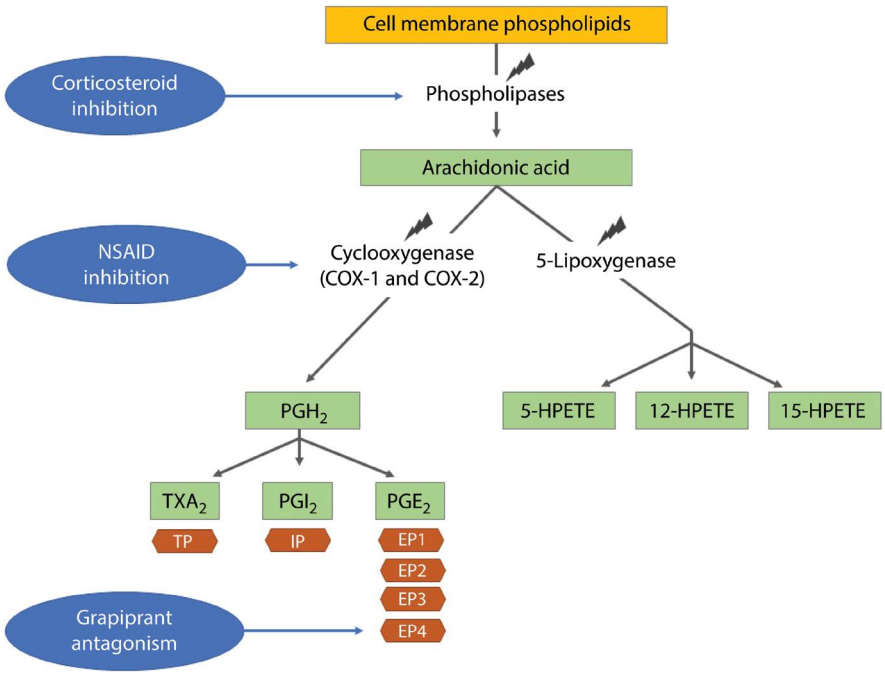


FIGURE 24.22 A simplified version of the arachidonic acid cascade with focus on cyclooxygenase (COX)-dependent prostaglandin production and points of various types of drug activity. Corticosteroids act by inhibiting the action of phospholipase enzymes early in the cascade. Nonsteroidal anti-inflammatory drugs (NSAIDs) act by inhibiting COX-1 and COX-2 enzymes with consequent inhibition of prostaglandin biosynthesis. Grapiprant is an antagonist of EP4 receptor. EP1–EP4, prostaglandin E2 receptor; HPETE, hydroperoxyeicosatetraenate; IP, prostacyclin receptor; PGE2, prostaglandin E2; PGH2, prostaglandin H2; PGI2, prostacyclin; TP, thromboxane receptor; TXA2, thromboxane. (*Reprinted from* Vet Clin North Amer Sm Anim Pract, *49, Monteiro and Steagall, Anti-inflammatory drugs, 993–1011, Copyright (2019). Reprinted with permission from Elsevier*.)

are added to the protocol. Client education and continuous monitoring are paramount.

Relative contraindications include history of gastrointestinal disease, NSAID intolerance, uncontrolled renal or hepatic disease, anemia, coagulopathy, hypovolemia or dehydration, hypotension, and administration should be concomitant or in close association with corticosteroids or other NSAIDs. The risks and benefits of NSAID therapy should be considered for all patients.

Intolerance can happen with one NSAID but not others. When switching between NSAIDs, a washout period of 3–5 days is anecdotally used in patients without clinical signs. Other analgesics should be provided during this period.

NSAIDs can be safely administered long term to cats with concomitant chronic pain and stable chronic kidney disease. In this case, the following should be respected/considered:

- Stable chronic disease (IRIS stages 1 and 2)
- Long-term maintenance of hydration
- Minimal effective dosage should be used
- General guidelines for the management of chronic kidney disease (CKD) should be followed
- Owners should be educated about possible risks and actions to take
- Continued monitoring is imperative
- Environmental optimization, weight control and other nonpharmacological analgesic therapies must be used in combination with NSAIDs

Grapiprant acts further down on the arachidonic acid cascade (**Figure 24.22**). This drug is licensed for the management of pain and inflammation associated with canine OA (2 mg/kg orally every 24 hours) in several countries. Acetaminophen has weak anti-inflammatory properties but produces analgesic and antipyretic effects (inhibition of prostaglandin E2 in the CNS). It is absolutely contraindicated in cats (risk of acetaminophen toxicosis). Its use in dogs is mostly anecdotal. Corticosteroids can have potent anti-inflammatory and immunosuppressive properties, yet they should not be viewed as a classic analgesic. There is little evidence to support their use as analgesics and they can produce serious adverse effects.

GABAPENTIN

Gabapentin is an anticonvulsant drug with analgesic properties. It produces analgesia by reducing neuronal excitability and blocking calcium channels. In dogs and cats, the drug has high oral bioavailability; elimination half-life is approximately 3–4 hours, suggesting the need for frequent oral dosing.

There is a conflicting body of evidence in people regarding the role of preoperative administration of gabapentin or pregabalin in reducing pain and opioid consumption in the postoperative period. In dogs and cats, studies generally favor the use of gabapentin perioperatively when combined with opioids and other analgesics. For example, in a study in cats undergoing ovariohysterectomy, gabapentin (50 mg per os (p.o.) administered 12 and 1 hour before surgery) with buprenorphine provided similar analgesia as meloxicam with buprenorphine. The perioperative use of gabapentin might be particularly relevant in situations of limited drug availability or in patients in which NSAIDs are contraindicated.

Gabapentin is widely used the management of neuropathic pain in dogs and cats, including persistent postsurgical pain (e.g., amputation, chronic pain syndrome after feline onychectomy), feline orofacial pain syndrome, diabetes-induced neuropathy, IVDD, OA-related pain, cancer-related pain, Chiari-like malformation, and syringomyelia.

Gabapentin is considered a safe drug with no known contraindications. It is eliminated by the kidneys and for this reason might be used with caution in patients with renal disease. Sedation and ataxia can occur. Start the treatment at lower doses and increase gradually until analgesic response is observed. An analgesic trial of 4–6 weeks may be required. Note that nonveterinary pharmacies might carry formulations of gabapentin containing xylitol, which can be toxic at large doses in dogs.

TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants, such as amitriptyline, are the first line of analgesics for neuropathic pain in people along with gabapentin. In veterinary medicine, it has been used in the management of oncologic and neuropathic pain in dogs, pain associated with interstitial cystitis in cats, and chronic osteoarthritis. Amitriptyline inhibits the reuptake of norepinephrine and serotonin and possesses α_1 antagonistic, antihistaminic, and anticholinergic effects. Onset of peak effects generally occurs after 2–4 weeks of oral administration and, therefore, is not recommended in the management of acute perioperative pain. Generally dosing for pain is 1–4 mg/kg p.o. administered once to twice daily. Dosing up to 12.5 mg/kg p.o. once daily have been used in cats to treat interstitial cystitis with minimal adverse effects. Adverse effects include sedation, weight gain, and reduced grooming. Limited studies are available in dogs and cats. Avoid administration in combination with other serotoninergic drugs, including tramadol, due to the risk of serotonin toxicity.

CANNABINOIDS

Cannabinoids bind to cannabinoid receptors to modulate the release of neurotransmitters and neuronal excitability, activate inhibitory pathways, and reduce neuroinflammatory signaling. They exist in three forms: Endocannabinoids, produced by the body; phytocannabinoids, produced from plants; and synthetic cannabinoids, produced in laboratories. Delta-9-tetrahydrocannabinol

(THC) is generally associated to the psychoactive properties whereas cannabinol (CBD) to the analgesic properties. Three recent clinical trials involving dogs with OA show analgesic efficacy of CBD oil (1–2 mg/kg b.i.d.) when used alone or in combination with other analgesics (NSAIDs, gabapentin, amitriptyline). In these studies, CDB oil treatments were administered via oral or transmucosal route for 4–12 weeks, and no clinically relevant adverse effects were reported.

The pharmacokinetics of a single dose of CBD oil (2 mg/kg p.o.) showed marked differences in absorption and elimination between dogs and cats. Administration of this same dose for 12 weeks in healthy dogs and cats did not show any detrimental effects based on complete blood count and biochemistry values. However, administration was stressful in cats, resulting in excessive licking and headshaking. Based on the data available to date, administration of these dosages in dogs seems to be generally safe and effective. The use of cannabinoids in cats is not yet recommended due to limited pharmacokinetic data, stressful administration, and unknown efficacy and/or dosage regimen.



FIGURE 24.23 A cat comfortably recovers from anesthesia and surgery under warm blankets in a quiet location. "Tender loving care" concepts are applied in addition to analgesics to keep the cat comfortable with no pain, stress, fear, or anxiety. (*Reprinted from* J Feline Med Surg, *21, Steagall and Monteiro, Acute pain in cats: Recent advances in clinical assessment, 25–34, Copyright (2019), with permission from SAGE Publishing.*)

MONOCLONAL ANTIBODIES

Nerve growth factor (NFG) is a cytokine that regulates key mechanisms involved in inflammatory and neuropathic pain contributing to peripheral and central sensitization. Canine- and feline-specific anti-NGF monoclonal antibodies were investigated in dogs and cats with OA, respectively. Following a single subcutaneous injection, anti-NGF antibodies were shown to be safe and effective, providing 4–6 weeks of analgesia (increased levels of activity and improved owner-reported clinical signs) with no observable adverse-effects in dogs and cats. The clear advantages related to administration, duration of effect, and safety profile make them promising analgesics, and these drugs are becoming available in some countries including the United States.

NONPHARMACOLOGICAL PAIN MANAGEMENT STRATEGIES

Nonpharmacological therapies are highly important in the management of pain. They include the general concept of "care" or "TLC" (tender loving care) (**Figure 24.23**) as well as ice therapy, acupuncture, weight control, nutrition, nutraceuticals, physical therapy, massage, transcutaneous electrical nerve stimulation, photobiomodulation therapy, targeted pulse electromagnetic field therapy, etc. However, some of these therapies might not be accepted by all patients, and others have little to no evidence to support their use. The decision to incorporate nondrug therapies is affected by patient- and owner-associated factors as well as by their potential for analgesic effects, scientific evidence available, cost and time commitment, and acceptability to the patient, all of which must be thoroughly discussed with owners, particularly in chronic pain management. As previously discussed, emotions can modulate pain. Thus, any nondrug therapy that is well accepted by the patient and promotes positive mental states should be encouraged.

In acute pain management, nondrug therapies would include ice therapy, control of nausea, providing thermal comfort, noise reduction, stress and fear reduction, frequent and supported opportunities for urination and defecation in mobility impaired patients, promoting positive interactions with caretakers, massage, petting, brushing, providing clean and comfortable housing, and using feline-friendly handling techniques in cats (**Figure 24.8**).

In chronic pain management, particularly OA, strategies for the control of weight and increase in physical activity are paramount. In dogs, a careful dietary program in combination with slowly progressive increase in physical activity using leash walks is performed. Environmental adaptations such as the provision of carpets or ramps are considered. In cats, weight control is also performed in combination with environmental optimization, including the provision of condos, shelves, scratch posts, disposition of key environmental resources around the house, steps to facilitate jumping up and down, etc. (**Figure 24.24a, b**). For dogs and cats, the use of feed puzzles is highly encouraged to prolong feeding times, increase satiety, and promote physical and mental stimulation around feeding. Play sessions could also be prescribed to increase physical activity. Finally, euthanasia must remain as the ultimate treatment option to end pain and suffering in cases of poor prognosis, scheduling or financial constraints, or lack of response to therapy.



FIGURE 24.24 Homemade and commercially available options for environmental optimization. On image **(a)**, the cat is fetching food from a homemade puzzle feeder (shoe box and toilet paper rolls). Image **(b)** shows commercial physical activity optimization. (*Reprinted from* Vet Clin North Amer Sm Anim Pract, *50, Monteiro, Feline chronic pain and osteoarthritis, 769–788, Copyright (2020), with permission from Elsevier.*)

CASE EXAMPLE

Case 24.1: Pain Management for a Dog with a Pathologic Long Bone Fracture

Signalment

11-year-old intact male Labrador Retriever mixed-breed dog (**Figures 24.25** and **24.26**)

Presenting Complaint

Presented for an acute onset of non-weight-bearing lameness and severe redness and swelling of the left hindlimb.

Pertinent Medical History

No history of concurrent medical conditions.



FIGURE 24.25 A 4-year-old male dog in the immediate postoperative period.

Diagnosis

Pelvic limb radiographs show left femur fracture with marked soft tissue swelling and osteolytic lesion over the left femur.

Diagnosis and Surgical Procedure

Pathologic fracture due to osteosarcoma of the left hindlimb. Emergent surgery for a left hindlimb amputation.

Pain Assessment

Short Form of the Glasgow Composite Pain Scale Score: 11/15 (section B and C omitted). Severe, acute, somatic, with potential for neuropathic and wind-up development.



FIGURE 24.26 The same dog 48 hours postoperative.

Analgesic Regimen Suggestions

- Perioperative plan
  - CRI suggestions (choose one or a combination of)
    - Fentanyl (loading dose (LD) 3–5 mcg/kg IV followed by 5–10 mcg/kg/h)
    - Lidocaine (LD 1–2 mg/kg IV followed by 2–4 mg/kg/h)
    - Ketamine (LD 1–2 mg/kg IV followed by 0.3–1 mg/kg/h)
    - Dexmedetomidine (LD 0.5–1 mcg/kg IV administered slowly over 10 minutes followed by 0.5–1 mcg/kg/h)

  - Local regional anesthesia (one or the combination of)
    - Lumbosacral epidural with 0.5% bupivacaine at 0.5–1 mg/kg combined with morphine at 0.1 mg/kg diluted (if needed) to a total volume of 0.2 mL/kg
    - Nocita 0.4 mL/kg infiltrative administration at the site of incision during surgical closure
- Postoperative suggestions
  - Immediate 24–72 hours
    - Lumbosacral epidural may provide up to 24 hours of analgesia
    - Nocita May provide up to 72 hours of analgesia
    - Continue CRIs if needed but at lower dosages (choose one or a combination of)
- Fentanyl 3–5 mcg/kg/h
- Lidocaine 1.5–2 mg/kg/h
- Ketamine 0.3–0.5 mg/kg/h
- Dexmedetomidine 0.5–1 mcg/kg/h
  - Pending health status consider injectable NSAIDs (i.e., carprofen or meloxicam)
  - Following 48–72 hours
  - Wean off CRIs over a 24-hour period
  - Transition to oral analgesics for 7–10 days pending patient's comfort level (a combination of)
- NSAIDs (carprofen or meloxicam as directed)
- Tramadol 2–6 mg/kg twice daily
- Gabapentin 5–10 mg/kg once to twice daily
- Amantadine 3–5 mg/kg once to twice daily

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CHAPTER 25

Nutrition of the Critically Ill Dog and Cat

Justin Shmalberg

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INTRODUCTION

Nutrition is increasingly recognized as an essential component of veterinary evaluation and treatment. The provision of adequate calories and nutrients in critically ill patients has received significant attention in recent years. Nevertheless, controversy and varying quality of evidence persist. Noninterventional retrospective studies demonstrate that critically ill patients are less likely to be fed to meet estimated caloric requirements and are also more likely to have extended hospital stays. However, the retrospective nature of these studies limits the ability to draw a clear link between caloric deficit and patient outcome. Such studies do document a failure by clinicians to provide specific nutritional orders, suggesting that nutrition is often overlooked regardless of clinician opinion on the merits of nutritional support. One controlled study of early enteral nutrition in puppies hospitalized for parvovirus infection did document an earlier clinical improvement in those patients fed through a nasoesophageal tube. Therefore, specific critical patients are likely to benefit from voluntary and assisted enteral nutrition.

CURRENT EVIDENCE

Critical care veterinary nutrition has been poorly studied in hypothesis-driven research. Consequently, nutritional evidence from human nutritional research often guides interventions in clinical practice. Acute illness in both humans and other animals is characterized by a reduction in appetite and increased catabolism of endogenous reserves of protein. These effects are mediated by a complex milieu of cytokines, including tumor necrosis factor-alpha, interleukin (IL)-6, IL-1B, hormones such as cortisol, epinephrine, glucagon-like peptide 1, changes in resting metabolic rate, and the immune response. The decline in lean body mass secondary to protein catabolism has been associated with prolonged hospital stay and rehabilitation in human patients. Provision of protein and/or essential amino acids has decreased the magnitude of muscle loss in some studies. Such data have not been collected for veterinary patients but are thought to be similar. Fasting may have protective effects, however, on some aspects of recovery. Starvation is associated with increases in protein recycling through the ubiquitin–proteasome pathway, which processes damaged or potentially toxic proteins. Other studies in human subjects determined that delivery of the full calculated nutritional requirement was associated with increased morbidity compared with those patients receiving more conservative nutritional interventions. Therefore, the timing and the type of nutritional intervention in critical patients is still the subject of much debate.

Human nutritional studies in acute or hospitalized patients are often characterized by small sample sizes and differing patient populations, making meta-analyses challenging. The paucity of data in the veterinary literature makes definitive conclusions even more elusive. Experience with hospitalized human subjects suggests that nutritional best practices may vary with different diseases; recommendations for patients with acute kidney injury (AKI) or chronic kidney disease (CKD) are quite different, for example. As such, veterinary patients likely also experience different condition- and individual-specific requirements for nutrients and for calories. The level of sophistication of evidence-based interventions in veterinary medicine is therefore poor. Interestingly, dogs display increased adaptability to starvation compared with humans and are evolutionarily

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programed for significant postprandial fasting. Cats, conversely, have constitutive upregulation of gluconeogenesis and a lower gastric volume, suggesting adaptability to frequent feedings. Future studies are needed to better refine clinical knowledge, and the guidelines contained herein should be critically evaluated in such a context.

CLINICAL EVALUATION

Nutritional intervention relies on a complete and thorough clinical examination. Specific attention must be paid to body condition score (BCS), muscle condition, visible markers of nutritional status such as dermis and coat, and appropriate identification of comorbidities. A detailed diet history is equally critical. The initial diet history may be complicated by triage and stabilization of the patient as well as owners' focus on other critical aspects of their animal's care. However, historical diet information should be obtained at the earliest opportunity. This permits detection of chronic malnutrition due to hyporexia, chronic gastrointestinal (GI) abnormalities, or previous dietary deficiencies. The provision of nutrition should ideally be tailored to the individual based on the clinician's subsequent synthesis of owner input and examination findings.

History

A diet history is a commonly overlooked aspect of nutritional assessment. Historical information can provide information about a patient's caloric requirements, feeding habits, recent caloric intake, and food preferences. The latter is especially important in cats, who may be neophobic, especially during acute hospitalization. An awareness of recent calorie consumption can determine the timing of nutritional intervention. For example, a hospitalized cat with several weeks of marked hyporexia should receive nutritional support sooner to prevent hepatic lipidosis, compared with a cat with acute anorexia. Some individual dogs may receive food in the home environment at an amount close to the resting fed energy requirement used for hospitalized patients. Dogs of some breeds, such as Labrador Retrievers, Newfoundlands, and Corgis, commonly consume less than calculated with predictive equations. Such factors are critical when individualizing care.

A thorough diet history may not be possible at a patient's initial presentation. However, technicians or the supervising clinician should try to obtain this information following triage. The diet history should include:

- The type of food commonly fed, including brand, type, and flavor
- The type and quantity of treats and supplemental foods
- Specifics regarding dietary supplements
- Feeding habits (free-choice, meal fed)
- Food allergies, aversions, or preferences

Clients may need to investigate packaging at home before providing pertinent details given the diversity of foods on the market and the distracted focus of many owners during their pet's illness. Such detailed information is necessary to determine the caloric content and nutrient profile of various foods. Dietary supplements are increasingly encountered, and the potential for toxicity and interactions between herbs and drugs has been reported. Knowledge of feeding habits can provide useful information regarding the likelihood of a patient eating on a particular schedule. Some dogs, with small breeds appearing overrepresented, are accustomed to being fed free-choice and may not be accustomed to the scheduled feeding initiated during hospitalization. Food allergies and intolerance are frequently reported by owners; regardless of the merits of these claims, care should be taken to avoid significant dietary changes in order to prevent acute GI signs. A diet history form can be designed to incorporate these questions and be tailored to a particular practice; such forms can also be employed during therapeutic weight loss.

Body Weight and Condition

Body weight is frequently measured in clinical patients, primarily for assessing fluid status. Acute changes are most likely fluid related, but repeated measures in chronically treated patients can suggest inadequate nutritional intake. Ideal body weight is also the basis for predictive caloric requirement equations. Patients with effusions, edema, and extensive neoplasia are more reliably assessed by BCS and muscle condition score (MCS) than by body weight.

Body condition scoring provides an assessment of energy reserves, primarily adipose tissue. A 9-point system of scoring has been objectively validated, with 4–5/9 representing ideal body weight (**Figure 25.1**). This is characterized by a clearly visible waist, an "abdominal tuck" when viewed from the side, and minimal fat covering over the ribs. Many sighthounds display a normal body condition of 3/9. Some breed standards and purebred dog owners may regard 6/9 as ideal for the breed, but unlike sighthounds, there is no physiologic advantage to this preference.

Ideal body weight is calculated for overweight dogs (BCS 6–9/9) using simple conversions. Assessments of patient adiposity demonstrate that each BCS over 5 represents 10%–15% over a patient's ideal body weight in dogs. For example, a 40 kg dog with a BCS of 8/9 is 30%–45% over ideal weight. Using the upper end of this range, the dog's measured body weight is 145% of ideal body weight, and, therefore, ideal body weight is equal to (40 kg)/(145%) or about 28 kg.

The ideal weight of most cats can be estimated by visual assessment. Most cats should be between 3 and 5 kg, so mathematical formulas are unnecessary. Overweight cats are predisposed to a number of conditions encountered in critical care medicine, including hepatic lipidosis, lower urinary tract obstruction, and diabetes mellitus.

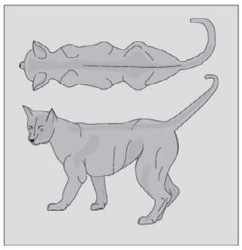
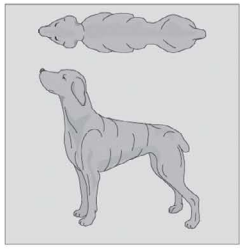
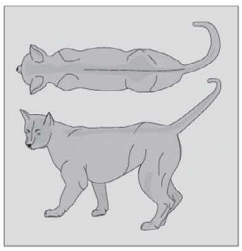
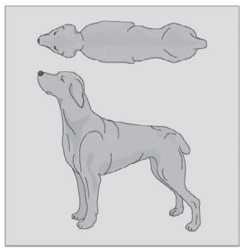
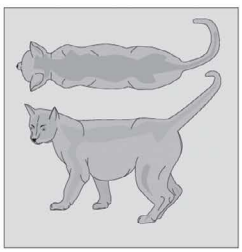
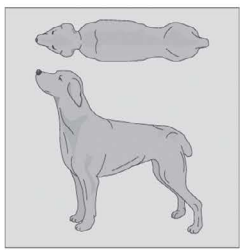
5 Point	Cat	Description	Dog	9 Point
1/5		Dogs: Ribs, lumbar vertebrae, pelvic bones, and all bony prominences evident from a distance. No discernible body fat. Obvious loss of muscle mass. Cats: Ribs visible on short-haired cats; no palpable fat; severe abdominal tuck; lumbar vertebrae and wings of ilia obvious and easily palpable.		1/9
1.5/5		Dogs: Ribs, lumbar vertebrae and pelvic bones easily visible. No palpable fat. Some evidence of other bony prominence. Minimal loss of muscle mass. Cats: Shared characteristics of BCS 1 and 3.		2/9
2/5		Dogs: Ribs easily palpated and may be visible with no palpable fat. Tops of lumbar vertebrae visible. Pelvic bones becoming prominent. Obvious waist. Cats: Ribs easily palpable with minimal fat covering; lumbar vertebrae obvious; obvious waist behind ribs; minimal abdominal fat.		3/9
2.5/5		Dogs: Ribs easily palpable, with minimal fat covering. Waist easily noted, viewed from above. Abdominal tuck evident. Cats: Shared characteristics of BCS 3 and 5.		4/9
3/5		Dogs: Ribs palpable without excess fat covering. Waist observed behind ribs when viewed from above. Abdomen tucked up when viewed. Cats: Well proportioned; waist observed behind ribs; ribs palpable with slight fat covering; abdominal fat pad minimal.		5/9

FIGURE 25.1 Objective 9-point body condition scoring (BCS) system. (*Continued*)

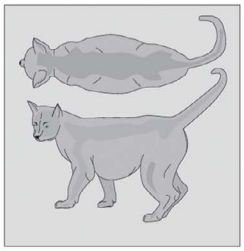
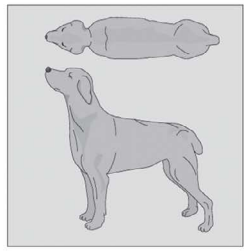
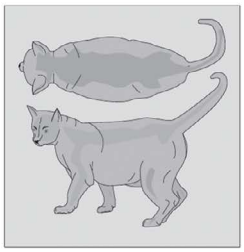
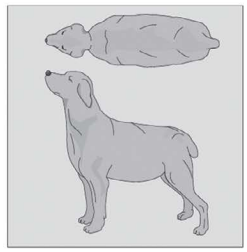
5 Point		Description		9 Point
3.5/5		Dogs: Ribs palpable with slight excess fat covering. Waist is discernible viewed from above but is not prominent. Abdominal tuck apparent. Cats: Shared characteristics of BCS 5 and 7.		6/9
4/5		Dogs: Ribs palpable with difficulty; heavy fat cover. Noticeable fat deposits over lumbar area and base of tail. Waist absent or barely visible. Abdominal tuck may be present. Cats: Ribs not easily palpable with moderate fat covering; waist poorly discernible; obvious rounding of abdomen; moderate abdominal fat pad.		7/9
4.5/5		Dogs: Ribs not palpable under very heavy fat cover, or palpable only with significant pressure. Heavy fat deposits over lumbar area and base of tail. Waist absent. No abdominal tuck. Obvious abdominal distension may be present. Cats: Shared characteristics of BCS 7 and 9.		8/9
5/5		Dogs: Massive fat deposits over thorax, spine, and base of tail. Waist and abdominal tuck absent. Fat deposits on neck and limbs. Obvious abdominal distention. Cats: Ribs not palpable under heavy fat cover; heavy fat deposits over lumber area, face, and limbs; distension of abdomen with no waist; extensive abdominal fat pad.		9/9

FIGURE 25.1 Objective 9-point body condition scoring (BCS) system. (*Continued*)

Muscle Condition

Protein catabolism and loss of lean body mass is poorly assessed with body condition scoring. A separate score has been developed to assess muscle, which is the primary source of amino acids in catabolic animals. Multiple methods of scoring are available, and some may be referred to as a cachexia score. The author uses a 3-point scale where 3/3 indicates normal muscle mass, 2/3 mild muscle wasting, 1/3 moderate, and 0/3 marked (Figure 25.2). The high rates of weight loss (>2% per week) seen in prolonged anorexia are characterized by loss of lean body mass as well as adipose stores. Therefore, a decline in both muscle condition and body condition is a sign of malnutrition.

Laboratory Markers

Laboratory values from significantly malnourished animals are often within normal limits. Biochemical profiles and complete blood counts are unreliable indicators of nutritional status. Severe hypoalbuminemia, for example, is rarely encountered with prolonged starvation as production is prioritized by the animal. Patients presenting with this condition are more likely to have decreased production or increased loss from another cause. Specialized diagnostic testing, such as amino acid profiles and vitamin levels, is available at some academic research laboratories. The extended turnaround times and limited published information on many of these tests in critical care settings limit their

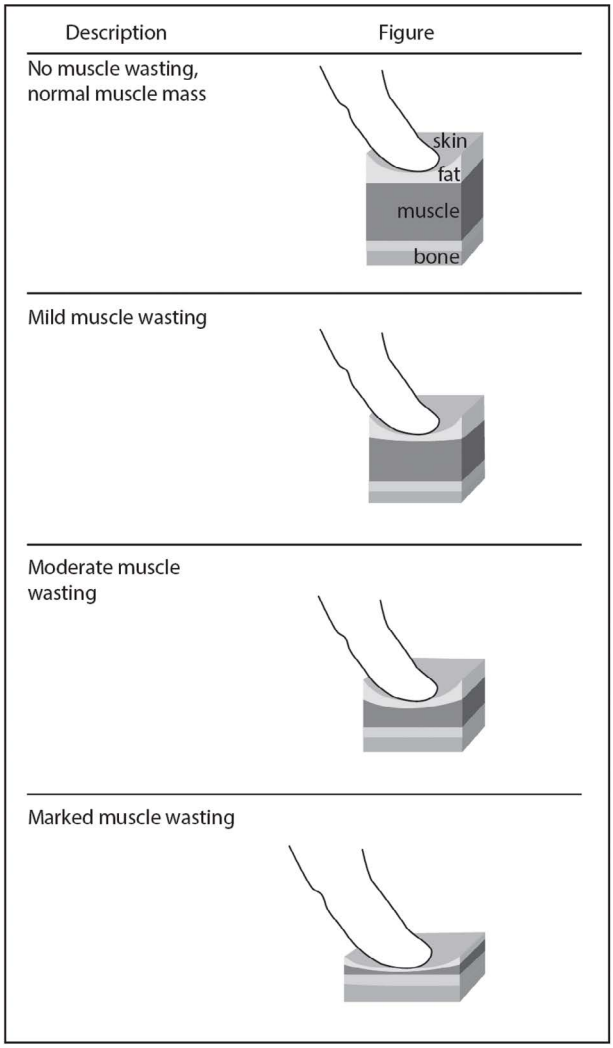


FIGURE 25.2 Objective 3-point muscle scoring system.

use to those cases where clinical suspicion of nutrient deficiency is high, such as in dilated cardiomyopathy in dogs fed lower protein diets or in suspected thiamine deficiency in cats.

TIMING OF NUTRITIONAL SUPPORT

The decision-making rubric for when to intervene with nutritional support is the most contested aspect of critical care nutrition. Current clinical guidelines in humans promote early enteral feeding and in the event of severe or lengthy caloric deficits parenteral nutrition (Figure 25.3). The trials that suggested a survival benefit for early enteral nutrition were small and contained interventions in the control group, such as parenteral nutrition, which could have worsened survival. A comparable controlled study in veterinary medicine enrolled puppies with parvovirus infection. All dogs in that study survived, so the statistically significant outcome measure was a 1-day reduction in clinical signs in dogs fed a liquid diet via a nasoesophageal tube. Enteral nutrition in dogs with septic peritonitis appeared to confer a survival benefit without any increased complication rate. Dogs are documented to survive longer with complete starvation compared with people, suggesting an adaptive ability to tolerate extended fasting. Dogs also display higher rates of fatty oxidation at rest and may therefore be uniquely suited to accommodating for increased lipolysis and beta-oxidation. Nutritional support is often provided earlier in the course of disease in cats due to concerns about hepatic lipidosis. However, only 1 of 12 cats experimentally receiving 25% of their energy requirements developed hyperbilirubinemia after 1 month, and provision of a high-protein diet at this reduced intake decreased hepatic lipid concentration. Early interventional nutrition at low caloric intakes may be protective against complications during illness,

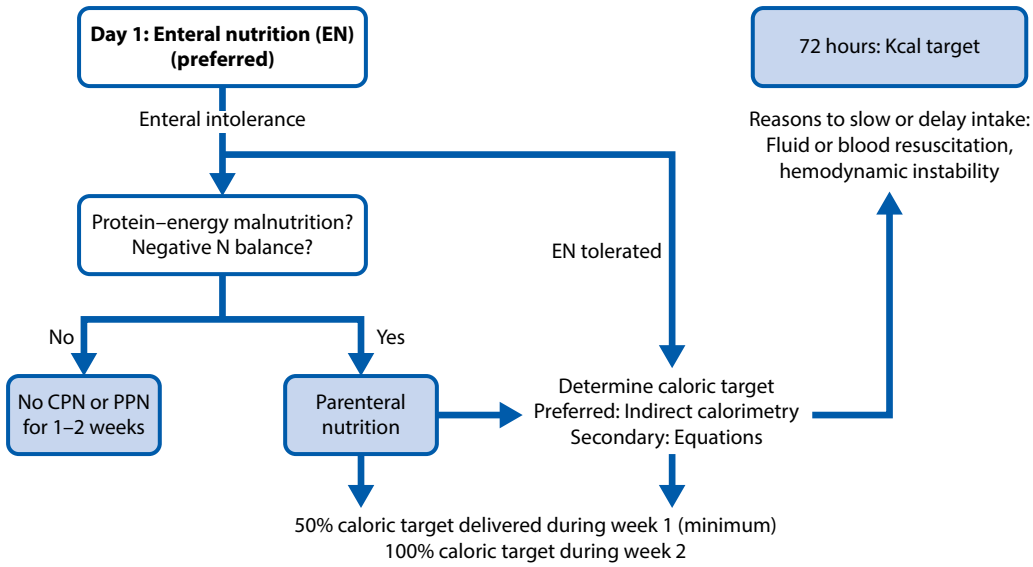


FIGURE 25.3 Human nutritional intervention rubric. CPN, central parenteral nutrition; N, nitrogen; PPN, peripheral parenteral nutrition. (*Adapted from American Society for Parenteral and Enteral Nutrition Guidelines.*)

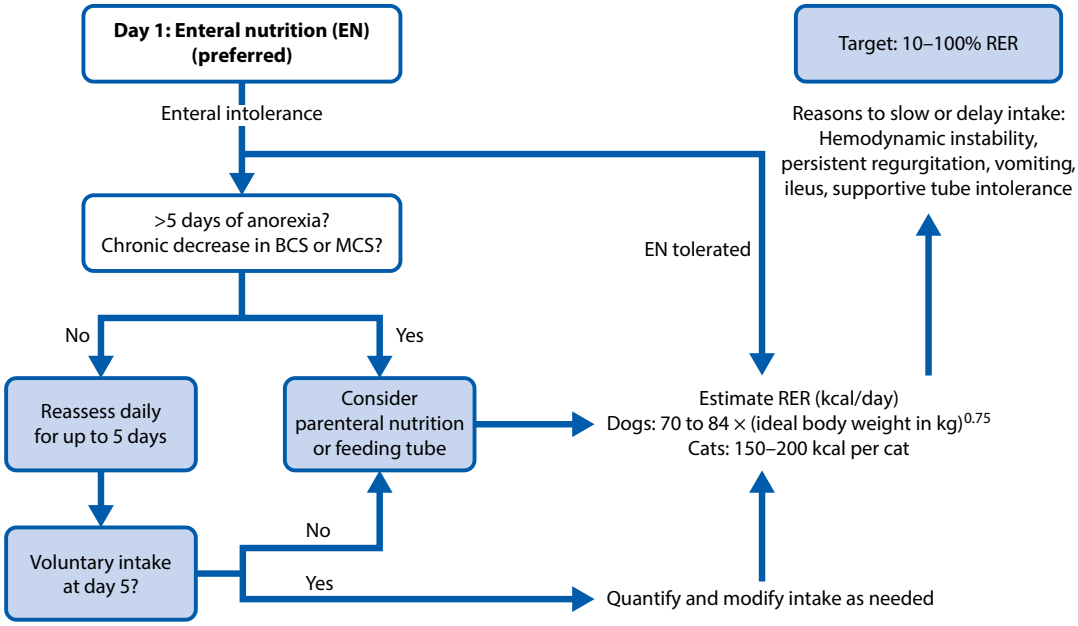


FIGURE 25.4 Proposed veterinary nutrition decision tree for critically ill patients. BCS, body condition score; MCS, muscle condition score; RER, resting energy requirements.

but further work is required and species-specific studies may not be translational to other animals. A simplified algorithm for veterinary patients is suggested in the absence of definitive information (Figure 25.4).

NUTRITIONAL AND CALORIC REQUIREMENTS

Dietary nutrient percentages or concentrations define a food's composition, but knowledge of the amount of food fed is critical to determining the dose of nutrients to be administered. Therefore, calculation of caloric needs and an accurate assessment of intake are critical in nutritional support. The hospitalized animal is generally less active than when at home, with the exception of some cats who may be less active during daily routines. The resting energy expenditure (REE) is commonly used as an assessment of fasting, resting land mammals in thermoneutral environments, which characterizes most hospitalized patients. The so-called Kleiber equation (70 × [ideal body weight in kg]$^{0.75}$) is used to calculate this figure. The logarithmic component explains why small animals consume more calories per unit of mass than large animals. For dogs between 5 and 25 kg, a simplified linear equation ([30 × ideal body weight in kg] + 70) kcal per day is employed. Ideal body weight is calculated from current body weight in obese patients to prevent overfeeding, as adipose tissue is less metabolically active than lean body mass.

Patients receiving nutritional support are not fasting, and therefore resting fed metabolic rate is more appropriate than REE. The digestion and conversion of nutritional substrates requires energy, generally about 10%–20% more than in fasting animals. The dramatic differences in energy expenditure between animals largely negate the benefits of using this higher amount, which requires a more complex formula or a second multiplication step. Clinicians historically also applied illness factors for specific conditions thought to be associated with increased metabolic rate (e.g., burns, sepsis, neoplasia). However, studies suggest that these factors are unnecessary and overestimate true caloric needs.

Cats, unlike dogs, present with relatively homogeneous ideal body weights of between 3 and 5 kg. Most resting cats, which includes both those hospitalized and indoor pets, should consume 200–250 calories per day. Equations are unnecessary in cats, and the author typically uses an estimate of 150 kcal per day for a small cat and 200 kcal per day for a larger cat. Most owners dramatically overfeed domestic cats, which could be detrimental if continued during treatment.

The percentage of energy requirements met with nutritional support is likely to affect morbidity and possibly mortality. Human energy requirements can be guided by indirect calorimetry, whereby a medical device measures oxygen consumption to determine the actual instantaneous metabolic rate of that individual. Such measurements are technically difficult and expensive. Human studies relying on predictive equations, similar to those used in veterinary medicine, produced hyperalimentation in some patients, which may increase overall morbidity. Conversely, in studies examining permissive underfeeding where the intentional provision of caloric intake is less than the calculated or measured requirements, the results generally show favorable or better outcomes compared with those receiving full caloric intake.

Parenteral nutrition in humans, when compared with fasting for up to a week, has in some studies produced poorer outcomes. The complications of IV nutrition include hyperglycemia, secondary infections, activation of the reticuloendothelial system, hyperlipidemia, and

thrombophlebitis. Hyperglycemia is the most commonly reported complication in the dog, but this is likely related to provision of high concentrations of dextrose. Dogs and cats appear to tolerate low-dextrose, high-amino acid, and high-fat diets better than human patients. It is therefore unclear if comparisons of enteral and parenteral nutrition in humans accurately reflect the clinical picture in small animals. Further research in veterinary medicine is necessary to compare fasting, permissive underfeeding, and feeding to meet calculated requirements.

DIET EVALUATION AND COMPARISON

Commercial pet foods are difficult to evaluate and compare using product packaging. Most veterinarians are interested in nutrient comparisons and generally turn to the guaranteed analysis on the product label to identify critical nutritional information. The label itself, which is generally modeled after Association of American Feed Control Officials suggested guidelines in the United States, may be misleading. First, the amounts listed are the minimum or maximum "guaranteed" to be present, and the percentages are "as fed," which includes the dietary moisture. Canned diets, containing approximately 80% water, have lower listed nutrient percentages than dry foods containing 10% moisture or less. Second, conversion to dry matter percentages overcomes the moisture variable, but there are other nutrients that add weight to the food but not calories, including fiber and ash. Nutritionists and veterinarians, therefore, should only compare foods on a caloric basis, commonly expressed as the grams of a particular nutrient per 1,000 calories (kcal) or 1 Mcal.

The caloric basis for commercial pet foods can be calculated using the guaranteed analysis and caloric density located on the bag. Specific simplified formulas are available (Figure 25.5). Some diets with low fat

STEP BY STEP: ESTIMATING NUTRIENT CONCENTRATION ON A CALORIC BASIS

Step 1	• Add 1.5% to protein percentage from pet food label • Add 1% to fat percentage from pet food label
Step 2	Divide kcal/kg by 10,000
Step 3	Divide estimated protein % and fat % by number obtained in Step 2

COMPARISON OF PET FOODS BY CALORIC BASIS

Canine Diets	**NRC RA*** (g/1000 kcal)	**Low** (g/1000 kcal)	**Moderate** (g/1000 kcal)	**High** (g/1000 kcal)
Protein	25	< 60	60–90	> 90
Fat	13.8	< 30	30–50	> 50
Carbohydrate	n/a	< 50	50–90	> 90
Feline Diets	**NRC RA*** (g/1000 kcal)	**Low** (g/1000 kcal)	**Moderate** (g/1000 kcal)	**High** (g/1000 kcal)
Protein	50	< 80	80–120	> 120
Fat	22.5	< 40	40–60	> 60
Carbohydrate	n/a	< 35	35–70	> 70

*National Research Council recommended allowance[2]

CONVERSION OF GUARANTEED ANALYSES + COMPARISON OF TWO COMMERCIAL DOG FOODS

Ingredient	**PET FOOD 1 (DRY)**	**PET FOOD 2 (WET)**
GUARANTEED ANALYSIS		
Crude protein (min)	25%	8%
Crude fat (min)	15%	5%
CALORIE CONTENT		
kcal/kg	3606	1198
CONVERSION		
Protein	**1.** 25% + 1.5% = 26.5% **2.** 3606 kcal/kg /10,000 = 0.3606 **3.** 26.5 / 0.3606 = **74 g/1000 kcal**	**1.** 8% + 1.5% = 9.5% **2.** 1198 kcal/kg/ 10,000 = 0.1198 **3.** 9.5 / 0.1198 = **79 g/1000 kcal**
Fat	**1.** 15% + 1% = 16% **2.** 3606 kcal/kg / 10,000 = 0.3606 **3.** 16 / 0.3606 = **44 g/1000 kcal**	**1.** 5% + 1% = 6% **2.** 1198 kcal/kg / 10,000 = 0.1198 **3.** 6 / 0.1198 = **50 g/1000 kcal**
FINAL RESULT	**Moderate protein / moderate fat**	**Moderate protein / high fat**

References

1. Hill RC, Choate CJ, Scott KC *et al.* (2009) Comparison of the guaranteed analysis with the measured nutrient compostion of commercial pet foods. *JAVMA* **234(3):**347-351.

2. National Research Council Ad Hoc Committee on Dog and Cat Nutrition (2006) *Nutrient Requirements of Dogs and Cats.* National Academies Press, Washington DC

FIGURE 25.5 Caloric basis calculations and comparisons. (*Reprinted from Shmalberg J (2013). Beyond the guaranteed analysis: Comparing pet foods.* Today's Veterinary Practice *3(1):43, with permission.*)

TABLE 25.1 A selection of commercial liquid diets administered to dogs in the United States

Nutrient density	Abbott Ensure Plus (use in dogs only)	Abbott Jevity 1.5 (use in dogs only)	Nestle Vivonex Plus (use in dogs only)	Royal Canin recovery liquid (canine, feline)	Royal Canin GI low-fat liquid (canine)	Royal Canin renal support liquid (canine)	Royal Canin renal support liquid (feline)
Protein (g/Mcal)	37	43	45	91	101	37	75
Fat (g/Mcal)	31	33	7	57	22	60	59
Carbohydrate (g/Mcal)	146	144	190	57	131	104	69
kcal/mL	1.5	1.5	1	0.9	0.9	1.3	0.9

Consult product guides for current specifications.

percentages on the label are not, in fact, fat restricted and, therefore, inappropriate for the long-term management of chronic active pancreatitis. Many weight loss diets appear restricted in nutrients on the label due to the inclusion of large amounts of fiber, but when fed at an appropriate number of calories, are often higher in nutrients. The caloric basis in many product guides is now readily available to veterinarians. Current nutrient profiles for diets encountered in many critical care centers are provided (see Table 25.1).

NUTRIENT CONSIDERATIONS

Water

Water is an important essential nutrient, the requirement for which is directly related to caloric requirements. Dogs generally require 1 mL of water per kcal consumed, and cats only about 0.6 mL of water per kcal consumed. Careful attention should be paid to voluntary water intake, and hydration should be frequently assessed to determine if intervention is needed.

Protein

Many acute illnesses increase the rate of skeletal muscle proteolysis and contribute to a decrease in lean body mass. Dietary protein can ameliorate some of this protein loss and is generally well-tolerated, with the common exceptions of severe renal disease or hepatic encephalopathy. In addition, if a patient's food intake is reduced, then a higher protein concentration in the diet is required to meet daily minimums. A hyporexic patient with AKI often should not consume a protein-restricted renal diet, for example, because it may be insufficient in the amount consumed to replace amino acid losses.

Specific amino acids have been discussed as an adjunct to nutritional therapy in the critically ill patient. Glutamine, a nonessential amino acid, is a nitrogen donor produced by skeletal muscle to provide substrate for amino acid production in critical tissues such as the GI mucosa and liver. Decreased glutamine levels have been documented in hospitalized human patients, but data on supplemental doses of glutamine have been mixed. Clinical studies in dogs are lacking, but a research study of fasted dogs suggested some positive effects on GI glutathione status. Most foods contain glutamine, especially animal protein sources, so the provision of dietary protein is likely more important than glutamine supplementation. Arginine, an essential amino acid in the dog and cat, is a precursor to nitric oxide and an intermediate in the urea cycle. Clinical utility in immunomodulation has been suggested, and one therapeutic diet administered to lymphoma patients includes elevated levels. However, patient selection for supplementation in human subjects is unclear, and no information is available for dogs and cats. Nevertheless, it is prudent to meet minimal requirements, as with all amino acids. The recommended allowance for protein is 25 g and 50 g per Mcal, respectively, for dogs and cats. Hospitalized animals may consume less than average pets, and, therefore, a provisional minimal concentration of 50 g of protein in dogs and 75 g of protein per Mcal in cats is recommended.

Fats

Fats and protein are essential macronutrients; there is no requirement for dietary carbohydrate. Glucogenic amino acids can form glucose, but fatty acids cannot and must be processed through beta-oxidation. Many fasting animals have higher rates of beta-oxidation than when fed, and small animals, especially the dog, may be distinctly adapted to high-fat diets during starvation. Fats are also more than twice as energy dense as protein and carbohydrate. The recommendations for dietary fats for maintenance are 13.8 and 22.5 g/Mcal in dogs and cats, respectively. As with protein, dietary concentrations should be increased for reduced intake; values of 30 g and 40 g, respectively, are advised. The type of fat may also modulate response to disease. Polyunsaturated fatty acids of the omega-3 and omega-6 fatty acid series are converted to inflammatory mediators in the prostaglandin and leukotriene classes as well as thromboxanes. In general, omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic (DPA) found in marine sources such as fish, produce less potent inflammatory mediators, whereas omega-6 fatty

acids such as linoleic acid produce more potent mediators. A therapeutic dose of 1–3 mg of EPA+DHA per calorie has been suggested as an adjunct measure in the treatment of renal disease in order to possibly increase glomerular filtration rate, osteoarthritis due to a reduction in intra-articular cytokines, and in neoplasia likely due to chemosensitization. Parenteral lipid solutions have often contained minimal omega-3 fatty acids, although new products high in lipids derived from fish oil are now manufactured. The influence of these various lipid types when administered parenterally in clinical veterinary patients is not yet known.

Vitamins

Fat-soluble and water-soluble vitamins are commonly added to commercial pet foods. Water-soluble vitamins are of greatest concern in acute disease given the limited storage pools and the effect of diuresis on vitamin loss. B vitamins are the most common conditional deficiencies and broadly function as cofactors to cellular metabolism. Vitamin B12 deficiency requires long-term reduction in dietary intake. The lack of intrinsic factor production by the pancreas in cats (as opposed to the pancreas and stomach in dog) with chronic pancreatitis or with impaired absorption due to severe ileal disease in either species could warrant prophylactic supplementation of B12. Injectable B complex can be used to provide other B vitamins. Thiamine deficiency in cats causes anorexia, postural changes including ventroflexion, short seizures, and death if untreated. Clinical supplementation is warranted if these symptoms are encountered, especially in cats historically fed canned or unprocessed fish-based diets. In most clinical situations, supplementation of vitamins A, D, E, and K is not advised.

Minerals

Many minerals are stored in sufficient quantity by tissues so that acute supplementation is not needed except with obvious deficiencies. Adult dogs and cats, for example, have accessible calcium stores in bones. Conditions that cause acute electrolyte shifts, however, may prompt supplementation. Re-feeding syndrome has been reported in cats and humans; it has been theorized to occur in dogs but is poorly documented. The mechanism of re-feeding syndrome in severely emaciated patients is thought to be due to a rapid infusion of carbohydrate into the duodenum, which stimulates a large release of insulin, triggering intracellular electrolyte shifts and resulting in severe hypokalemia, hypophosphatemia, and hypomagnesemia. Fatal sequelae are possible. Therefore, diets given to emaciated animals should be replete in minerals and ideally high in protein and fat while low in carbohydrate; kitten and puppy foods generally provide suitable diets. Supplementation of other minerals, such as zinc for effects on immune function and selenium as a component of the intracellular antioxidant glutathione, has been recommended but poorly supported.

ROUTES OF ADMINISTRATION

Voluntary Intake

Voluntary food intake by hospitalized or acutely ill patients is ideal given the low cost and the ability of the animal to control the rate of feeding. Interventional nutrition is generally associated with a greater potential for iatrogenic harm than voluntary intake, except in those patients that have refractory vomiting or regurgitation despite normal appetite. Ideally, the animal's previous diet should be offered during hospitalization, especially for cats. Only if necessary should a single new and sacrificial diet be offered. Therapeutic diets intended for long-term feeding should not be offered during hospitalization or acute illness to avoid the development of food aversion. Similarly, offered foods should not be left in a cage with an animal unless that animal has a history of free-choice feeding and clinical suspicion is high that they will voluntarily consume food. The constant smell of a particular diet within the cage during a period of illness has been hypothesized to also trigger aversion. Ideally, voluntary intake should be precisely quantified to determine the percent of caloric requirement being met. Weighing of the food may be necessary for smaller animals.

Assisted Enteral Feeding

The decision to provide assistive support is guided by the patient's diet history, clinical assessment, and interventional logarithms (see Figure 25.4). Selection of the appropriate assistive strategy is critical for ensuring the best patient outcome.

Nasoenteral Feeding Tubes

Nasoenteral feeding tubes are generally employed for short-term inpatient feeding. These tubes can be placed without anesthesia or special equipment (Figure 25.6a–g). The measurement of the tube before placement varies based on the intended location of the distal aspect of the tube. Nasoesophageal tubes should be measured from the tip of the nose to ribs 7–9. Nasogastric tubes are measured from the tip of the nose to the last rib. Nasojejunal tubes are reported but require a weighted tube and fluoroscopy for accurate placement. Nasoenteral tubes are usually of 3- to 8-French size and are placed ventromedially in the nasal cavity following intranasal administration of a local anesthetic gel or topical ophthalmic solution. Entry into the ventral meatus permits passage of the tube through the nasal cavity into the esophagus. Animals should ideally be monitored for swallowing as the tube is passed. The distance from the nose to the medial canthus can be marked on the tube to guide when a swallow should be observed. The tube is passed to the measured length determined previously. Tubes are generally affixed to one of the nares with suture (a 22-gauge needle can be inserted first with suture passed through the sharp end of the needle and then the needle removed leaving the suture in tissue). Adhesive "super" or tissue glue may also be used, but



FIGURE 25.6 Nasoesophageal tube placement. **(a)** The nasoenteral tube is positioned for measurement. Rib 13 is used as a landmark for nasogastric tubes and ribs 7–9 for nasoesophageal tubes. **(b)** The desired length is marked with permanent ink. The distance from the naris to the medial canthus can also be marked to provide visual feedback as to when to monitor for a swallow response. **(c)** The tube is placed ventromedially to facilitate entry into the esophagus. Topical local anesthetic is recommended. **(d, e)** The tube is passed to the previous mark, and the tube affixed with a Chinese finger trap suture pattern, a skin staple, or glued to the fur near the lateral aspect of the naris. **(f)** One or two additional affixing sutures are placed to position the tube between the eyes so that the feeding end of the tube is caudal to the head. **(g)** An Elizabethan collar is placed to prevent the patient from dislodging the tube. Radiographs should confirm appropriate placement following placement. The aspiration of negative pressure and a lack of a cough with sterile saline administration can provide additional confirmation but may be inaccurate as the sole method of assessing placement.

removal of the tube can be more difficult and is presumably more painful for the patient. The tube is affixed in one or two additional sites in order to place it away from the eyes and for additional security. Placement is confirmed with a two-view thoracic radiograph. Negative pressure should be present if the tube is placed in the esophagus, and administration of sterile saline should not elicit a cough. Nasogastric tubes have been theorized to cause irritation of the lower esophageal sphincter and increased regurgitation or vomiting, but there have been no documented differences in complication rates. Nasogastric tubes facilitate assessment of residual gastric volumes, but large residual volumes are not associated with increased GI signs, and, therefore, routine monitoring and removal cannot be recommended. Complications of nasoenteral tubes include rhinitis, transient epistaxis, patient intolerance, and tracheal placement or feeding. Only liquid diets can be administered, either as a continuous infusion or in bolus feedings. Bolus feedings using nasojejunal tubes have been successful in clinical studies.

Esophagostomy Tube

Esophagostomy tubes are a convenient means of short- or long-term nutritional support that are well tolerated and free of significant side effects, with the exception of possible abscess formation around the tube site (**Figure 25.7a–m**). The tube is most easily placed in the left midcervical region with the patient anesthetized and in right lateral recumbency. A red rubber catheter or a commercially available feeding tube with a size greater than or equal to 5-French is measured from rib 7 to 9 to the anticipated exit point, and that measure is marked on the tube. For large dogs requiring significant volumes of food, stallion urinary catheters can be used to provide a greater diameter tube. Curved hemostats or Carmalt forceps are placed in the mouth following aseptic preparation of the lateral neck. The instrument tip is placed in the proximal esophagus, and lateral pressure is applied to "tent" the skin over the esophagus using the curved aspect of the forceps. An incision through all the tissue overlying the instrument tip is made until the instrument tip is exteriorized. The instrument handle is then opened and the tip of the catheter clamped firmly over the distal end of the tube. The tube is withdrawn aborally and the tip redirected orally into the esophagus as the tube is slowly withdrawn at the level of the skin until it "turns" and advances down the esophagus until the previous mark is reached. Two-view thoracic radiographs should be obtained in order to confirm placement. The tube can be used following anesthetic recovery, and both canned and liquid diets can be administered.

Gastrostomy Tube

Gastrostomy tubes are generally reserved for planned long-term nutritional support when esophageal bypass is clinically necessary due to megaesophagus, esophageal stricture, cervical disease, or for large volume feedings. "Low-profile" gastrostomy tubes may also be better tolerated than chronic esophagostomy tubes in some patients that require months to years of assisted feedings. Gastrostomy devices have a larger lumenal diameter (18–24 French) than esophagostomy tubes, allowing for a larger volume of fluid or food to be more easily administered. Tubes can be placed percutaneously with or without endoscopic support or surgically. The left side of the patient is aseptically prepared 1–2 cm caudal to the last rib and about one-third of the distance from epaxial muscles to ventral midline. Endoscopic insufflation of air permits endoscopic visualization of the stomach and allows for closer contact between the stomach and the abdominal wall. The endoscope permits tactile and visual (due to the light source) assessment of the position of the stomach to facilitate needle penetration (18 gauge, 1.5 inch) into the gastric lumen. A sterile flexible stylet or suture is then passed through the needle, grasped with endoscopic forceps in the stomach, and removed through the patient's oral cavity. A gastrostomy tube is then attached to the suture and the suture pulled orally until the tube exits the abdominal wall. A balloon or other device at the end of the tube prevents it from pulling through the abdominal wall, but the position of the tube should be marked to allow easy assessment of migrating tubes. A retainer flange is used to provide apposition of the stomach and the abdominal wall. Alternatively, the blind technique usually involves a special curved device, which is sized for the patient and passed orally into the stomach to provide visual assessment for needle penetration. Appropriate placement of blindly inserted tubes can be confirmed with liquid contrast and radiographs. Surgical techniques, described in greater detail in surgical texts, have the advantage of direct visualization of the tissues along with the ability to place intra-abdominal appositional sutures to prevent leakage of gastric contents due to separation of the peritoneal wall and gastric surface.

Gastrostomy tubes are generally well tolerated by small animals. However, Elizabethan collars must be employed in the first 2 weeks following placement, and animals should always be carefully monitored for licking or attempts at tube removal. Prevention of bacterial contamination in the tissues around the skin is critically important, as abscessation or chronic dermatitis can force premature removal of the tube. Both esophagostomy and gastrostomy tubes should be replaced as quickly as possible if inadvertently removed, as natural closure will rapidly occur.

Jejunostomy Tube

Jejunostomy tubes are reserved for patients that require gastric or duodenal bypass feeding. Such circumstances include severe pancreatitis, persistent vomiting or regurgitation, gastric or duodenal neoplasia, gastric hypomotility, or gastric outflow obstruction. Surgical placement with or without laparoscopy is generally required. Tubes cannot be removed for 7–14 days following insertion as creation of a stoma is required to prevent septic peritonitis, the most catastrophic of jejunostomy tube complications. Jejunostomy tubes may also be placed through



FIGURE 25.7 Esophagostomy tube placement. **(a)** The left lateral neck is aseptically prepared. **(b)** The esophagostomy tube is measured from the expected point of insertion to rib 7–9 and that distance marked on the tube with permanent ink. **(c)** A curved instrument is passed orally into the esophagus, and lateral pressure is applied until the instrument tip is palpated. **(d)** A stab incision is made over the tip of the instrument. **(e)** The curved instrument tip is moved laterally to exit the incision. **(f)** The distal end of the tube is grasped with the instrument. **(g)** The tube is pulled aborally with gentle traction. **(h)** The end of the tube is passed orally back into the esophagus while slowly pulling laterally on the syringe end of the tube in order to facilitate movement of the tube into the distal esophagus. **(i)** The tube is inserted to the level of the previous mark. **(j)** Chinese finger trap sutures are used to secure the tube to the dermis. **(k)** Antibiotic ointment and/or gauze is applied over the esophagostomy site. The catheter end of the tube is capped. **(l)** A nonocclusive bandage is applied to protect the area and secure the tube. **(m)** A thoracic radiograph confirms appropriate placement. (The arrow indicates the tip of the esophagostomy tube in front of the lower esophageal sphincter.)

a gastrostomy tube, but endoscopic or intraoperative guidance of the tube into the intestinal lumen is usually required. In both cases, tube diameter limits feeding to liquid enteral diets, and such diets are most commonly administered as a continuous infusion. However, three bolus feedings per day were not associated with increased adverse effects in one study. Dogs and cats also clinically appear to tolerate liquid diets of varying composition.

Tube Management

Tube feedings can be complicated by obstructions within the tube caused by saponification of fat, improperly mixed diets, pH changes, incompatible medications, and similar substances. Tubes are commonly flushed with warm water before and after each use, with an amount consistent with the volume of the tube. Carbonated beverages and pancreatic enzyme solutions may also prove helpful if obstructions do not respond to water alone.

Water is first administered following placement of an assistive feeding tube. Nasoenteral and esophagostomy tubes may be used shortly following recovery from any sedation or anesthesia. Other tubes that critically rely on stoma formation, such as gastrostomy or jejunostomy tubes, should be tested with water 12 hours after placement, and food can be administered about 24 hours after insertion. Esophagostomy and jejunostomy tubes should be wrapped when not being used and cleaned daily with disinfectant solution.

Dietary options for feeding tubes are dictated by the size of the feeding tube and the required caloric density. Clinical veterinary and human liquid diets with caloric densities of about 1–1.5 kcal/mL are used for small diameter tubes such as nasoenteral and jejunostomy tubes (Table 25.1). Human enteral diets should not be used in cats, given the more stringent nutritional requirements of this species, including an obligatory need for taurine and arachidonic acid, and higher protein intakes compared with dogs and humans. Canned diets can be employed in most other assistive feeding devices. Any canned diet is theoretically an option, but high-fiber diets have a very low-caloric density when mixed with sufficient water. High-calorie, low-fiber, moderate-to-high protein and fat diets facilitate the highest caloric densities (~1 kcal/mL; Table 25.2). Many "recovery" diets are commercially manufactured to permit ease of administration through a feeding tube.

Animals with feeding tubes may require frequent feedings. No significant differences in continuous infusions as opposed to bolus feedings have been identified. Aspiration and measurement of gastric residual volumes is not beneficial in most cases. Gastric volume is the limiting factor in determining the number of feedings. Clinical experience suggests that cats tolerate about 60 mL per feeding when administered over 10–15 minutes and, therefore, require about four feedings per day. Dogs display much greater gastric expansion with sufficient time. A figure of 50 mL/kg is commonly employed as an estimate of tolerated volume, but dogs are known to consume about 10% of body weight in a single meal. Many dogs can be fed on routine twice daily schedules with feeding tubes. Owners should be instructed that less frequent feedings may be possible but will require additional time at each feeding.

Parenteral Nutrition

IV administration of nutrients is reserved for those cases with documented or anticipated periods of prolonged hyporexia or anorexia. However, patients with low BCSs or MCSs may benefit from earlier intervention with parenteral nutrition. This method of nutritional support may be appropriate for animals with prolonged ileus, those receiving ventilator support, and those who display diffuse refractory GI symptoms. Parenteral nutrition requires specialized techniques and solutions that may not be available at all practices. The cost to feed patients with this method can be substantially higher than with enteral feeding.

IV nutrition can be administered through a central line (central parenteral nutrition) or through a dedicated peripheral catheter (peripheral parenteral nutrition). The terms total and partial parenteral nutrition are no longer used, as most veterinary parenteral nutrient mixtures do not meet the total nutrient requirements for patients. Frequent complications of parenteral nutrition include hyperglycemia and thrombophlebitis. Lowering the dextrose content of the solution can reduce the risk of the former, and the latter is reduced by placement of a central line. Peripheral parenteral nutrition solutions should have an osmolality no >650 mOsm/L. Infection, possibly leading to sepsis, is theoretically possible as some components of parenteral nutrition, such as IV lipid, could serve as a bacterial media. However, the high osmolality of parenteral nutrition solutions and careful technique usually prevent contamination of the fluid itself. Most parenteral nutrition-related infections occur due to migration of bacteria around the catheter site, so aseptic catheter technique is critically important. Only a dedicated catheter or a dedicated port on a multilumen catheter should be used. Injections should not be given through the same port as parenteral nutrition.

TABLE 25.2 Commercial diets marketed for tube feeding critical patients in the United States

Diet	Protein (g/1,000 kcal)	Fat (g/1,000 kcal)	Carbohydrate (g/1,000 kcal)	Caloric density (kcal/kg)
Royal Canin Recovery	97	63	11	1,039
Science Diet A/D	91	68	29	1,352
Purina CN	79	74	25	1,175

Consult product guides for current specifications.

TABLE 25.3 Common components of parenteral nutrition

Component	kcal/mL	mOsm/L
50% dextrose	1.7	2,525
5% dextrose	0.17	253
20% lipid	2.0	260
8.5% amino acids without electrolytes	~0.57	~700
8.5% amino acids with electrolytes	~0.57	~920

Peripheral solutions should be limited to <650 mOsm/L. The addition of electrolytes may increase osmolality. Hypertonic saline provides 1.2 mEq of sodium and chloride per milliliter and contains 2.4 mOsm/mL.

TABLE 25.5 A general parenteral nutrition solution for central administration

Component	Volume (mL)
8.5% amino acids without electrolytes	1,000
20% lipid	250
5% dextrose	500
Hypertonic (7.2%) saline	60
Heparin (1,000 units/mL)	1.8

The calorie distribution of nutrients is 20% protein (50 g/Mcal), 50% carbohydrate (125 g/Mcal), and 30% as lipid (33 g/Mcal). The caloric density is 0.93 kcal/mL, and the calculated osmolality is 1,200 mOsm/L. Electrolyte composition is 58 mEq/L sodium, 41 mEq/L chloride, and 2 mEq/L phosphorus. Additional electrolytes, minerals, and vitamins should be added as the patient's status dictates.

Parenteral mixtures generally contain carbohydrate, fat, and protein in the forms of dextrose, lipid emulsion, and amino acids (Table 25.3). Carbohydrate is not required in the formulation, and both cats and dogs have been managed with mixtures of only lipid emulsion and amino acids. The concentration of dextrose appears related to the incidence of hyperglycemia. IV lipid emulsions have been reported to impair reticuloendothelial system function in other species, which could have implications for their use in septic patients. Such solutions could also worsen hyperlipidemia and have been hypothesized to worsen pancreatitis. However, the effect of IV lipid on canine and feline pancreatitis is rarely reported, and both species have been managed for this condition with high-fat solutions. Peripheral parenteral nutrition solutions commonly contain increased lipid compared with centrally administered solutions, as lipid possesses a lower osmolality compared with other constituents (Tables 25.4 and 25.5). The higher basal rate of fatty acid oxidation has prompted some authors to advocate the use of lipid concentrations higher than those used in human nutrition.

Multiple amino acid solutions are available, each with a different blend of essential and nonessential amino acids. Products are produced with or without electrolytes. Electrolyte-containing products generally require supplemental potassium and phosphorus, especially in animals that have experienced prolonged anorexia or tissue catabolism. Insulin release causes both an intracellular shift of potassium and an increased cellular phosphate utilization related to the increased production of energy stores, such as adenosine triphosphate or creatine phosphate. Phosphorus is typically added to achieve a concentration of 5–10 mmol/L. Electrolyte-free amino acid solutions can be modified to include sodium and chloride at rates consistent with maintenance or replacement fluids as required through the addition of hypertonic (7.2%) saline.

Provision of water-soluble vitamins supports normal energy metabolism by providing essential cofactors in metabolic reactions. Some IV B complex solutions are low in vitamin B12, so this should be administered subcutaneous (SC) if deficiency is predicted. Fat-soluble vitamins may be added and are included in some multivitamin combinations designed for parenteral nutrition, but substantial reserves are likely present in many patients. Trace elements for parenteral administration are available but controversial.

The amount of protein in the form of amino acids to administer is controversial. Protein requirements may be expressed as a percentage of calories in some resources or as an amount in grams to be fed per day. Protein may also be given on top of the calculated caloric requirement (200 kcal for most cats, 70 × [ideal body weight in kg]$^{0.75}$ kcal for dogs) by some clinicians. The theory is that protein, when given above the calorie needs of an animal, will be more likely used for anabolic reactions rather than for ketogenesis or gluconeogenesis. The provision of dietary protein only partially reverses catabolism in many disease states characterized by high rates of nitrogen turnover and suspected protein loss. Provision of 20% of calories as protein (50 g/1,000 kcal) is adequate for most patients, although encephalopathy may warrant values as low as 40 g/1,000 kcal, and patients with other conditions with high protein requirements can be given solutions up to 28% of calories (70 g/1,000 kcal). Patients fed less than their expected caloric requirements need a solution with greater amino acid or fat concentrations to maintain a consistent "dose." Administration of low-concentration amino acid solutions (3%) is unlikely to prevent muscle

TABLE 25.4 A general parenteral nutrition solution for peripheral administration

Component	Volume (mL)
8.5% amino acids without electrolytes	500
20% lipid	250
5% dextrose	250
50% dextrose	25
Hypertonic (7.2%) saline	40
Heparin (1,000 units/mL)	1

The calorie distribution of nutrients is 23% protein (56 g/Mcal), 12% carbohydrate (30 g/Mcal), and 66% as lipid (73 g/Mcal). The caloric density is 0.71 kcal/mL, and the calculated osmolality is 600 mOsm/L. Electrolyte composition is 61 mEq/L sodium, 46 mEq/L chloride, and 4 mEq/L phosphorus. Additional electrolytes, minerals, and vitamins should be added as the patient's status dictates.

catabolism, especially in the absence of other macronutrients, as most of the amino acids would be converted to energy. Therefore, protein without adequate caloric intake is unlikely beneficial.

Parenteral nutrition requires special monitoring and careful administration. Parenteral nutrition solutions should be refrigerated and kept for no longer than 7–10 days after mixing. Vitamins, if administered, should be added just before hanging a bag to prevent degradation during storage. Careful aseptic techniques should be employed when connecting parenteral nutrition, and a new fluid line should be used with each new bag. Sterile gloves are used when spiking each bag and when connecting a new line to the patient's catheter. Injection ports can be disinfected and covered with sterile gauze, as can all connections between the bag and the patient. Some vitamins degrade with ultraviolet light, and when exposure is likely, the bag and the line should be covered with special amber sleeves, bandage material, or aluminum foil. The patient should be disconnected from parenteral nutrition only once daily. The bags can be wrapped and taken outside with the patient if necessary. Parenteral solutions may benefit from the inclusion of 1 unit of heparin per milliliter of mixture to prevent local thrombosis formation and prevent the need for periodic flushing with heparinized saline. Recommended monitoring includes electrolytes twice daily along with a hematocrit/total protein and a visual check of the serum for hyperlipidemia. Most patients can receive parenteral nutrition at one-half of the calculated energy requirements during hospitalization over the first 6–12 hours, with an increase to the full calculated rate thereafter, assuming that the patient tolerates the volume and is unlikely to suffer severe electrolyte shifts secondary to re-feeding.

Nutritional Reassessment

Nutritional reassessment is difficult in critically ill patients, as many commonly measured laboratory parameters are unreliable indicators of malnutrition. Electrolytes should be closely monitored during any nutritional intervention as feeding can create and correct potential abnormalities. Body weight is affected by fluid status, and both body condition and muscle condition scoring systems are unlikely to change during a hospitalization period of 1 week or less. Frequent monitoring of compliance to nutrition orders is preferred, as patient procedures, anesthetic events, failure to follow treatment sheets, and other factors may influence daily caloric intake. Tolerance to feeding plans should also be assessed because persistent vomiting, regurgitation, or diarrhea may warrant alterations to the nutrition orders.

Disease-Specific Considerations

A number of conditions encountered in critically ill patients may benefit from specific nutritional strategies. Each patient should be evaluated as an individual, but general recommendations exist for a variety of conditions.

Pancreatitis

Dietary triggers for acute and chronic active pancreatitis are well described, with ingestion of foods high in fat being the most common. Hyperstimulation of cholecystokinin has been hypothesized as a possible mechanism in combination with other patient factors, such as elevated cortisol, obesity, or hyperlipidemia. Evidence-based data on the nutritional treatment of acute pancreatitis are lacking. Many practitioners argue that withholding enteral nutrition in favor of fasting or parenteral nutrition decreases pancreatic stimulation and therefore reduces premature activation of pancreatic enzymes. However, pancreatic responses to nutrition may be abnormal in pancreatitis, so that enzyme activation is actually decreased in response to lumenal nutrition. Jejunostomy tube feeding in dogs and in humans has been tolerated in both species. Humans display lower morbidity when fed through such a tube compared with parenteral nutrition, but it is unclear if this is due to worsened outcome with total parenteral nutrition rather than a beneficial effect of enteral nutrition alone. Luminal nutrition is associated with reductions in the systemic inflammatory response and in preservation of the mucosal barrier, thereby reducing bacterial translocation. The ideal timing of enteral nutrition is unclear. Studies in canine parvovirus infection showed that early enteral nutrition improved outcome and that feeding was well tolerated irrespective of whether patients were vomiting or regurgitating.

Additional studies are required before definitive recommendations are made on the timing and type of feeding in canine pancreatitis. Dogs with chronic pancreatitis, however, do benefit from low-fat diets (<30 g/Mcal) following discharge. Most therapeutic diets labeled for pancreatitis meet this criterion. Clinicians should consider the expected caloric intake of a patient before making a dietary recommendation. Patients consuming large amounts of food to maintain an ideal body weight would require a lower concentration of fat than dogs consuming a very small amount. Access to high-fat treats and prepared diets intended for consumption by the owner should be restricted.

Serum triglycerides are an important aspect of patient monitoring as free fatty acids, very-low-density lipoprotein, and low-density lipoprotein increase in this condition. A decrease in lipoprotein lipase, causing a subsequent increase in triglyceride and chylomicrons, has been observed in humans but not yet in dogs. Low-fat diets reduce the hypertriglyceridemia in many cases, and provision of omega-3 fatty acids (EPA, DHA) could have an additive benefit along with niacin.

Feline pancreatitis displays many features distinct from those observed in dogs. Concurrent hepatobiliary or inflammatory bowel disease is commonly identified in cats affected with this condition. Premature activation of trypsinogen has been postulated as the mechanism, but the etiology is unclear. Cats presenting with pancreatitis display less vomiting than dogs, and enteral feeding is therefore less complicated. Supportive enteral feeding tubes (nasoenteral, esophagostomy) are often recommended for feline pancreatitis, as hepatic lipidosis

(discussed later) is a common clinical sequela in anorectic cats. Jejunostomy tubes are only rarely required. Fasting should be avoided. There is no evidence that dietary fat restriction is necessary in cats, which is in stark contrast to the evidence and clinical experience in dogs. Cats should receive parenteral vitamin B12 injections because intrinsic factor, the requisite cofactor for B12 absorption, is produced only in the pancreas in cats as opposed to both the stomach and pancreas of dogs.

Chronic Gastrointestinal Disease

Acute gastroenteritis and colitis often respond to fasting, and no specific nutritional interventions are required. There is emerging evidence that probiotics may shorten the duration of acute GI signs and that antibiotic administration may cause deleterious long-term shifts in the microbiome without a significant improvement in clinical signs. Patients may present with chronic GI complaints requiring stabilization. Such patients may suffer from malabsorption, protein-losing enteropathy, maldigestion, and reduced total and lean body mass. Many animals will have concurrent anorexia, and therefore consideration of assistive feeding devices is recommended. Feeding tubes appropriate for at-home use should be prioritized, as a protracted period of stabilization may be required while the underlying disease is managed. Food allergy or intolerance is a common differential for chronic GI disease, and diagnosis or exclusion of these conditions requires a strict food trial. Such trials are best started following patient discharge and only if an animal is voluntarily eating, as food aversion can develop due to perceived associations between diet and disease. Animals with a feeding tube can begin the diet immediately. Some authors advocate the routine use of hydrolyzed diets in the theory that food allergy may develop in patients with a compromised GI barrier. Novel protein diets are the other class of diets used to assess food allergy, but their use requires collection of a thorough diet history to exclude the possibility that an animal has previously received a particular protein source. Previously rare dietary protein sources such as rabbit, kangaroo, alligator, and venison are now available over the counter. Diet trials should last 12 weeks, and no other proteins, treats, or flavored medications should be given.

Chronic colitis may respond to hydrolyzed or novel protein diets. Dietary fiber and probiotics are additional considerations. Dietary fiber is generally classified as soluble or insoluble. Soluble fiber sources, such as gums and beet pulp, provide substrates for bacterial fermentation. Insoluble fibers, such as cellulose and peanut hulls, increase fecal bulk. Fiber modification influences intestinal transit, stool consistency, bacterial flora, and fecal moisture. Psyllium supplementation of foods has gained considerable attention. Psyllium, a partially fermentable fiber, contains mucilage that absorbs water and helps to normalize GI transit. It is frequently employed in the dietary management of feline megacolon. Probiotics, living microorganisms administered for health effects, may influence immune responses and nutrient absorption in the colon. Several veterinary specific probiotics have been shown to reduce the duration of diarrhea. However, product quality has been poor for some probiotic products marketed for animal use. The benefits of probiotics in patients receiving concurrent antibiotics are unclear but may help avoid undesired shifts in the microbiome.

Hepatic Lipidosis

Excessive accumulations of triglycerides in the hepatocytes of some anorectic, generally overweight cats produce hepatic dysfunction and cholestasis. The occurrence of this condition in cats but not in dogs is likely related to the metabolic peculiarities of the cat, a true carnivore. Cats display significant mobilization of triglycerides during fasting, which are transported to the liver for use as energy. In lipidotic cats, however, the rate of mobilization exceeds the rate of clearance. Carnitine complexes with fatty acids to facilitate transport across the mitochondrial membrane, and deficiency of this compound has been proposed as a cause in some cats. Oxidative stress may also be increased, and some B vitamins may be decreased as a function of prolonged anorexia or the condition itself. A variety of nutraceuticals have been recommended, such as carnitine (250 mg daily), SAMe (100–200 mg daily), B complex vitamins (added to fluids), and vitamin B12 (0.5–1 mL [500–1,000 µg] SC daily). Administration of caloric needs is likely more important than supplementation. Supportive feeding measures should be pursued as soon as possible in the disease course. Fat restriction is unnecessary. Despite the intrahepatic lipid accumulation, fat ingestion, when combined with other nutrients, decreases the release of peripheral lipid stores due to the action of insulin. High-protein diets (>90 g/Mcal) are commonly recommended as they may support tissue regeneration. Severely affected cats may display hepatic encephalopathy, and in these rare cases, the protein concentration of the diet should be reduced.

Hepatic Encephalopathy

Hepatic encephalopathy warrants immediate nutritional modification following initial stabilization. In addition to lactulose, which converts ammonia to ammonium, thus preventing absorption, neomycin, which decreases ammonia-producing urease-positive bacteria, and the correction of alkalosis, which prevents worsening of encephalopathy, dietary protein restriction is indicated in most patients. Estimates suggest that one-third of blood ammonia is from bacterial production and the remainder from dietary protein intake because encephalopathic patients lack adequate urea cycle activity to convert ammonia to blood urea nitrogen. Therefore, most dogs with average caloric intake ($90 \times BW^{0.75}$ kcal per day) should receive enough protein to prevent muscle catabolism and provide maintenance requirements, approximately 40–50 g/Mcal. Cats, with higher protein requirements, should receive around 70 g/Mcal. Protein-restricted diets may also be restricted in purine content, as the crude protein of the diet is derived from measurement of nitrogen, which includes amino acids, purines, and pyrimidines. Impaired

conversion of purines to allantoin results in increased uric acid excretion, predisposing to urate uroliths. Most therapeutic hepatic diets are appropriate for encephalopathic patients; however, patients consuming few calories may be fed a normal diet. Renal diets are not commonly recommended for extended feeding of the encephalopathic patient, as such diets tend to be alkalinizing, which worsens clinical signs. In addition to the standard therapies listed previously, soluble fiber has been suggested in the management of encephalopathy, mainly due to lactulose-like effects on lowering intestinal pH.

Renal Disease

Most patients with AKI or CKD do not require immediate dietary modification (see also Chapter 13). Azotemia may predispose to anorexia and nausea, and attempts to administer a new diet can result in profound food aversion. The role of nutrition in AKI is unclear, but it is generally accepted that such patients have high rates of protein catabolism and may therefore benefit from normal maintenance diets. If animals consume little food during hospitalization, high-protein diets may even be appropriate to prevent loss of lean body mass. CKD patients can typically be fed their historical diet during hospitalization. The effects of diet in CKD are well studied in both dogs and cats and directly impact survival when fed for extended periods. Advanced stages of renal disease may require assistive feeding tubes, primarily esophagostomy or gastrostomy, in order to facilitate owner administration of calories and sufficient water.

The features of most diets designed for CKD include reduced phosphorus and protein, elevated omega-3 fatty acids, reduced sodium, and increased caloric density. One diet fed to dogs with stage 3 and 4 CKD permitted a median survival time of about 600 days compared with 200 days in the control group. Similar findings of a feline diet marketed for renal disease were reported: 633 days versus 264 days. Another study of a different feline diet found a median survival time of 750 days. Commercially available kidney diets and calcitriol administration in dogs are, in fact, the only interventions for which grade 1 evidence exists. Different diets labeled for use in renal disease contain different ingredients and nutrient concentrations; therefore, product guides should be carefully reviewed if a patient requires more or less of a certain nutrient or if one particular product is refused. The amount of protein to administer to patients with renal failure is controversial and should probably be increased to the amount needed to maintain muscle condition. Protein does not appear as toxic to renal tubules in dogs and cats as in rodents, but protein frequently contains a large percentage of dietary phosphorus, which is reduced to prevent renal secondary hyperparathyroidism. No clinical studies exist that compare protein modification independent of phosphorus concentration. Animals who consume little food may benefit from higher protein diets. Those patients in stage 4 renal disease (www.iris-kidney.com) may require feeding tubes if voluntary intake is insufficient to maintain body weight. Therefore, interventions should be tailored to the patient's caloric intake and International Renal Interest Society (IRIS) stage (Figure 25.8).

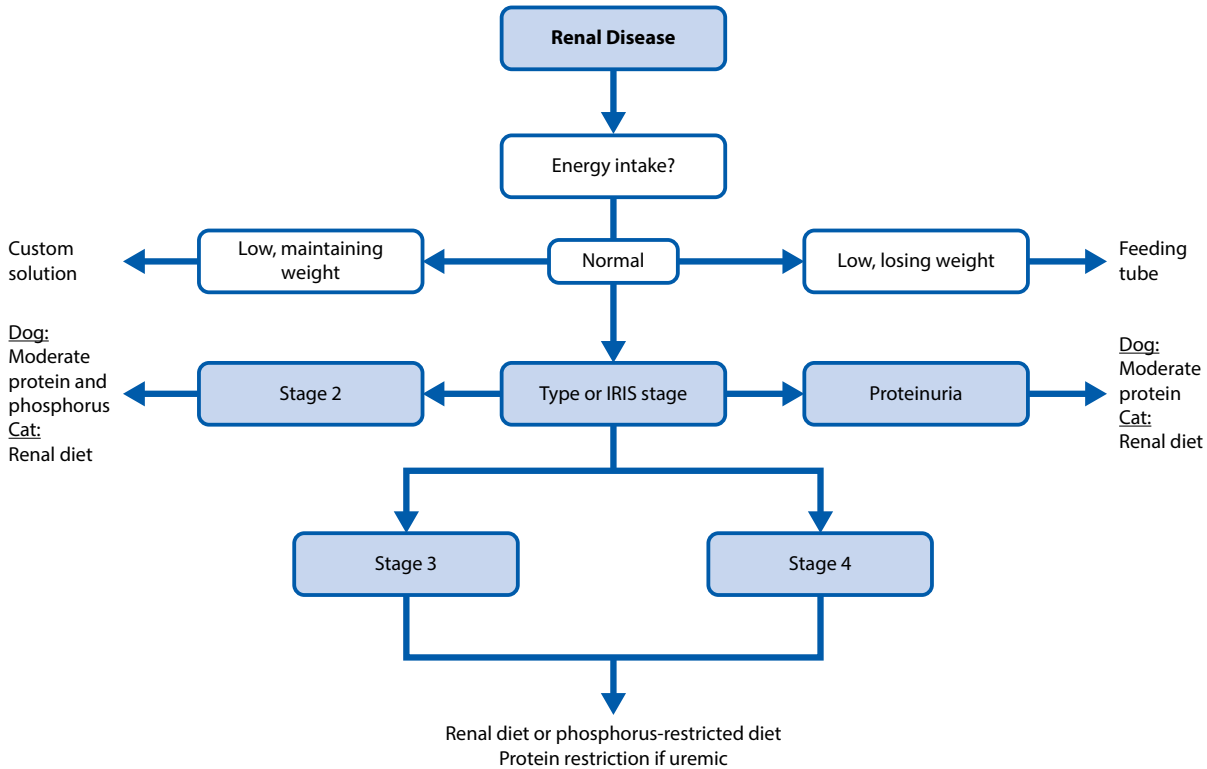


FIGURE 25.8 An algorithm for nutritional management of patients with renal disease.

CONCLUSION

Critical care patients benefit from frequent nutritional assessments during hospitalization. Controversies exist regarding when, how, and what to feed critically ill patients. However, most conditions benefit from a methodical approach to nutritional support. Those animals with significant anorexia, hyporexia, or reduction in MCS or BCS may require earlier interventions compared with animals who present with acute illness and adequate tissue reserves. Certain conditions such as sepsis may benefit from permissive underfeeding. In many conditions, the provision of some calories is preferred compared with no calories or caloric excess. Specific attention should be given to patients presenting with GI disease, pancreatitis, hepatic encephalopathy, hepatic lipidosis, and renal disease, as these conditions have well-defined nutritional considerations. Additional randomized controlled trials are needed to better characterize the influence of nutrition on patient outcome.

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CHAPTER 26

Management of the Obese Dog or Cat

Alexander J. German

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DEFINITION AND OVERVIEW

Human Obesity

In humans, obesity is defined as a disease in which adipose tissue has been accumulated to the point that health can be adversely affected. There are various methods of quantifying adiposity in people, the most common of which is the body mass index (BMI; weight [in kg] divided by height [in m^2]). Although not perfect, for the majority of the human population, this measure approximates to body fat mass. Epidemiologic studies have suggested that the optimal BMI for adult Caucasians is 20–25 and have further demonstrated that disease and mortality risk progressively increase when BMI exceeds this. Increased BMI has been categorized into "overweight" (BMI 25–30), "obese" (BMI 30–40), and morbidly obese (BMI >40), with each representing a progressive increase in disease and mortality risk. Some recent work has questioned whether people with an overweight BMI are genuinely at an increased risk of mortality and developing concurrent disease. This phenomenon might be explained by confounding, since some people with an ideal BMI have a concurrent disease that has caused them to lose weight. There has been a dramatic increase in the prevalence of this disease in the human population. According to the Centers for Disease Control in the United States, more than a third (35%) of adults are obese. However, this is not a problem that is limited to the westernized world and, indeed, the Overseas Development Institute has recently highlighted a growing concern in developing countries, with almost a billion adults now being classed as obese. Thus, obesity truly is an epidemic of global proportions.

Canine and Feline Obesity

As with humans, excess adiposity in companion animals can be categorized either as overweight or as obese, depending on the degree with which current weight exceeds ideal weight. Rather than using a measure equivalent to the BMI, most veterinarians will classify on the basis of the body condition score (BCS) (see **Figure 25.1**).

The WSAVA Global Nutrition Committee has recently recommended using the 9-integer unit BCS, with BCS 4/9–5/9 being ideal, 6/9–7/9 being overweight, and 8/9–9/9 being obese. Given that beyond 5/9 each integer unit represents ~10%–15% of excess weight, overweight animals are typically up to 20% above their ideal weight, while obese dogs are >20% above ideal. As in humans, various studies have suggested that adverse health effects can arise when dogs and cats are not maintained in optimal body condition. A number of recent international studies have determined the prevalence of excess body weight in dogs and cats: For dogs, 29%–39% are defined as overweight and 5%–20% as obese, while, for cats, 19%–29% are defined as overweight and 8%–10% as obese. Differences represent variations in the populations studied and methodology. Furthermore, as with human obesity, prevalence is increasing, with recent reports suggesting a 37% and 90% increase in prevalence over the last 5 years for dogs and cats, respectively.

ETIOLOGY AND PATHOPHYSIOLOGY

Etiology

For body weight to remain stable, energy intake in food must match expenditure from basal metabolic rate, activity, and thermoregulation. When energy intake

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exceeds expenditure, usually as a result of a number of risk factors, the net energy gained is stored in body fat. Adipose tissue can expand both by hypertrophy and/or hyperplasia: In some individuals, the response to energy imbalance is adipocyte hypertrophy while for others hyperplasia predominates, with a lesser degree of hypertrophy. Differences in the degree of hyperplasia to hypertrophy have recently been shown to be associated with the metabolic derangements that manifest as a result of obesity. Intriguingly, recent research has demonstrated that some cats can maintain a stable weight despite *ad libitum* feeding, likely by self-regulating intake. However, others are unable to do this and, if excess intake remains unchecked, weight gain develops gradually.

Thus, slow and insidious energy imbalance is a major factor, perhaps explaining why obesity is most prevalent in middle aged dogs and cats.

Pathophysiology

The clinical significance of obesity relates not to the accumulation of adipose tissue, *per se*, but to the effect this has on the function of other organs. There are two proposed mechanisms for such effects: "Mechanical" and "endocrine." Mechanical effects can occur from excessive weight of adipose tissue, and this can cause excessive loading of structures of the musculoskeletal system. Alternatively, effects may arise from the excess volume of the tissue and the effect this has on compressible structures, for instance of the respiratory (affecting breathing function) or urinary (causing incontinence) system. In addition, the excess volume and weight can affect the ability to groom, while the insulating effect of adipose tissue can create problems with reduced heat dissipation.

However, in addition to these mechanical problems, there may be effects due to derangement of the endocrine functions of white adipose tissue. A range of cytokines, chemokines, and other inflammation-related proteins, collectively termed "adipokines," are now known to be synthesized, suggesting that adipose tissue can influence the function of a variety of organ systems (**Figure 26.1a, b**). When there is expansion of adipose tissue, it can become hypoxic, causing derangement in adipokine synthesis and release. This can lead to a body wide state of chronic mild inflammation and, ultimately, to a range of end effects. In humans, increases in the production of certain inflammatory adipokines (e.g., leptin, tumor necrosis factor a, interleukin 6, plasminogen activator inhibitor 1, and haptoglobin) have been causally linked to the development of metabolic syndrome and other disorders linked to the obese state. As mentioned earlier, adipose tissue can expand both by hypertrophy (through increased cell size) and hyperplasia (through synthesis of new cells from preadipocytes). Individuals that predominantly react by adipocyte hypertrophy have greater hepatic fat deposition and more marked metabolic disturbances than those who do not. It is thought that these differences may arise through mitochondrial dysfunction, since the same studies demonstrated that mitochondrial gene expression pathways

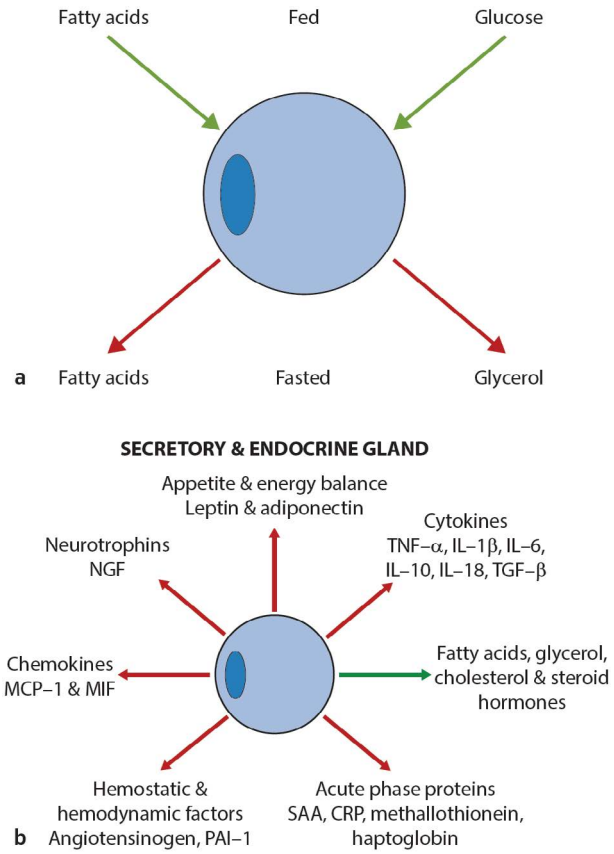


FIGURE 26.1 Evolving views of the biological functions of adipose tissue. **(a)** Adipocytes were previously considered to be inert storage depots releasing fuel as fatty acids and glycerol at times of fasting or starvation. **(b)** Recently, however, it has become increasingly clear that adipocytes are endocrine cells, which secrete important hormones, cytokines, vasoactive substances, and other peptides. This figure outlines the range of such proteins secreted from adipose tissue. CRP, C-reactive protein; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MIF, macrophage migration inhibitory factor; PAI-1, plasminogen activator inhibitor-1; SAA, serum amyloid A; TGF-b, transforming growth factor-b; TNF-a, tumor necrosis factor-a. (*From German AJ, Ryan VH, German AC, et al. (2010). Obesity, its associated disorders and the role of inflammatory adipokines in companion animals.* Vet J *185:4–9, reprinted with permission.*)

are downregulated, while inflammatory pathways are upregulated in the adipose tissue of affected individuals.

Inflammatory adipokine gene expression has been documented in both canine and feline white adipose tissue, and studies are now highlighting their effects in these species. As with humans, metabolic derangements are most evident. Increased plasma leptin concentrations have been shown to be independently associated with insulin sensitivity in lean and overweight cats. Other studies indicate decreased circulating adiponectin in obese dogs and cats, and this is also linked to insulin resistance. Furthermore, low serum adiponectin has been associated with failure of a subsequent weight loss program and excessive lean tissue loss during weight management. Increases in serum paraoxonase 1

have also recently been demonstrated and, once again, this is associated with insulin resistance. Further work is ongoing to better characterize these effects.

Risk Factors for the Development of Obesity

A number of risk factors are known to predispose to the development of obesity in dogs and cats, as outlined later.

Co-Existing Health Problems

Some diseases, such as hyperadrenocorticism, can cause polyphagia, and if the animal is allowed to consume more food, weight gain can occur. Other diseases can reduce energy expenditure, for instance by decreasing physical activity or slowing the basal metabolic rate. Orthopedic diseases that lead to lameness are a classic example of a disease that decreases activity, while hypothyroidism is, perhaps, the best example of a disease predisposing to weight gain by decreasing metabolic rate. Although thought to be a common endocrinopathy, relatively speaking, hypothyroidism is actually an uncommon cause of obesity in dogs. In this respect, the prevalence of hypothyroidism is reported to be <1%, and less than half are overweight (see Chapter 11), while the current prevalence of dogs that are above their ideal weight is much greater (typically 34%–59%); thus, only a minority of the overweight dogs attending veterinary practices are likely to have concurrent hypothyroidism. Furthermore, given that hypothyroidism is extremely rare in cats, it is a negligible cause of obesity in this species.

Beyond this, some therapeutic interventions can predispose to weight gain. One example is the use of drugs that stimulate appetite (e.g., glucocorticoids or anticonvulsants) but not energy requirement; here, weight gain can occur if the owner provides more food. A second example is surgical sterilization (spaying/neutering), which alters behavior by decreasing physical activity while increasing food-seeking behavior.

Rapid Early-Life Weight Gain

In humans, overly rapid gain of weight during the early years of life predicts the likelihood of being obese during adulthood. A similar phenomenon has recently been identified in cats. Although the reason for this phenomenon is not yet known, genetic factors are suggested to play a role. Armed with such knowledge, a simple comparison of the ratio of bodyweight between 2 months (i.e., 2nd vaccination) and 12 months of age (first annual booster) could be used to identify at-risk cats, enabling preventive strategies to be implemented (see ahead given in the text).

Age

As mentioned previously, the prevalence of both canine and feline obesity gradually increases throughout life, with the condition being most prevalent in middle aged animals. However, some individuals can become overweight even during growth. The prevalence of overweight and obesity decreases in senior animals, possibly due to the onset of various chronic diseases associated with the aging process.

Sex and Neutering

Some canine studies have suggested that female dogs are predisposed, while a recent feline study suggested males to be overrepresented. More importantly, neutering is an important risk factor for obesity in both species, with studies suggesting that this is the result of behavioral alterations rather than a direct effect on metabolism. In this respect, the hormonal changes produced by obesity lead to an increased food intake, decreased physical activity, or both. Given that neutering is typically an elective procedure, unwanted post-neutering weight gain is arguably preventable if body weight is monitored closely, and food intake adjusted accordingly (see ahead given in the text).

Breed

On rare occasions, single gene disorders can cause obesity in humans, but polygenic effects are more common with a number of predisposing genes recently identified. At the current time, no single-gene disorders have been described in either dogs or cats. Since there are a number of known breed predispositions in both dogs (e.g., Cocker Spaniels, Beagles, Labrador Retrievers, Golden Retrievers, Shetland Sheepdogs, Rottweilers, and mixed-breed dogs) and cats (e.g., Domestic Shorthair), genetic influences remain likely, although these are more likely to be due to polygenic effects. Gene mapping studies are underway to characterize the genetic influences in these companion animals.

Environment and Activity

Dogs and cats that live indoors are reportedly at greater risk of developing obesity than those who go outside. Similar findings have also been seen for indoor cats, including those that are apartment dwelling. Furthermore, cats that live with one or two other cats or with a dog may also be at increased risk.

Dietary Factors

Some published studies have suggested associations between companion animal obesity and diet type, but others have not. In one study, no difference in obesity prevalence was observed between dogs fed commercial food versus those fed a homemade diet. However, the cost of food might play a role, with inexpensive (grocery store) diets more likely to have been fed to obese dogs compared with more expensive foods; in contrast, obese cats are more likely to have been fed a premium food. Although, there have been many anecdotal suggestions that feeding a high carbohydrate diet to cats predisposes to obesity and diabetes mellitus, there is no evidence to support this assertion. In fact, increased dietary fat

rather than carbohydrate predisposes to weight gain in cats. Furthermore, obese cats more commonly have free choice of food intake. For dogs, obesity is correlated with the number of meals and snacks, the feeding of table scraps, and the animal being present when owners prepared or ate their own meal.

Owner Factors and Behavior

The owners of overweight dogs have a lower income than dogs of ideal weight, but this is not the case for cats. Owners of obese dogs also tend to overhumanize them, and this is also the case for cats, where owners often utilize their cat as a substitute for human companionship. Owners of overweight cats also spend less time playing with their pet and reward with food rather than extra play. Owners of both overweight cats and dogs are more likely to be overweight themselves, less interested in preventive health, and to observe their pet more closely during feeding.

Some studies have suggested that there may be behavioral influences on the development of feline obesity, including anxiety, depression, failure to establish normal feeding behavior, and failure to develop control of satiety. The human–animal relationship is also of importance and appears to be more intense in owners of obese cats. Cat owners usually feed their cats two meals per day, even though the wild ancestors of domestic cats are "trickle feeders" and eat many small meals each day. Misinterpretation of feline behavior on the part of the owner is a critical factor in feline obesity, with owners misreading behavior signals with regard to eating. In this respect, domestic cats prefer to eat alone and have no requirement for social interaction during this time. Thus, when a cat initiates contact, this would not normally be for food-related reasons. However, owners often mistakenly believe their cat to be hungry and asking for food; if they give food at this point, the cat will quickly learn that initiating contact results in a food reward. Another misconception is that it is only young cats that need play activity, but this is needed throughout life. Therefore, most cat owners do not bother to play with their cat once it has reached adulthood.

PATHOLOGICAL CONSEQUENCES OF OBESITY

Obesity-Associated Disorders in Humans, Dogs, and Cats

Obesity is known to have a number of significant effects in the dog and cat besides its adverse effects on the human body (Table 26.1), the most notable of which is

TABLE 26.1 Diseases associated with overweight and obesity in humans, dogs, and cats

Disease category	Species		
	Human	**Dog**	**Cat**
Endocrine and lipid	Type II diabetes, metabolic syndrome, dyslipidemias	Hypothyroidism, hyperadrenocorticism, diabetes mellitus, insulin resistance, metabolic syndrome (experimental)	Diabetes mellitus, hepatic lipidosis
Cardiorespiratory	Coronary heart disease, atherosclerosis, hypertension, obstructive sleep apnea, asthma	Tracheal collapse, expiratory airway dysfunction (experimental), hypertension (of doubtful clinical significance), portal vein thrombosis, myocardial hypoxia	
Orthopedic and impaired mobility	Osteoarthritis, musculoskeletal pain, gout	Osteoarthritis, cruciate ligament disease, humeral condylar fractures, intervertebral disc disease, hip dysplasia	Increased lameness
Oncological	Various cancers, including breast (postmenopausal), renal, endometrial, prostatic, esophageal, colonic/rectal, hepatocellular carcinoma	*Variable neoplasia risk:* Transitional cell carcinoma, mammary carcinoma (some but not all studies)	Increased neoplasia risk
Urogenital	Diabetic nephropathy	Urinary tract disease, urethral sphincter mechanism incompetence, calcium oxalate urolithiasis, transitional cell carcinoma, glomerular disease (experimental), dystocia	Increased risk of urinary tract disease
Alimentary	Pancreatitis, hepatic steatosis, cirrhosis	Pancreatitis	Increased oral cavity disease and gastrointestinal disease
Other	Depression, postoperative complications, various dermatologic diseases	Immune function	Increased risk of dermatoses

From German AJ, Ryan VH, German AC, et al. (2010). Obesity, its associated disorders and the role of inflammatory adipokines in companion animals. *Vet J* 185(1):4–9, reprinted with permission.

metabolic syndrome, whereby metabolic and vascular derangements develop that predispose the individual to type II diabetes mellitus and cardiovascular disease. As fat mass increases (especially within the abdomen), so does the severity of insulin resistance and, ultimately type II diabetes mellitus. Given this close association, it is not surprising that the prevalence of type II diabetes mellitus has increased at an equivalent rate to that of obesity. Obesity, through metabolic syndrome, also leads to cardiovascular disease, with an associated increased prevalence of coronary heart disease, atherosclerosis, hypertension, and dyslipidemias in people who are overweight. Most notably, metabolic syndrome is a predictor of a future vascular event and, therefore, its presence should prompt interventions aimed at reducing the risk of such problems.

Other obesity-associated comorbidities include respiratory disorders (especially sleep apnea and asthma), kidney disease (especially diabetic nephropathy), and osteoarthritis. Obesity is now the most important cause of liver disease, given the increased likelihood of affected patients developing steatosis, cirrhosis, and hepatocellular carcinoma. Obesity also increases the risk of certain types of cancer, most notably affecting the breast, prostate, ovary, colon/rectum, kidney, and esophagus.

Obesity-Associated Disorders in Companion Animals

Life Span

In a long-term prospective study, restricting caloric intake (by approximately 25%) in dogs was shown to maintain optimal body condition (BCS 4.5/9 vs. 6.8/9), and extend life span (based on time to euthanasia) by almost 2 years. In the same study, the restricted dogs were less likely to develop hip dysplasia (during growth) and osteoarthritis later in life (especially of the hip and shoulder joint). Finally, these dogs had improved glucose tolerance and lower circulating triglyceride concentrations compared with the *ad libitum* fed and overweight dogs.

Quality-of-Life Effects

In a recent study, health-related quality of life was assessed in obese dogs before and after weight loss. Quality of life was worse than for dogs at optimal weight but improved as a result of successful weight loss. These effects were most notable for "vitality" factors, which improved dramatically, and there was also less evidence of factors indicating chronic pain and emotional derangements. Moreover, the more body fat the dog lost, the greater the improvement in vitality. Dogs that failed to complete their weight loss program had worse quality of life at the outset than those successfully losing weight, most notably worse vitality and greater emotional disturbance.

Orthopedic Disorders

Of all disease associations, the link between obesity and orthopedic disease is most important in dogs. An increased prevalence of a variety of orthopedic disorders has been noted, including cranial cruciate ligament rupture, intervertebral disc disease, humeral condylar fractures, hip dysplasia, and osteoarthritis. Based on force plate analysis, weight reduction in obese dogs with osteoarthritis can lead to a substantial improvement in mobility.

As with dogs, obesity may be a risk factor for feline orthopedic disease. One study suggested that obese cats were five times more likely to be lame than normal condition cats, although not all studies confirm this finding. Further work is required to determine whether obesity truly has a causal effect on feline orthopedic disorders and, if so, what diseases specifically.

Endocrine and Metabolic Diseases

In dogs, associations between obesity and diabetes mellitus, hypothyroidism, and hyperadrenocorticism have been demonstrated; for cats, the only association is with diabetes mellitus. Cats most often suffer from a form of diabetes mellitus resembling human "type II" diabetes, with insulin resistance being a major factor. Successful weight loss improves insulin sensitivity, significantly reducing the requirement for exogenous insulin therapy.

In diabetic dogs, there is progressive beta cell loss and absolute insulin deficiency, meaning that an affected dog will always need lifelong insulin therapy. The pathogenesis of beta cell loss is poorly understood and might not be the same as human type I diabetes. Putative causes include pancreatitis and autoimmune-mediated beta cell destruction. Furthermore, a large-scale epidemiological study in dogs demonstrated an association between obesity and diabetes mellitus. Since obese dogs are also prone to pancreatitis, it might be that concurrence of this condition provides the causal link with diabetes mellitus. However, insulin resistance may also play a role because it is known to occur in experimental models of canine obesity. Indeed, a recent study of naturally occurring obesity in dogs has demonstrated that the percentage of body fat correlates with the degree of insulin resistance, and insulin sensitivity is improved significantly on successful weight loss.

Obesity can have marginal effects on thyroid homeostasis, but the changes are not biologically significant and are unlikely to affect the interpretation of thyroid function tests. In this respect, obese dogs have slightly greater total thyroxine (T4) and triiodothyronine (T3) concentrations than ideal weight dogs, but generally remain within the reference interval, and free T4, thyroid stimulating hormone (TSH), and TSH tests are not significantly different.

Hyperlipidemia and Dyslipidemia

Feline obesity has long been known to predispose to hepatic lipidosis, and epidemiological studies have confirmed this link. Experimental studies in obese dogs have demonstrated mild (but likely clinically insignificant) hypercholesterolemia, hypertriglyceridemia, and increased circulating phospholipid concentrations.

In contrast, experimental studies of canine obesity have demonstrated increased plasma nonesterified fatty acid and triglyceride concentrations (increased very low-density lipoprotein and high-density lipoprotein; decreased high-density lipoprotein cholesterol), which associate with insulin resistance.

Respiratory Function

A number of studies have now demonstrated that excessive body fat can adversely affect respiratory function in dogs, and the same is likely to be true in cats. Such effects are similar to those seen in humans and may help to explain the link between obesity and certain respiratory diseases in dogs, most notably tracheal collapse, laryngeal paralysis, and brachycephalic airway obstruction syndrome. The exact nature of the effects on respiratory function differs depending on the study. In one experimental study, airway resistance was markedly increased during hyperpnea but not when breathing normally. A second study demonstrated that obese dogs had a decreased tidal volume and increased respiratory rate, as well as increased airway reactivity. In a further study, obesity had a significant effect on oxygenation but not on oxygenation indices, being most closely negatively associated with thoracic fat percentage. Finally, in a further study, obesity was shown to negatively affect cardiopulmonary function, as determined by the 6-minute walk test. The human term "Pickwickian syndrome" is sometimes used to describe respiratory impairment in morbidly obese pet animals. This is taken from Charles Dickens' character, Mr. Pickwick, who showed the signs that the syndrome is named after.

Cardiac Function

In dogs, obesity is known to affect cardiac function, as demonstrated by alterations in cardiac rhythm and increases in left ventricular volume; there is no evidence of a similar association in cats. However, overweight cats with heart failure have reduced survival times compared with cats in normal body condition. Mild hypertension does occur in canine obesity, but the effect has not yet been shown to be as clinically significant as in humans.

Finally, obesity in dogs may be associated with portal vein thrombosis and myocardial hypoxia.

Neoplasia

Although epidemiological studies have demonstrated an association between obesity and the presence of neoplasia in both dogs and cats, such a link has not been confirmed in all studies. Other studies have examined associations with specific cancer types and, although not conclusive, links have been suggested with transitional cell carcinoma and mammary carcinoma.

Renal System Function and Disease

In experimental dogs, the onset of obesity is associated with glomerular pathology and changes in function, including increased plasma renin and insulin concentrations, mean arterial pressure, and renal blood flow. In a more recent study, a number of renal biomarkers were assessed in obese dogs with evidence of subclinical decreases in renal function, which improved after weight loss. However, it is unclear as to the significance of these changes and, most importantly, whether or not they may predispose to renal disease, as in humans. Associations have also been demonstrated between obesity and urethral sphincter mechanism incompetence, while obese animals have an increased risk of dystocia.

Other Disorders

Epidemiological studies have demonstrated associations between feline obesity and oral cavity disease, dermatologic disorders, and diarrhea. However, the reasons for such an association are not known.

CLINICAL PRESENTATION

Obesity is typically a disorder that develops insidiously and is most commonly seen in early middle age, with peak prevalence occurring in 6- to 10-year-old dogs and 5- to 11-year-old cats. In both species, prevalence declines in old age and is also less in growing dogs. The disease can be seen in dogs and cats of either sex, and typically (but not always) they are neutered. Any breed may be affected, although there are certain predispositions including Cocker Spaniels, Beagles, Labrador Retrievers, Golden Retrievers, Shetland Sheepdogs, Rottweilers, and mixed-breed dogs.

Clinical signs vary depending on how overweight the dog or cat is and the extent of obesity-associated diseases. Common signs directly attributable to the obesity include lethargy, exercise intolerance, increased respiratory rate and effort, abnormal respiratory tract sounds (e.g., stertor and stridor, often commonly while recumbent or sleeping), and altered gait (typically due to the mechanical effects of excessive truncal and limb fat deposition). Appetite can be variable; while some dogs are polyphagic and scavenging, some owners may report that their dog has a picky appetite and does not eat all of the food in its bowl. The latter is thought to be due to owners providing food vastly in excess of requirements and, often, giving significant numbers of food-based rewards. This means that the dog or cat can still overeat despite not eating everything they are given. Examples of clinical signs include lameness (orthopedic disease), abdominal pain (pancreatitis), vomiting (pancreatitis, hepatic lipidosis), icterus (hepatic lipidosis), polydipsia and polyuria (diabetes mellitus), coughing (respiratory disease), and incontinence (urethral sphincter mechanism incompetence).

On physical examination, altered body shape is always readily apparent, most easily determined using body condition scoring (see ahead given in the text). There may be signs of an associated disease, for instance abdominal pain with pancreatitis or pain on joint manipulation. Poor skin and coat condition is

often present, and cats that are markedly obese often have fecal soiling of the perineum due to inability to groom. In dogs with concurrent hypothyroidism or hyperadrenocorticism, alopecia and other typical skin changes may also be evident. Auscultation and abdominal palpation can be problematic given excess truncal fat deposition, both subcutaneously and within both body cavities. Likewise, while a pulse is usually palpable, it can be more difficult to determine pulse quality due to excess subcutaneous fat in the inguinal region. Thoracic auscultation can be muffled because of intra- and extrathoracic fat deposits.

DIFFERENTIAL DIAGNOSIS

In addition to body fat mass accumulation, other possible reasons for weight gain include changes in hydration status (usually iatrogenic) and intracavitary fluid accumulation (e.g., ascites). In such cases, the weight change is rapid, and other signs are expected. Thus, they can be readily distinguished from weight gain due to obesity. In male cats, gradual weight gain can also arise secondary to acromegaly, although weight gain results from increases in muscle mass, organomegaly, and increased bone mass, in addition to adipose tissue. Therefore, this can usually be distinguished on physical examination; however, this might be counteracted by co-existing diabetes mellitus.

Therefore, if weight gain is gradual, obesity is the most likely cause and the aim of the clinician is to distinguish "simple obesity" (due to energy imbalance) from cases that have arisen secondary to another disease, most notably hyperadrenocorticism or hypothyroidism (dogs). Other than this, possible differential diagnoses relate to the presence of other signs that may have developed secondary to associated diseases. Such lists can sometimes be extensive, given that the signs associated with obesity can be both diverse and nonspecific, and the diagnosis of simple obesity can only be made once other possibilities have been adequately excluded. Therefore, the differential diagnosis list needs to be tailored to the individual case. For example, in cases presenting with respiratory tract signs, consideration should be given to other possibilities that present insidiously in middle age such as upper respiratory tract diseases (e.g., laryngeal paralysis, brachycephalic airway disease), airway diseases (e.g., chronic airway disease), pulmonary disease (e.g., pulmonary neoplasia), and other intrathoracic diseases. In a similar manner, tailored differential diagnosis lists should be created when there are signs of lameness, vomiting, abdominal pain, and incontinence.

DIAGNOSIS

The overall aim is to confirm that the weight gain is the result of increased adipose tissue mass, determine which risk factors are present, and determine whether there is evidence of an underlying cause (e.g., endocrinopathy, iatrogenic weight gain) and whether other concurrent diseases might be present. In addition, the clinician should aim to determine current health status (which will influence how the case is investigated and managed) and quantify the degree of obesity. With regard to health status, it is critical to identify all concurrent diseases, whether or not they are likely to be directly related to the obesity. This will then enable the clinician to determine the most appropriate plan for weight management, determine both the ideal weight and an appropriate target weight, and also to decide on the safest and most effective approach for weight loss. The exact tests that are required in the individual case can then be decided.

History and Physical Examination

The first stage of diagnosis is to obtain a history, including diet history, and perform a physical examination. In addition to a standard medical history (including any prior or current therapy), the history should include details of diet, exercise, environment, the family unit (pets and people), lifestyle, and neuter status. Physical examination should focus on quantifying the obesity and determining the presence of associated diseases that are either causing or contributing to weight gain or presenting as incidental findings.

Body Weight Measurement

The dog or cat should be weighed on electronic scales that, ideally, have been calibrated for precision and accuracy, as well as being serviced regularly (e.g., annually). If test weights are not available, an item of known weight can be used instead (e.g., bag of dry dog food). It is advisable for the practice always to use the same set of electronic weigh scales for weight measurements, since this will minimize errors from readings obtained with different sets of scales. Adopting a practice policy of weighing all animals at every visit throughout life is recommended, combined with regular BCS assessment (see ahead given in the text); given that most cases of obesity develop later in life, there may be a historical record of an early adult weight (i.e., 1 year for cats, 2 years for dogs), where the animal was in ideal condition. This can be used to estimate the ideal weight of the patient (see ahead given in the text).

Clinical Assessment of Body Shape and Composition

Body Condition Scoring

The most widely accepted clinical method of assessing body composition is body condition scoring. BCS schemes assess adipose tissue mass through visual assessment and palpation. Although a number of methods are available, including a modification called the body fat index, the WSAVA Global Nutrition Committee has recently recommended the use of the 9-integer unit system, with an additional assessment for muscle mass

Box 26.1 Calculations for estimating ideal weight in obese cats and dogs

In published studies, each unit on a 9-point BCS scheme approximates to 10% of excess body weight. Therefore, a simple equation can be used to estimate the ideal weight of a dog or cat from current body weight and BCS:

Current weight = 50 kg

↓

Current condition score = 9/9 (~40% overweight)

↓

Ideal weight = 50 kg – (50 × 40/100) = 30 kg

Note: While this is a reasonable guide, due to individual variability, this equation can over- or underestimate ideal weight. If necessary, as weight loss progresses, adjustments to the estimated ideal weight may be needed.

(as + or –) (see Figures 26.2 and 26.3). This ensures consistency among clinicians.

Systems for determining BCS are the simplest indirect measures of body composition currently available. Such systems are repeatable when used by trained individuals and correlate well with body fat mass measured by dual-energy X-ray absorptiometry (DEXA), although owners tend to underestimate the shape of their dogs. BCSs can also be used determine how overweight a patient is, with each point (for a 9-unit system) correlating with ~10%–15% of excess total body weight. This will enable the degree of obesity to be determined and will enable the ideal weight to be estimated (Box 26.1). BCSs should also be used periodically during the weight program to check on progress and adjust target weight if required. However, this should not be done too frequently, as changes in body composition are relatively insensitive with, on average, a 10% change in body weight being required to change scores.

Zoometry

Various zoometric approaches have been described, usually performed with a tape measure. Measurements that correlate with overall "stature" (e.g., head, thorax, and limb length) are combined with measures that correlate with adiposity (e.g., body weight and body [thorax, abdomen, or neck] circumference). Equations are then used to predict body fat mass from these measurements. An early example was the Feline Body Mass Index™ while, more recently, a new zoometric system (Hill's Healthy Weight Protocol) was reported, which used a combination of four (dog) or six (cat) measurements. Both of these systems correlate well with body fat mass measured by DEXA. However, while these may be more objective than traditional BCS assessment, it is arguable as to whether or not they offer any real advantage. In this respect, they are more complicated to perform and require greater patient compliance. In addition, they may be more prone to errors of inaccuracy among investigators (who may measure differently) or to small patients (where minor errors in measurements could have a profound effect). Finally, the accuracy of such measurements decreases as patients become leaner.

Bioimpedance is another noninvasive method potentially applicable to first-opinion practice. However, handheld machines designed for dogs can be unreliable and are inferior to body condition scoring. Finally, photographs can provide a subjective means of demonstrating longer term changes in body weight to clients, thus highlighting success (Figure 26.2a–f). Techniques for indirect body condition assessment from photographs have also been described.

Further Investigations

Routine hematologic examination, clinical biochemistry, and urinalysis can provide general information on health but are not essential in all cases. Such procedures are more commonly performed in older animals or in animals where there are concerns about concurrent disease (based on the historical and physical examination findings). Depending on the case and the judgment of the attending clinician (i.e., if there is a suspicion of an associated disease), additional investigations may be required in some circumstances, with the exact tests required being at the discretion of the clinician. For instance, some cases may require measurement of blood pressure, assessment of thyroid and adrenal gland function in dogs, pancreatic enzyme measurement, fructosamine measurement for diabetes mellitus, survey radiography for possible orthopedic and respiratory disease, abdominal ultrasonography (most commonly to assess pancreas, liver, adrenal glands, kidneys, and lower urinary tract), fine-needle aspiration cytology, and/or liver biopsy (for suspected hepatic lipidosis). Bacterial culture of urine, bladder ultrasonography, and radiographic contrast studies might also be needed for cases presenting with lower urinary tract diseases.

Other Investigations

Advanced Body Composition Measurement

Body composition can be assessed in various ways. DEXA is precise and reliable and has been used extensively in research studies and in referral clinical practice (Figure 26.3a–c). It can help to determine ideal body weight and also be used to monitor progress with weight loss (i.e., determining loss of lean tissue). However, it is a specialist procedure, so is not needed in first-opinion practice where simpler methods suffice. Instead, such procedures should be considered for problem cases where weight loss has been problematic despite instigating a weight management regimen (see ahead given in the text).

Other advanced techniques, which have been validated for use in dogs and cats, include CT and MRI. Such techniques are arguably better at determining regional body fat mass distribution than DEXA.

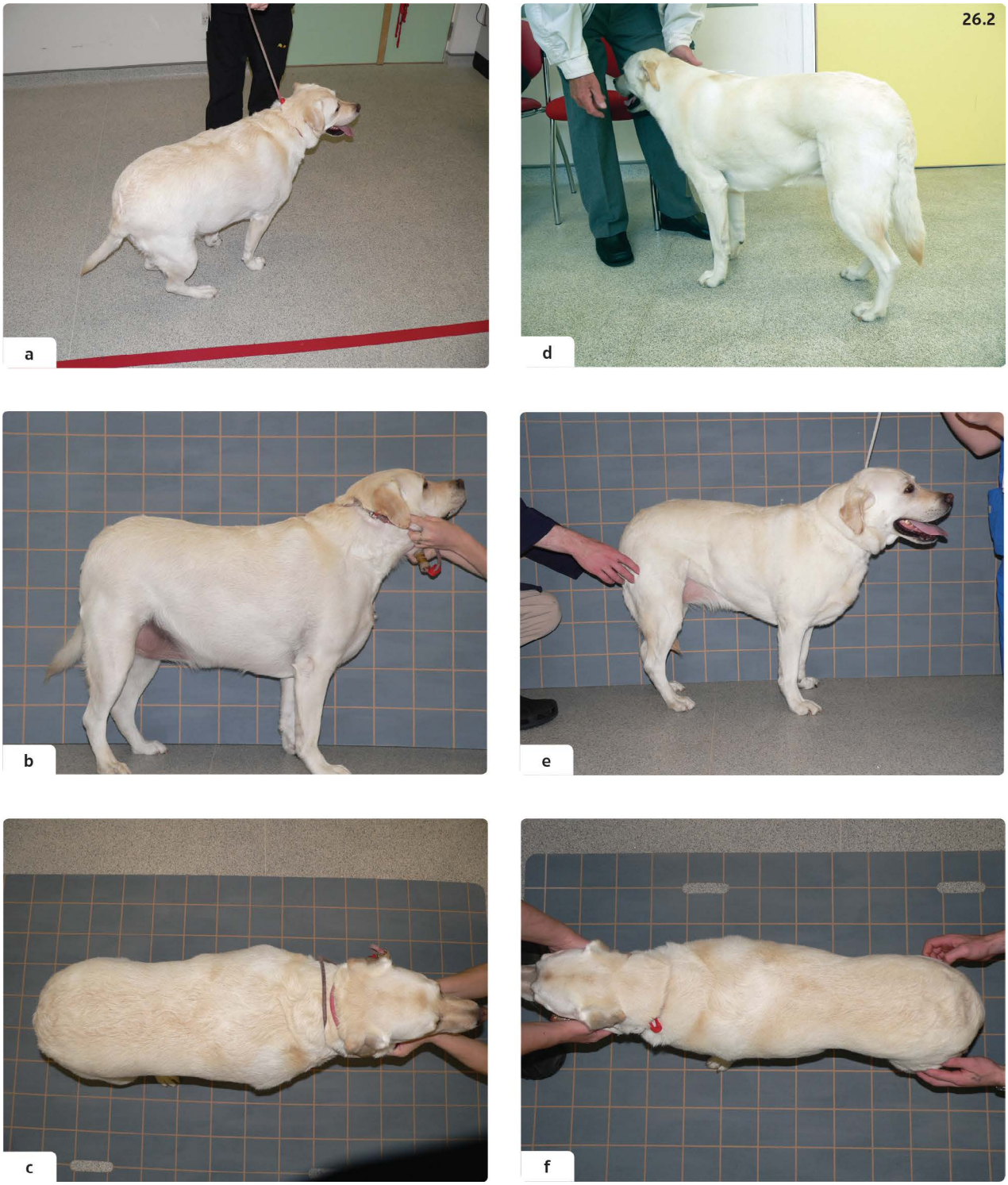


FIGURE 26.2 **(a–c)** Photographs of an obese 5-year-old neutered female Labrador Retriever weighing 49.0 kg (108.0 lb) and with a body condition score of 9/9. **(d–f)** Photographs of the same dog, 268 days later, after successful weight loss on a high-protein, high-fiber diet. Body weight had decreased to 33.6 kg (74.1 lb.), and condition score was 5/9. Total weight lost was 31% of starting body weight, at a rate of 0.8% per week.

However, they are more expensive and again are limited to referral institutions and have limited availability; once again, therefore, they are more appropriate for referral rather than primary care cases. Finally, assessment of total body water (typically using isotope studies) has been used extensively in a research setting for determining body composition in dogs and cats. However, such methods have not yet found a clinical application.

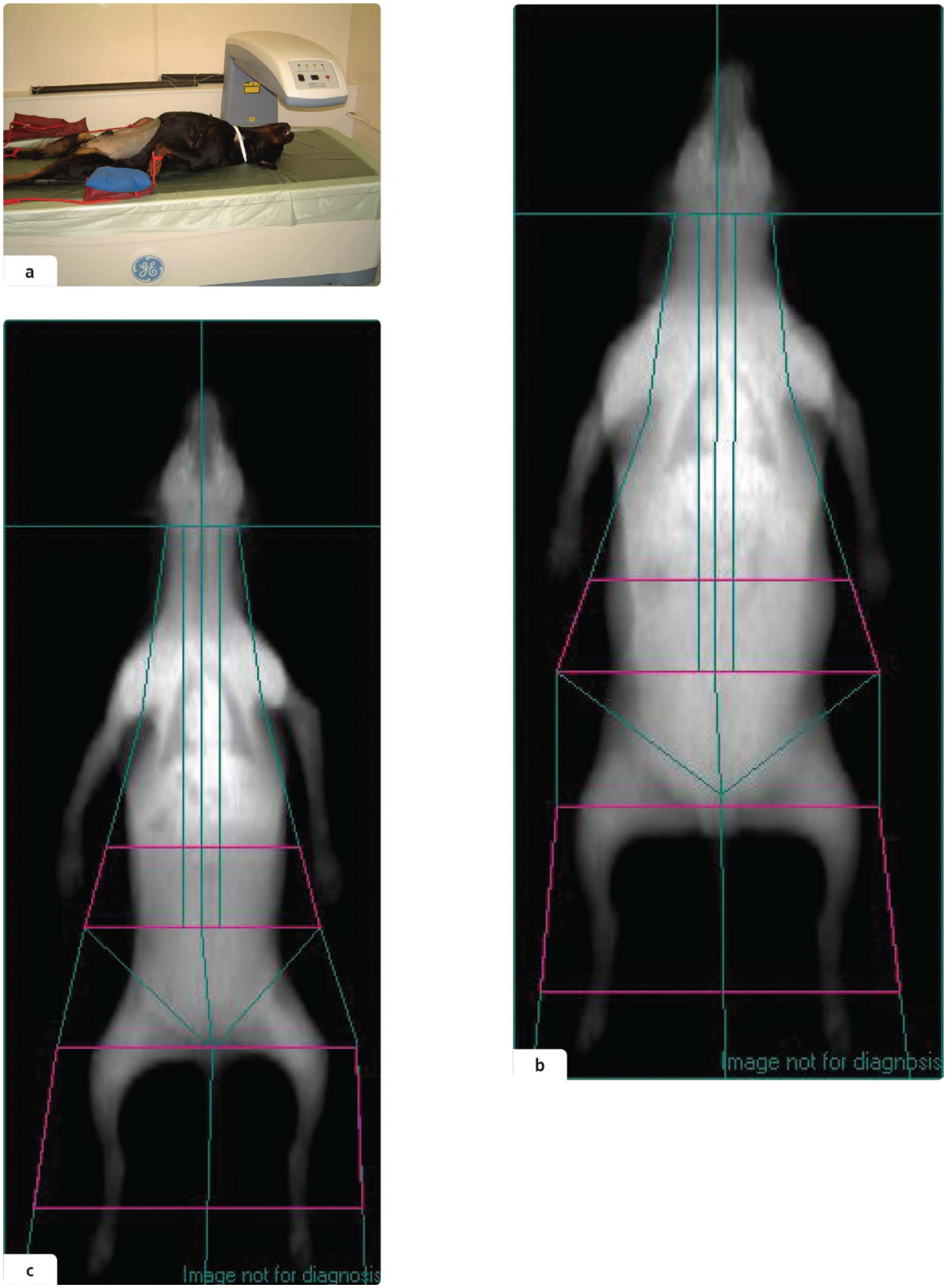


FIGURE 26.3 Dual-energy X-ray absorptiometry (DEXA) as a noninvasive means of determining body composition. **(a)** A fan-beam DEXA machine. **(b)** Image from a pre-weight-loss DEXA scan performed on the dog featured in **Figure 26.2**; body fat mass was estimated to be 51%. **(c)** Post-weight-loss DEXA scan from the dog featured in **Figure 26.2** demonstrating that body fat mass had declined to 36%. Based on the DEXA figures, the estimated composition of the body tissue lost was 83% fat and 17% lean.

Assessment of Metabolizable Energy Requirements and Energy Expenditure

For success in weight management, it is usually necessary to estimate the metabolizable energy requirement to maintain body weight (a.k.a. maintenance energy requirement [MER]). The most common method of determining MER is to use predictive equations, but such equations represent little more than an educated guess and, even in healthy individuals, may miss actual requirement by 50%. Research methods for determining MER include feeding experiments, while methods for determining energy expenditure (EE) (a proxy measure for MER) include indirect calorimetry and tracer studies such as double-labeled water. Arguably, indirect calorimetry is most applicable to the clinic; it has been widely used in human patients including for the determination of EE in the morbidly obese. Indirect calorimetry can provide reliable measurements of EE in healthy dogs, trauma cases, and cancer patients. However, this technique has not yet found a clinical application for obesity management. Portable indirect calorimeters have recently been developed for human patients and, once validated for dogs and cats, might provide a useful tool to help in weight management.

MANAGEMENT

In humans, the most successful approach to achieve weight loss is through bariatric surgery, but this is not likely to be either practical or ethically justifiable in companion animals. Dietary therapy is the most widely accepted method of weight management, although drug therapy (using microsomal membrane transfer protein [MTP] inhibitors) is also approved for the weight loss phase in dogs but not cats. The weight loss phase can be variable in length but is typically 6–18 months and occasionally prolonged (i.e., over 2 years).

Weight management in cats and dogs involves two stages: The weight loss phase whereby there is steady fat mass loss, and weight maintenance, which involves stabilizing body weight and preventing rebound. The fundamental aims of weight management are to improve quality of life and reduce associated disease risk. In so doing, you aim to change the relationship between pet and owner to one that promotes a healthy lifestyle. Thus, the amount of weight loss that you recommend and the target weight can vary. Unless the habits of the owner change for the long term, the management will fail, and weight regain will occur.

Target Weight, Ideal Weight, and Tailoring the Individual Plan

In setting a weight loss plan, it is essential to know the ideal weight, since this will be used to set the initial caloric intake (see ahead given in the text). The ideal weight is defined as the weight at which fat mass is optimal for that animal. In reality, there will be a range of weights that are deemed to be ideal, rather than a single weight (typically body fat <20% for domestic cats and <35% for dogs). If a historic weight measurement is available (e.g., an early adult weight), where the animal was in optimal condition, that weight corresponds to the animal's ideal. If such a weight is not available, an alternative approach is to determine ideal weight from the current weight and BCS. In this regard, each unit on the scale between 5/9 and 9/9 approximately corresponds to 10%–15% of excess weight. Therefore, with a simple calculation, the ideal weight can be calculated (see **Box 26.1**).

Although often used interchangeably, the terms target weight and ideal weight are not the same. The target weight is defined as the weight that the clinician determines to be an appropriate endpoint for weight loss. For some animals, the target weight and ideal weight may be equivalent, while for others target weight is greater. The main benefits of aiming for ideal weight (as your target) is that the greatest beneficial effects on disease prevention and life span extension might be expected. Such an approach would be most beneficial for young animals with a long-expected life span and free from concurrent disease. However, such benefits diminish in older cats and dogs, where remaining life span is shorter and concurrent diseases may already exist. Instead, weight management should focus on improving quality of life, and it may not be necessary to achieve ideal weight to achieve this. In fact, a study in dogs has revealed that reductions in severity of disease typically occur with modest (i.e., >5%) reductions in weight. Therefore, aiming for partial weight loss would be more realistic, quicker, and, arguably, more appropriate in older animals, especially those with concurrent disease. In humans, an "obesity paradox" has been identified. In this respect, being overweight increases the risk of developing certain diseases, but once that disease develops, increased BMI can improve survival. Examples of a similar obesity paradox have also been seen in animals with chronic kidney disease and cardiac disease, with a recent study demonstrating longer survival times in overweight cats. In such cases, only a modest weight reduction (of 5%–10%) would be recommended but aiming to maintain the patient within its overweight range. Such a weight loss protocol will not lead to significant loss of lean tissue but can improve quality of life.

Expected Rate of Weight Loss

The recommended rate of weight loss is controversial, since initial recommendations of 1%–2% per week were based on obese dogs managed in a colony setting, and not client-owned dogs. While such rates can be achieved early in the weight loss process (i.e., first 1–2 months), it becomes increasingly difficult to maintain this over the long term. Instead, an average rate of weight loss of 0.5%–1.0% per week is more realistic and appears to be safe. Overly rapid rates of weight loss (>2% per week) are not recommended since there is a potential to cause problems (e.g., excessive lean tissue loss or hepatic lipidosis [cats only]). However, in reality such rates are rare.

Slower rates of weight loss (<0.5% per week) might be acceptable, although the whole process will likely take longer and might be a source of owner frustration.

Dietary Management

Diet Formulation

Purpose-formulated weight loss diets are recommended because energy content is reduced. This helps to promote weight loss because rate is principally determined by energy intake. Weight loss diets are also supplemented with protein (amino acids) and micronutrients, relative to their energy content, and this ensures that deficiency states do not arise despite energy restriction. A recent study has demonstrated that, despite often marked energy restriction, nutrient deficiencies are not observed. While supplementing protein, relative to energy content, does not speed up the rate of weight loss, it ensures that lean tissue loss is minimized, and also has beneficial effects on satiety (see ahead given in the text). L-carnitine facilitates transport of fatty acids in mitochondria, assisting their oxidation, and supplementation in a weight loss diet also assists with maintaining lean tissue mass during weight loss, while supplementation of micronutrients, relative to energy content, ensures that deficiency states do not arise.

Altering the macronutrient content of a weight management diet can also improve satiety, and the most common approach is to supplement fiber content. However, in dogs, supplementing both protein and fiber provides an additive benefit, and such diets improve the outcome of weight loss by speeding up the overall rate, increasing the likelihood of reaching target weight, and preserving lean tissue. The situation is more complex for cats, since protein content is a key determinant of voluntary food intake and incorporating more can increase rather than decrease voluntary food intake. Furthermore, incorporating too much fiber can make the diet unpalatable. Therefore, for cats, the greatest effect on satiety occurs when fiber and protein are both moderately, rather than markedly, supplemented.

Energy Intake during Weight Loss

There are various approaches to calculating the energy intake required for controlled weight loss. Some clinicians recommend first calculating resting energy requirements for the current body weight (i.e., for dogs: 70 kcals × body weight 0.75/day), and then feeding 80% of this amount. While this has the benefits of simplicity, it does not take into account the degree of excess body weight and the initial response may be more variable. Adjustments may be required in the early weeks to determine the correct energy intake for the individual case.

The author prefers an approach whereby energy intake is, instead, based on ideal body weight and not the current weight. Arguably, this approach enables the clinician to produce a more precise starting point for the energy intake required for weight loss because the magnitude of excess weight is better factored in. Ideal weight can be estimated in various ways (see mentioned in the text earlier). Exact recommendations on energy intake are then varied depending on the species, gender, neuter status, and presence of co-existing (especially orthopedic) disease. In dogs, a recent study suggested that a typical starting allocation for weight loss should be approximately 60 kcal/kg metabolic body weight (MBW) at target weight 0.75, with neutered dogs requiring less energy than entire dogs and female dogs less than male dogs. However, while this initial allocation might be sufficient during the first few weeks of the weight loss program, energy intake often needs subsequently to be modified, as and when weight loss slows. Typically, small adjustments (of up to 5%) are made on each occasion. Indeed, in the canine study described earlier, mean energy intake over the entire weight loss period was 57 kcal/kg MBW at target weight.

Calculating energy intake for weight loss is simpler in cats, where a linear equation is suitable. In one study, an average starting allocation of 40 kcal/kg target weight was successful in most cats, with mean energy intake over the whole of weight loss being 32 kcal/kg. With this degree of restriction, the mean rate of weight loss is 0.8% body weight per week.

Whatever the method of determining food intake, precision in portioning is absolutely critical in order to ensure success. Use of measuring cups should be avoided since portion sizes are imprecise and variable (usually being overestimated). Instead, electronic kitchen scales to weigh out food portions are strongly recommended. If at all possible, owners should not give any additional food (e.g., table scraps or treats) and care should be taken to prevent the patient from scavenging. If desired, food can be given in two, or more, meals per day, preferably providing more food at times when the owner is with the pet (since this is when begging is most likely to occur). However, use of an interactive feeding device is preferred (e.g., puzzle feeding toy or modified feeding bowl). These devices have the effect of slowing food intake, thereby improving satiety.

Occasional treats may be sanctioned (preferably some of the weight management food or a dog treat of known caloric content [e.g., dental treat]), but it is essential to take them into account so that they are included in the overall allocation and provide <5% of total daily requirements.

Pharmaceutical Therapy and Weight Loss

Two drugs have been licensed for use in dogs (but NOT cats): Mitratapide and dirlotapide. Although they have now been available for a number of years, and there is reasonable evidence of efficacy, they have not been used widely in a clinical setting. Both of these drugs are MTP inhibitors and have a local effect on the intestinal epithelial cell, blocking the assembly and release of lipoprotein particles into the bloodstream. Dietary caloric intake is decreased both by decreasing lipid absorption and by decreasing appetite (the latter thought to be due to release of a satiety signal that acts centrally on the appetite center). The efficacy of these drugs declines if they are administered in conjunction with a low-fat

(<10%) diet. In Europe, both mitratapide and dirlotapide are licensed, but only dirlotapide is licensed in North America.

Mitratapide is only licensed for short-term use (i.e., 8 weeks) and was designed to kick-start a conventional weight loss program. In contrast, dirlotapide is licensed for continuous use for up to 12 months, which is sufficient for many, but not all, weight loss programs. Weight loss occurs at a steady rate (0.75% per week on average), but periodic increases in dose are required to maintain weight loss.

The most common side effects are vomiting and diarrhea, and these are observed in up to 20% of patients. If owners are forewarned that it may occur, then it is usually better tolerated. Anorexia can also occur. While these drugs can be successful in promoting weight loss, appetite returns rapidly when they are discontinued, and so other strategies (feeding and behavioral) must also be implemented to be successful. Without this, a rapid and predictable rebound occurs.

Lifestyle Management

Increasing physical activity is also recommended for most affected animals since it can assist in lean tissue preservation and, possibly, help to prevent the rapid regain in weight that can occur after a period of successful weight loss. It is also rewarding for owners since it represents an alternative to giving food-based rewards. Suitable exercise strategies in dogs include lead walking, swimming, hydrotherapy, and treadmills. Cats can be encouraged to increase their activity through regular play sessions with cat toys (e.g., fishing rod toys), motorized units, and puzzle feeders (see mentioned in the text earlier). Ideally, daily exercise should be taken and, for dogs, 30 minutes or more is preferred. For cats, short periods of play activity are used, typically 1–2 minutes at a time two or more times per day. The exercise program should be tailored to the individual and take account of any concurrent medical concerns.

Monitoring Weight Loss

Regular weight checks should be scheduled during weight loss. At the start of the program, it is best to book reweigh sessions at 2-week intervals, since this is the time when the owner is becoming accustomed to dramatic changes in lifestyle, and adjustments to the plan may be required if weight loss is progressing too quickly or too slowly. Thereafter, in patients where weight loss is progressing steadily, the interval between checks can be increased, but should not, ideally, exceed 4 weeks. More frequent checks may be needed in cases where weight loss is slow or stalls regularly. It is usually best if a dedicated member of staff takes charge of weight management. That way, they can get to know the client, and build up a trusting relationship, improving the likelihood of success. Given that some clients require intensive support throughout the program, it is advisable for staff to be trained in owner counseling.

Once the target weight is reached, food intake is increased gradually (typically in increments of up to 5%), until body weight stabilizes. Thereafter, weight checks should continue but the frequency can be gradually decreased. It is essential to continue to monitor body weight after ideal weight has been achieved to ensure that weight that was lost is not regained. Weight regain is a recognized phenomenon in humans who diet, although the reasons are still unclear. The most likely explanation is that when obese humans are returned to a lean state, their resting metabolic rate slows. Studies in dogs have also demonstrated a tendency for weight regain, although it affects fewer patients and rarely do dogs regain all the weight lost. Other studies have demonstrated that, as in humans, the MER is less after weight loss. In a recent study examining follow-up after successful weight loss, almost half of the dogs regained weight. Critically, when the diet was switched from the purpose-formulated weight management diet to a different diet (typically a standard maintenance diet), dogs were 20 times more likely to regain weight. Thus, owners should be strongly recommended to continue to feed the weight management diet, albeit to maintain weight rather than achieve further weight loss. In a similar study in cats, weight regain was again identified, and the problem was of a similar magnitude to dogs. However, the most notable factor associated with weight regain was age, with younger cats (<9 years of age) more likely to rebound.

PROGNOSIS

When an animal is predisposed to obesity, both through individual and environmental factors, many of these predispositions will remain after weight loss. Further, the post-weight loss MER is significantly less than it was prior to weight loss. For these reasons, obesity can only be managed and never cured, and the prognosis for long-term success is guarded. In the author's experience, most (80%–90%) cats and dogs lose at least 10% of weight on a program, with approximately two-thirds reaching their target weight. Recent work by the author has identified that initial body fat mass is negatively associated with the likelihood of reaching the target weight. Furthermore, dogs fed a dry weight management diet were more likely to succeed than those fed either wet food or a combination of wet and dry food. The remaining dogs and cats fail to lose significant weight and are commonly lost to follow-up. Owners of these animals often decide not to return to the clinic and become noncontactable. Thus, the exact reasons for discontinuing the program are difficult to determine.

PREVENTION

Given the variable outcome of weight management diets, prevention of obesity is likely to have a more significant beneficial effect on the health and welfare of all dogs and cats, rather than by treating once the problem

has developed. Advice on correct nutrition and exercise should be included in all puppy and kitten consultations and continued throughout the life of the animal. Body weight and BCS should be assessed at every consultation and also during the annual health check. Regularly monitoring body weight and BCS throughout life can enable subtle changes (e.g., ±5%) to be identified and rectified before the problem worsens. Veterinarians should also be alert to the weight gain that can occur as a consequence of neutering. It is advisable to schedule 2–3 checks for weight and BCS in the first 6–12 months after neutering to identify those patients that gain excessive amounts of weight at this time.

Finally, knowledge of pet ownership styles could ultimately be used to help in obesity prevention. If certain ownership styles were known to predispose to weight gain and obesity, then targeted owner education could be applied to owners with such styles. A recent study has identified that different populations of cat exist that respond differently to long-term *ad libitum* feeding. Some cats are unable to regulate their food intake, leading to gradual lifelong weight gain, while others maintain stable weight and optimal body condition lifelong, presumably by regulating intake. Therefore, this work suggests that different groups of cats have different feeding styles; some are regulators, while others tend to overeat. When it comes to preventing weight gain, attention should be paid to matching pet ownership style to feeding style. For example, an owner with an indulgent feeding style would be a bad match for a cat that overeats but is likely to be fine if they were to own a cat that self-regulates intake.

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