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To Jeff, Rance, and Ethan, in grateful appreciation of all they have done to support and encourage us in this and every endeavor of our lives.
Preface

It is impossible to practice equine medicine and surgery without confronting the many faces of infectious disease and its impact on the health and well-being of our patients. Although this statement has been true since the earliest days of veterinary practice, the past few decades have seen an exponential increase in the rapidity of spread of infectious diseases in horses around the globe. This is nowhere more clearly explained than in the chapter on Infectious Diseases and the International Movement of Horses by Dr. Peter J. Timoney, one of the premier equine infectious disease experts of our generation and current director of the Gluck Equine Research Center at the University of Kentucky in Lexington, Kentucky. With the increasing globalization of the equine industry and changing political realities of the world, equine veterinarians are finding themselves on the frontlines in an escalating battle against pathogens that have the potential to profoundly affect the health of our patients and the equine industry as a whole.

The germ of the idea for this book first infected our minds very early in our lives. We were eyewitnesses to the devastation of a brucellosis outbreak at a boarding facility at which horses were freely co-mingled with cattle. As young veterinarians it was difficult to understand the necessity for euthanasia of outwardly healthy horses to safeguard the health and well-being of the majority of the animals on the farm. As veterinarians, we have seen others go through the same struggle as apparently healthy horses were euthanized because of a positive Coggins test. We have watched the economic hardships that ensue when a boarding stable or training establishment must be quarantined because of a disease outbreak. We have watched the struggles of large breeding farms that lose horses to strangles year after year despite impeccable management strategies and state-of-the-art vaccination schemes. In each of these professional situations we sought to find answers regarding the disease, its pathogenesis, and its control. However, answers were scattered in bits and pieces throughout the veterinary literature, making it nearly impossible for practitioners without access to state-of-the-art computer databases and with limited time for research to find those answers.

At some point, we became aware of an incredible text titled Infectious Diseases of the Dog and Cat. This beautiful text, edited by Dr. Craig Greene of the University of Georgia, summarizes current knowledge related to almost every infectious disease of dogs and cats. It describes the etiologic agent, outlines the important aspects of pathogenesis, presents the advantages and disadvantages of available diagnostic and therapeutic choices, and even explains the public health implications of each disease. This book clarified in our minds exactly what was needed for equine practitioners, infectious disease experts, and other individuals interested in equine health care. We extend our grateful appreciation to Dr. Greene and acknowledge the critical inspiration and many ways his book has shaped this text. Our goal is to provide anyone interested in equine health with a single source summary of the important aspects of equine infectious diseases that occur worldwide. The extensive references to the primary veterinary literature that are included on the accompanying CD-ROM will serve as a springboard to an even deeper understanding of the research manuscripts and clinical reports that have been the source for information contained in each chapter. A direct link to PubMed citations will enable users of the CD-ROM to click and access scientific abstracts of most references so that more extensive research is facilitated as needed by each reader.

ACKNOWLEDGMENTS

Without the input and hard work of innumerable individuals, this book would never have been completed. We thank each and every author who worked hard to provide us with just the type of information that was needed for this book and for being patient with the sometimes extensive editorial changes that we requested. We hope that each author is as proud to be associated with this book as we are.

We thank all the clinicians, researchers, and microbiologists who unselfishly shared photographs and images. Inclusion of the many illustrations truly makes this a unique veterinary text.

The staff at Elsevier—especially Jolynn Gower, Liz Fathman, and Anne Altepeter—have been extremely supportive and never wavered in their commitment to this project, even as it became apparent that we were going to be many, many pages over the initial estimate!

We hope that this book will be of value and service to the equine veterinarians and students whom we serve. If, in reading this text, each of you learns just a small fraction of the amount that we learned in the writing and editing, then our purpose will have been served.

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SECTION • 1

Clinical Problems

CHAPTER • 1

Respiratory Infections

EQUINE RESPIRATORY TRACT

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Normal Respiratory Flora

Bacterial flora plays an important role in host health in a variety of tissues and organ systems, such as the skin, gastrointestinal tract, and urogenital system, as well as the respiratory system.1 The upper airway of healthy horses contains many bacteria, including a variety of aerobic and anaerobic species. This flora competes with pathogenic species that, when present in large numbers, can colonize the epithelial surface. Normal equine respiratory flora includes Streptococcus equi subsp. zooepidemicus, Pasteurella spp., Escherichia coli, Actinomyces spp., and Streptococcus spp. Anaerobes predominate in the normal equine oral cavity and consist of several bacterial genera, including Bacteroides fragilis, Fusobacterium spp., Eubacterium spp., Clostridium spp., Veillonella spp., and Megaspheara spp.2

Typically, horses with infectious lower airway disease are infected with one of these bacteria, consistent with the concept that contamination of the lower respiratory tract originates from the upper airways. Aspiration can be the mechanism by which such contamination occurs, because head elevation and long-distance transport contribute to lower airway contamination and accumulation of mucus.3 Contamination of the lower airway is common in apparently healthy horses, and many horses will have positive bacterial cultures when examined by tracheobronchial aspiration.

Pulmonary Defense Mechanisms

Endogenous pulmonary defense includes components of nonspecific and specific clearance mechanisms. Components of nonspecific clearance include anatomic barriers, mucosal lining, mucous secretions, and the mucociliary escalator. These nonspecific mechanisms are distinguished from specific immune effector molecules because they lack specificity and memory.

A major mediator of nonspecific clearance of debris and pathogens from the respiratory tract is the mucociliary escalator. The mucociliary escalator consists of a double layer of mucus that extends from the pharynx to the respiratory bronchioles. This mucus layer is propelled upward by the ciliated respiratory epithelium. Inhaled particles and debris are propelled in a proximal direction by a constant wave of upward movement by the cilia and mucus. The mucociliary system can become damaged by smoke inhalation and direct viral destruction.4,5

Influenza and herpesviruses replicate within and destroy ciliated epithelium, which requires approximately 21 days for regeneration. In addition, environment may play a role in clearance mechanisms because high ammonia concentration, such as that associated with a high degree of urine and fecal waste, will result in depressed ciliary motility.6,7 Dehydration may also contribute to reduced pulmonary clearance because effective ciliary movement will be depressed with reduced fluidity of the mucous layer.

The major mediators of specific pulmonary clearance mechanisms are within the bronchi-associated lymphoid tissue (BALT). BALT exists within the submucosa of the segmental bronchi and terminal bronchioles. As with other lymphoid organs, BALT is an area where antigen-specific responses stimulate cell-mediated and humoral immune defense. B lymphocytes within BALT can switch to all classes of antibodies, although the predominant antibody produced in the upper respiratory tract is immunoglobulin A (IgA). Immunoglobulin G (IgG) is secreted in greater quantities in the lower airways.8 The advantage of upper respiratory secretion of IgA is the blockage of adherence of pathogens to the upper respiratory tract epithelium, a process referred to as immune exclusion. Memory is conferred by this arm of the immune system and thereby results in long-term protection from infectious disease.

The goal of immunization against pathogens is to produce high concentrations of antigen-specific responses that will confer resistance at the site of infectious challenge. A disadvantage of many intramuscular vaccines is that high levels of IgG are induced in circulation, with minimal levels of IgA produced at the mucosal surface. The intention of intranasally delivered vaccines is to induce local IgA production. The IgG production becomes essential when pathogens gain access to the lower airways. This antibody isotype is critical for opsonization and removal of bacteria and foreign material. Effective opsonization will result in effective phagocytosis and removal from the lower airways and pulmonary parenchyma. Some pathogens (e.g., herpesviruses) are capable of surviving and replicating within BALT, resulting in necrosis of lymphoid nodules. This contributes to a postviral state of immunocompromise in which the patient is susceptible to infection with secondary pathogens.

Below the level of the mucociliary escalator and the BALT, cellular responses are critical for immune protection of the equine host. The first phagocyte of importance is the alveolar macrophage, located in the terminal bronchioles and alveoli. The alveolar macrophage provides a bridge between innate and adaptive immune responses. Although these cells can ingest foreign material nonspecifically, they also serve as important antigen-presenting cells for T lymphocytes and development of adaptive immunity. Particles that are inhaled and reach the alveolar spaces are removed by local alveolar macrophages. Once they contain foreign material, these cells may be coughed up and swallowed, or they may move from the alveolar space and enter general circulation for ultimate clearance by the lymphatic system. The function of these cells
depends on host status, long-distance transport or viral infection will destroy alveolar macrophages.\textsuperscript{12}

Another important cell in the pulmonary system of horses is the pulmonary intravascular macrophage (PIM). These cells are important for removal of particulate matter (e.g., bacteria, toxins) from general circulation. Species that have PIMs include horses, pigs, ruminants, and cats. Mammalian species that do not have PIMs utilize hepatic Kupffer's cells and splenic macrophages for similar purposes. PIMs are critical for removal of bacteria or endotoxin on the first pass through the lung, but they contribute to the inflammation induced after bacterial challenge.\textsuperscript{13} Disadvantages of PIMs include the resultant inflammatory reaction that follows their activation. For example, phagocytosis of endotoxin is associated with pronounced inflammatory mediator release, microthrombus formation, neutrophilic influx, vasoconstriction, pulmonary edema, and endothelial damage that may lead to other systemic disorders. Species variation in sensitivity to endotoxin relates to the presence of PIMs, and intensified sensitivity to endotoxin is related to the number of PIMs in the pulmonary vasculature.

Epithelial protection of the respiratory tracts is provided not only by the mucosal lining and leukocytes within the submucosa, but also by mechanisms of the innate immune system. Antimicrobial peptides play an important role in innate immune protection in the pulmonary system of many species. Cathelicidin peptides have been identified in pulmonary equine neutrophils collected from heaves-affected individuals.\textsuperscript{14} This class of antimicrobial peptide has been shown to play a role in pathogen clearance, having broad-spectrum activity against bacterial pathogens.\textsuperscript{15} Other similar peptides are expressed in epithelial cells as well as within leukocyte subsets.\textsuperscript{16,17}

Anatomic and Physiologic Considerations
The horse is an \textit{obligate} nasal airway breather, which means that even under strenuous exercise, no air is obtained through the oral cavity or oropharynx. This consideration impacts the pathogenesis of equine infectious disease in two ways. First, contamination of the nasopharynx (and subsequently the lower airway) by bacteria within the oral cavity and oropharynx likely comes from prolonged changes in head placement (e.g., transport), fatigue of the pharynx of the horse (e.g., intense exercise), or changes in the local immunity of the nasopharynx (e.g., viral infection). Second, any change in the upper airway results in an immediate decrease in the exercise capacity of the horse. Thus any inflammatory condition, even as "innocuous" as lymphoid hyperplasia, may have a profound impact on performance and health of the lower respiratory tract.

The equine airway has a \textit{monopodial} branching pattern, meaning that each branch gives rise to daughter branches. The respiratory tree is lined by mucous membrane and supported by lamina propria with cartilage and smooth muscle, depending on site. Ciliated cells and goblet cells (which produce mucus) line the bronchioles. The secretory cells change to Clara cells in the bronchioles. The alveoli are lined by a single layer of epithelial cells consisting of type I and type II pneumocytes. These cells are supported by a thin interstitium and a small amount of smooth muscle at each opening.

CLINICAL FINDINGS ASSOCIATED WITH INFECTIOUS RESPIRATORY DISEASE

In general, proper diagnosis of infectious respiratory disease depends on information gleaned from the history and physical examination, identification of abnormalities (problem list), and development of a diagnostic plan. Age and signalment and recent exposure to new arrivals may indicate viral respiratory disease. Long-distance travel before onset of respiratory signs indicates a horse is at high risk for pleuropneumonia. \textit{Rhodococcus equi} occurs primarily in foals between 3 and 5 months of age.

Clinical signs of infectious respiratory disease may initially be nonspecific, including fever, depression, and possible anorexia. Signs referable to the respiratory system may include nasal discharge, cough, and tachypnea. Either upper or lower respiratory disease can cause these clinical signs. Respiratory stridor (usually upper respiratory tract disease) and respiratory distress (upper or lower respiratory tract disease) may also be present. Other nonspecific signs include epistaxis and cyanosis. With either acute viral infection or chronic lower airway disease, exercise intolerance is a feature. Weight loss may occur with chronic respiratory infection.

Physical examination should be thorough and include examination of all body systems. Normal respiratory rate of foals is between 20 and 40 breaths/min and in adults is between 12 and 24 breaths/min. Breathing should be slow and deliberate with no nostril flare. Auscultation of horses can be difficult because of the normally slow rate and character of breathing. Depth of breathing can be increased by performing a rebreathing examination with a plastic bag placed over the nose of the horse. Normal horses generally do not cough when encouraged to take a deep breath with rebreathing. Normal horses do not cough when the trachea is palpated. Concomitant percussion during auscultation may indicate a fluid line.

DIAGNOSTIC APPROACH TO INFECTIOUS RESPIRATORY DISEASE

Endoscopy may be used to confirm the presence of upper airway disease and to perform diagnostic tests such as trans-tracheal aspirate (TTA) or bronchoalveolar lavage (BAL). Diagnosis of rhinitis, pharyngeal lymphoid hyperplasia, gullett pouch disease, and retropharyngeal lymphadenopathy (presumably from \textit{Streptococcus equi} subsp. \textit{equi} infection; Fig. 1-1) may be facilitated by endoscopic examination. Radiographs of the sinuses are essential for identification of fluid or masses within sinuses, gullett pouches, and thorax. Diagnostic-quality thoracic radiography is difficult with most field equipment. Lower airway radiography is important for determining the type of pattern present but is not specific for

Fig. 1-1 Endoscopic view of upper airway of horse with severe pharyngeal compression associated with \textit{Streptococcus equi} subsp. \textit{equi} infection.
identification of any particular etiologic agents. Thoracic ultrasound is easily performed in the field, and although nonspecific for etiology, it is particularly useful to detect lower airway disease, including consolidation of the peripheral lung lobes and identification of pulmonary fluid. A 5.0-MHz linear probe (used for most rectal ultrasound examinations) will suffice for the majority of these examinations.

Ancillary diagnostic testing is critical for correct etiologic identification of potentially contagious pathogens. Nasopharyngeal or nasal passage swabs are particularly useful for diagnosis of viral respiratory tract disease. Polyester-tipped swabs are preferred because viruses may adhere to cotton fibers, decreasing the likelihood of isolating virus from the sample. The swabs should be placed in sterile viral transport medium and kept on ice until further analysis. Maintaining moisture with physiologic saline is an alternative for very-short-term transport. Swabs for viral isolation need to be only of standard length (6 inches); the only requirement is contact with the nasal mucosa. Viral swabs may be analyzed in three ways: viral culture, polymerase chain reaction (PCR), and antigen enzyme-linked immunosorbent assay (ELISA). Virus isolation and paired serum titers can be obtained to confirm the diagnosis of specific viral infections. Clinical signs of disease, local population, history, and vaccination status will influence the likelihood of viral infection.

Diagnosis of equine influenza is based on virus isolation, virus antigen detection, and paired serum testing (see Chapter 12). An ELISA test is commercially available for the detection of influenza virus particles in nasal secretions (Directigen FLU-A, BD Diagnostic Systems, Franklin Lakes, NJ). This potential real-time test was not designed for equine use but has been validated for use in this species.

Diagnosis of infection with equine herpesvirus (EHV)-1 and EHV-4 depends somewhat on disease manifestation (see Chapter 13). For example, diagnosis of infectious respiratory disease may be confirmed by PCR or culture of nasal swab samples (or Buffy coat samples) or detection of increasing serum antibody titers to the virus. Virus isolation from a Buffy coat smear may allow swab, lung, and other tissues may provide improved diagnostic information. Additional diagnostic tests that may be considered include molecular characterization using the restriction endonuclease analysis of deoxyribonucleic acid (DNA) fragments. Cerebrospinal fluid (CSF) analysis should be performed in horses suspected of EHV myelopathy, often characterized by xanthochromia and albuminocytologic dissociation. Antibody titer analysis of CSF is of limited value for diagnosis of neurologic EHV disease because significant disruption of the blood-brain barrier has frequently occurred in affected horses.

Diagnosis of EHV-2 may be challenging because virus isolation does not provide consistently positive results. Paired serologic titers may provide suggestive information for establishing a diagnosis of upper respiratory disease in horses. PCR has also been used for diagnosis in horses.10

Definitive diagnosis of equine viral arteritis (EVA) infection is made on the basis of virus isolation from nasopharyngeal, vaginal or semen samples (see Chapter 14). PCR testing has improved sensitivity and specificity for detection of the virus in these samples. Acute and convalescent serum titers may provide additional information to facilitate confirmation of the EVA diagnosis in suspect cases. Gross examination of fetuses postmortem typically reveals edema, pleural effusion, and petechiation.

Equine rhinoviruses, such as equine rhinitis A virus (ERAV), are a cause of upper respiratory tract infection in horses (see Chapter 16). These infections are more challenging to diagnose than other viral respiratory tract infections because seroprevalence can be high.20 Of 28 cases where the rhinovirus was isolated from infected horses only six showed serologic evidence of viral exposure.21 Therefore, when equine rhininitis B virus (ERBV) infection is a diagnostic differential, virus isolation is the preferred diagnostic test. Although a third rhinovirus, ERBV3, has been investigated as a possible etiologic agent of equine viral tracheitis disease, its role remains unconfirmed.22

Culture of nasopharyngeal swabs or wash samples are useful for diagnosis of Streptococcus equi subs. equi (strangles) infection in horses (see Chapter 28). Detection of S. equi DNA using the PCR test is also confirmatory for a respiratory infection secondary to S. equi infection. Carrier horses may be challenging to identify without endoscopic evaluation that includes examination of the gullet pouches. Culture and PCR of samples obtained from the gullet pouch of these horses are recommended. If both tests are negative, the horse is unlikely to be an S. equi carrier. PCR testing for S. equi is more sensitive than standard microbiologic culture techniques.35

SeroLOGY for diagnosis of equine respiratory viral infections must be performed on paired sera obtained at least 2 to 4 weeks apart. A single paired serum titer is nondiagnostic and a waste of laboratory time and owner resources. Whenever possible, paired sera testing should be pursued and can be extremely useful if the index case is no longer shedding virus and for assessment of herd exposure. For herd testing, a minimum of 10% of the herd or group is necessary.

Communication with the appropriate diagnostic laboratory regarding differential diagnoses under consideration is recommended. Not all laboratories perform all types of diagnostic tests.

Fluid analysis of the trachea and lungs is often helpful in the diagnosis of lower airway disease. Tracheal wash technique is discussed in more detail later in this chapter. Bronchoalveolar lavage is essential for analysis of the alveolar spaces; however, this technique is regional at best. Samples of both types may be submitted for cytologic evaluation, viral detection, and bacterial and fungal culture.

## UPPER RESPIRATORY TRACT INFECTIONS

### Rhinitis and Sinusitis

Nasal airways can be infected with a variety of viral, bacterial, fungal, and parasitic agents with resultant sinusitis or rhinitis. In this chapter, rhinitis in the horse is defined as infection of the nasal passage independent of the sinus. Infection may include the nasal concha but does not involve the conchal sinuses unless caused by viral agents. Specific viral agents include equine influenza virus, EHV-1 and EHV-4, equine rhinoviruses, and adenovirus.20,22,24,26,29 Bacterial rhinitis is uncommon and usually occurs secondary to trauma or a foreign body. Mycoplasma spp. have been isolated at postmortem examination from horses with rhinitis.2,3,29,30 A variety of mycotic agents, such as Aspergillus spp. (see Chapter 56), Candida spp. (usually C. coronatus) (see Chapter 55), and Cryptococcus neoformans (see Chapter 57), may cause rhinitis in horses.14

The most common cause of parasite rhinitis is myiasis resulting from Haemonchus, Drassota (see Chapter 62), and the Russian fly, Rhinorhynchus penrurus.35 Enzootic lymphangitis or glands caused by Burkholderia mallei causes a specific granuloma within the sinus cavity (see Chapter 39).36,40

Horses with sinusitis most often have unilateral disease, unless the infection is viral or there is extensive involvement of the nasal septa. Most horses present with respiratory stridor and nasal discharge with diminished airflow.24,26,29,29 Therapy usually involves surgical debriement, debulking of
narial granuloma, and local therapy for the specific agent. Oral administration of itraconazole has been described for treatment of recurrent nasal mycoses. Although successful in this case, the pharmacokinetics of itraconazole are variable. Fluconazole may be a viable alternative. Detailed discussions of antifungal therapy in horses are presented in Chapters 56 and 71.

Sinonasal disease is very common in the horse. The horse has six pairs of sinuses, including the conchal sinuses, which exchange air with the nasal airway. The frontal sinuses may be affected with granulomatous masses (usually fungal or parasitic) or empyema (bacterial). The most common bacterial isolates are Streptococcus spp., with S. equi subsp. zooepidemicus and S. equi subsp. equi most frequently found. Staphylococcus spp. are the next most common isolates. Mixed bacterial infections may occur. Cryptococcus neoforans and Candida albicans also may cause granuloma formation within the paranasal sinuses (see Chapter 51).

In a study of 277 horses with sinusitis, 24% had primary sinusitis with no history of predisposing trauma or dental infection. Dental disease of the third to sixth maxillary cheek teeth was the most common predisposing factor for secondary sinusitis (22% of horses), followed by sinus cysts, neoplasia, progressive ethmoidal hematoma, trauma, mycotic infection, sinonasal polyps, and nasal epidermal inclusion cysts. Primary infection of a rostral maxillary cheek root infection was identified in only 4% of cases, although computed tomography (CT) evaluation was not used for diagnosis in many of these horses. Nasal discharge (most often unilateral but occasionally bilateral) and facial swelling were the most common clinical signs. Discharge can be mucopurulent to serosanguineous fluid with a foul smell. Clinical signs frequently persisted for several weeks (without other progressive systemic clinical signs). Other signs of frontal and maxillary sinus involvement included lacrimal discharge and exophthalmia.

Diagnostic techniques that may facilitate identification or characterization of sinusitis in horses include endoscopy, radiography, CT, and magnetic resonance imaging (MRI). Endoscopy can detect changes in airway structure (84% of cases) and rule out ethmoidal hematoma. Sinuscopy can also be performed through a space created in the skull by trephination in the standing horse.

Radiography is essential for identification of fluid and masses within sinuses (Fig. 1-2). If there is no fluid, this modality is valuable for detection of tooth root abscesses. Usually the first molar is involved. CT and MRI are exceptionally valuable for detection of tooth root involvement and bony changes, which often involve the maxillary bone and nasal crest.

Appropriate and effective treatment of sinusitis requires that underlying or predisposing conditions be accurately identified and treated, that debris be flushed from the sinus, and that associated infectious agents be properly identified. When fluid is present within a sinus, medical treatment with antibiotics alone is unlikely to be successful. Trephination and flushing or surgical debridement and drainage through a sinus flap are indicated. Establishment of ventral drainage of the affected sinuses may be required. Local flushing is likely to be the most important component of therapy, although systemic antimicrobial therapy may be indicated for any horse with signs of osteomyelitis.

Prognosis is guarded for complete resolution of clinical signs, especially when apical dental disease is present. Frequently, tooth removal is indicated. Recurrence is most common with ethmoidal hematoma and neoplasia.

**Lymphoid Pharyngeal Hyperplasia**

Lymphoid pharyngeal hyperplasia is a common condition involving the upper respiratory tract of 2- and 3-year-old racehorses (Box 1-1 and Fig. 1-3). Most mild cases respond favorably to reduced athletic activity combined with systemic and topical anti-inflammatory therapy. Dexamethasone can be administered at a dose of 0.02 to 0.05 mg/kg orally daily for 1 week, followed by half the original dose orally for 1 week, then the same dose orally every other day for an additional week. A throat sprain of nitrofurazone, dexamethasone, and dimethyl sulfoxide is reported to be of benefit when administered topically. Systemic immune modulation is reported to be effective for treatment of horses with lower airway inflammation and may also have some benefit in those with upper airway inflammation. Occasionally, chronic disease occurs; reports have suggested that these horses may respond favorably to cautery of the dorsal roof of the pharynx.

Organisms associated with a more prolonged course of pharyngeal hyperplasia include *S. equi* subsp. *equi*, equine influenza, EHV-1, EHV-2, and EHV-4. The condition is thought to result from chronic inflammation of the localized lymphoid tissues, particularly because these structures have a diffuse distribution within the mucosa of this species. Although some investigators have cultured the oropharynx of affected horses, no consistent etiologic agent has been identified. Normal inhabitants of the equine upper respiratory tract, such as *S. equi* subsp. *zooepidemicus*, *Bordetella bronchiseptica*, and *Moraxella* have been isolated; however, the direct association with lymphoid pharyngeal hyperplasia has not been determined. A grading system has been established for this condition; these horses with more severe inflammation have greater numbers of bacterial organisms isolated from their upper respiratory tract.
Grading Scheme for Lymphoid Pharyngeal Hyperplasia

- **Grade 1:** Small number of white follicles scattered over dorso-lateral pharyngeal wall. The follicles are small and inactive. This appearance is normal in horses of all ages.
- **Grade 2:** Many small, inactive white follicles over dorso-lateral walls of pharynx to level of gag pouches. Numerous follicles are larger, pink, edematous, and interspersed throughout.
- **Grade 3:** Many large, pink follicles and some shrunken white follicles distributed over dorso-lateral walls of pharynx. In some individuals the follicles extend onto the dorsal surface of the soft palate and into the dorsal pharyngeal diverticula.
- **Grade 4:** More numerous pink and edematous follicles packed close together, covering entire pharynx, dorsal surface of soft palate, and epiglottis and lining guttural pouches. Large accumulations appear as polyps.


Fig. 1-3 Grade 3 lymphoid pharyngeal hyperplasia in 2-year-old Thoroughbred colt (see Box 1-1).

Arytenoid Chondritis

Arytenoid chondritis is a progressive inflammatory condition of the arytenoid cartilages in adult horses, originating as an infectious condition. Most often, upper airway dysfunction is reflected in poor athletic performance and respiratory stridor. Diagnosis is based on upper airway endoscopy (Fig. 1-4). One manifestation of chondritis is the development of granulomas on the axial surface of the arytenoid cartilages. Clinical management of affected patients involves medical or surgical therapy. Although broad-spectrum antibiotic therapy has been attempted in many cases, it is rarely curative. Also of importance in the management of some horses with arytenoid chondritis is placement of a tracheostomy tube (Fig. 1-5).

Several techniques are described for placement of a permanent tracheostomy.6

Viral Diseases

*Equine influenza virus* is classified as an orthomyxovirus with a single-stranded, segmented ribonucleic acid (RNA) genome64 (see Chapter 12). Influenza viruses are classified on the basis of surface and internal protein antigens into three types: A, B, and C; only type A influenza is reported to infect horses. Major viral antigens include neuraminidase (NA) and hemagglutinin (HA). Two type A viral subtypes are known to cause disease in horses: H7N7 and H3N8.64 The strain H7N7 was initially isolated in 1956 in Prague and designated A/equine/Prague/56. This H7N7 variant, termed *equine-1 influenza*, has not been isolated since 1980 and is believed to have disappeared from the equine population.66 The H3N8 equine virus, called *equine-2 influenza*, was initially isolated in Miami in 1963 and designated A/equine/Miami/63.67-69 Antigenic drift has subsequently resulted in many subtypes of variant equine-2 among horses, including A/equine/Fontainebleau/79, A/equine/Kentucky/81, A/equine/Saskatoon/89, and A/equine/Newmarket/2/93. Although antigenic drift has been observed for many years, antigenic shift,
In self-limiting viral respiratory disease in young horses. Many investigators question the role of this virus as a primary etiologic agent of fulminant respiratory disease in horses. EHV-2 has been recovered from both normal horses and young horses with clinical signs of respiratory tract disease. Studies of seroprevalence and virus isolation reveal that young foals are often exposed to the virus. The virus could also be isolated from fluid collected by tracheal aspiration of young horses with clinical respiratory tract disease, whereas it was rare to isolate the virus from tracheal fluid of clinically normal foals. Experimental inoculation of foals with EHV-2 results in chronic pharyngitis. This organism may be a pathogen of concern in predisposing foals to bacterial pathogens such as P. actinomycetemcomitans.

Although most often recognized for its association with the equine reproductive tract, equine viral arteritis (EVA) causes a mild to moderate respiratory disease (see Chapter 14). The virus is maintained in equine populations in carrier stallions because testosterone is required for persistence and maintenance of the virus in vivo. Carrier stallions maintain the virus within the ampulla and vas deferens. Clinical manifestations of EVA are similar to those of other viral respiratory tract diseases. Variations in the severity of clinical signs result from strain differences in virulence, pathogen dose, and host immune function. Incubation requires several days to 2 weeks, with a more rapid course of disease after vernal transmission. Clinical signs associated with respiratory tract infection include serous nasal discharge, submandibular lymphadenopathy, mild to moderate cough, and ventral edema. Most infections are self-limiting, although edema may be severe and respiratory distress evident. Abortion typically occurs within a month of exposure and disease development. Abortion may occur, although other clinical signs of EVA have not been observed. Neonatal foals infected with the virus demonstrate respiratory difficulty and rarely recover from viral infection. Hematologic evidence of EVA includes leukopenia, characterized by a lymphopenia, and thrombocytopenia, which may be severe.

Equine rhinoviruses have been divided into two serogroups: equine rhinitis virus A and B (ERAV and ERBV) (see Chapter 16). ERAV is grouped in the Alphaherpesvirinae genus based on genotype and similarity with other members of this genus, such as foot-and-mouth virus, as well as the characteristic viremia and persistent shedding that occurs following infection with the virus. ERBV is the sole member of the genus Ebrivirus. A third serotype has been identified with the proposed classification in the Erboviridae as ERBV2; currently this virus is referred to as P13/75 and is classified in the family Picornaviridae. Clinical manifestations of disease typically include pyrexia, serous to seromucous nasal discharge, coughing, depression, anorexia, pharyngitis, and submandibular lymphadenopathy. Mild lymphopenia and increased plasma fibrinogen concentrations have been reported in affected horses.

**Strangles**
Clinical disease in horses associated with *Streptococcus equi* subsp. *equi* infection (strangles) is most common in horses younger than 5 years, but very uncommon in young foals (<3 months) born to mares previously exposed to the organism (see Chapter 28). Natural infection results from direct contact with an infected or carrier individual that may have overt clinical disease or that has maintained the organism within the upper airway, most frequently the guttural pouch. Transmission may also occur through fomites, such as on contaminated clothing or cleaning instruments.

Infection with *S. equi* primarily occurs through oral and nasal routes. Incubation from time of infection to manifestation
of clinical signs varies from a few days to a few weeks and is influenced by pathogen virulence, dose of inoculum, and host immunity at the time of challenge. Some of the earliest clinical signs include fever, depression, and reduced appetite. Nasal discharge may initially be serous but with disease progression will become mucopurulent. Lymph node enlargement and abscess maturation generally require approximately 7 days to occur. Early in the course of infection, affected lymph nodes are sensitive to palpation and firm in nature. As rupture becomes imminent, a soft center develops, and a serous crust on the surface may be observed. Submandibular and retropharyngeal nodes are most often affected; edema may be severe, resulting in dysphagia and respiratory stridor. After rupture of abscess(es), swelling will diminish rapidly. Severe obstruction may necessitate that a tracheostomy be performed.

The most common hematologic abnormalities in S. equi-infected horses are leukocytosis caused by neutrophilia, hyperfibrinogenemia, and anemia of chronic disease. Definitive diagnosis is based on aerobic culture of nasal secretions, preferably obtained from the abscessed lymph nodes, the guttural pouch, or a nasopharyngeal wash.

Therapy

Specific recommendations for treatment of S. equi subsp. equi and acute viral respiratory tract disease of horses is discussed in detail in the relevant chapters of this text. Because of the severity of epithelial surface damage and the potential for secondary bacterial infection, all virally affected horses should be rested from race training during the course of disease and recovery. A significant cough may persist for weeks after onset of clinical signs of viral respiratory disease. A standard rule of thumb is to implement a week of rest from strenuous exercise for each day the horse demonstrates a fever. Recovery of the respiratory epithelium should be complete before reintroduction of strenuous exercise. During periods of high fever, depression, anorexia, and myalgia, nonsteroidal antiinflammatory therapy is recommended. If significant nasal discharge and fever are persistent, additional testing is warranted to rule out bacterial contamination.

LOWER RESPIRATORY TRACT INFECTIONS

Etiology and Epidemiology

Bacterial Pneumonia

Under normal conditions the equine lung contains only small numbers of potential bacterial or fungal pathogens; when present, they are considered transient contaminants. These bacteria are typically cleared by the normal defense mechanisms, as previously discussed. However, when the normal defense mechanisms are overwhelmed or pulmonary immune defenses are impaired, proliferation of such contaminants may become pathogenic to the host. The most common source for contamination of the lower airways is aspiration of microorganisms from the upper respiratory tract. Gram-positive pathogens include Streptococcus equi subsp. zooepidemicus, Staphylococcus aureus, and Streptococcus pneumoniae. Gram-negative pathogens affecting the lower airways of horses include Pasteurella, Actinobacillus spp, Escherichia coli, Klebsiella pneumoniae, and Bordetella bronchiseptica. Anaerobic organisms that may infect the lower airways of horses include Bacteroides fragilis, Peptostreptococcus anaerobius, and Fusobacterium spp.

Miscellaneous Causes of Pneumonia

Infectious disease involving the lower respiratory tract is most often associated with bacterial infection, although fungal and viral pathogens are also potential invaders of the lower respiratory tract. Septic thrombophlebitis is considered a risk factor for metastatic spread of septic foci. Some reports suggest that the presence of anaerobic organisms warrants a more guarded prognosis when cultured from horses with pleuropneumonia. Polymicrobial infection may result from synergy among pathogens, particularly aerobic or facultative anaerobes and anaerobic organisms that favor survival of organisms that otherwise would not proliferate.

Pulmonary Abscess

Pulmonary abscess formation most often occurs in weanling foals in association with Rhodococcus equi infection (see Chapter 32). Streptococcus equi subsp. zooepidemicus is the organism most frequently cultured from the lungs of horses with generalized pneumonia and rarely results in abscess formation. Complications from S. equi subsp. equi infection include metastatic spread to various organs, including possible pulmonary abscess formation. Aspiration is another cause of focal pulmonary infection and abscessation. Aspiration pneumonia is a potential complication of esophageal obstruction or dysphagia in horses. Neonatal foals may develop dysphagia in association with hypoxic ischemic encephalopathy or nutritional muscular dystrophy, whereas adult horses may develop aspiration pneumonia after complete esophageal obstruction.

Pathogenesis

Bronchopneumonia occurs after colonization of the lower respiratory tract with bacteria. This colonization may occur after damage from viral infection or after an episode of impaired pulmonary clearance, as might occur after strenuous exercise or long-distance transport. Bacterial contamination of the lower airways may also lead to concurrent or subsequent pleuropneumonia or pulmonary abscess formation.

Primary viral respiratory tract infection predisposes adult horses to bacterial infection because of disruption of the surface epithelium, loss of the mucociliary elevator, and loss of surfactant production by type II pneumocytes. Pulmonary inflammation will lead to increased capillary permeability and pulmonary edema; such an environment is conducive to the survival and replication of contaminating pathogens, particularly those that survive under conditions of low oxygen tension (anaerobes).

High-level performance horses may be predisposed to lower airway infection because alveolar macrophages are reduced in efficacy after strenuous exercise. In addition, challenge is enhanced because horses in training are at greater risk for aspiration of pathogens and particulate matter. Horses used for performance activities often travel long distances, and persistent head elevation, as might occur in a trailered horse, reduces pulmonary clearance mechanisms within 6 to 12 hours. Although many strategies have been used to enhance protection in such individuals, neither antibiotic therapy nor intermittent lowering of the head appears to reduce substantially the incidence of pulmonary infection. Transportation for a distance greater than 300 miles in the preceding 2 weeks is an important risk factor for the development of pleuropneumonia in horses. Although uncommon, horses with severe gastrointestinal disease or those with pulmonary infection that remains unresponsive to antibiotic therapy may develop a pulmonary mycotic infection. Diagnostic testing should be implemented to rule out fungal organisms as primary or secondary invaders.

Clinical Findings

Clinical findings in horses with pulmonary disease most often include depression, fever, and reduced food intake. Coughing is
most frequently observed during physical exertion or with advanced disease. Horses with advanced disease may show respiratory distress as well as pronounced weight loss. Purulent nasal discharge with a fetid odor, evidence of thoracic pain, and epistaxis may occur in association with rupture of a pulmonary abscess. A sequela to severe disease may be lamination; therefore, abnormal gait or intermittent recumbency may accompany evidence of pulmonary infection.

Diagnosis
Although clinical evidence may suggest pulmonary infection as the primary problem in equine patients, a thorough evaluation is warranted to ensure that all problems and diagnoses are appropriately managed. Physical examination should include careful auscultation to evaluate the patient for pulmonary air movement. If respiratory distress is observed, further manipulation for auscultation should not be performed. If pulmonary sounds are difficult to detect, however, a rebreathing bag may be applied to enhance the ability to detect air movement. When diminished pulmonary sounds are present, an ultrasound examination should be performed to determine if pleural fluid or pulmonary consolidation exists.

Hematologic findings consistent with bacterial infection include neutrophilic leukocytosis with a left shift, toxic changes in neutrophils, hypergobulinemia, and hyperfibrinogenemia. Mild to moderate anemia may be associated with chronic disease.

Thoracic radiographs are useful to determine the extent and severity of pulmonary disease. Ultrasonographic examination will be helpful for detection of peripheral parenchymal conditions or those associated with pleural effusions. Sterile transtracheal aspirate samples should be obtained from the respiratory tract for culture and antimicrobial testing. Although endoscopy is a useful diagnostic test for horses with pulmonary disease, this usually is not the preferred method for collection of sterile samples for culture and sensitivity analysis. If *Pseudomonas* spp. are cultured from samples obtained by endoscopic transtracheal aspiration, results should be interpreted with caution because this organism is rarely a pathogen of the equine pulmonary system.

Therapy
Treatment of horses with historical, clinical, and hematologic evidence of pulmonary bacterial infection should include broad-spectrum antimicrobial therapy (pending sensitivity testing of isolates and implementation of more targeted antimicrobial therapy) and excellent supportive care. Although bacterial culture results are not available immediately on diagnosis of pulmonary infection, cytologic evaluation of pulmonary aspirates should give the clinician some indication of the type (Gram stain) and population (single or multiple classes of pathogens) of pathogens in the patient. Beta-lactam antibiotics combined with aminoglycosides provide good coverage for a variety of pathogens that may infect the lower airways of horses. Caution should be used in individuals that are debilitated or dehydrated.17 Because of nephrotoxicity, aminoglycosides are contraindicated for use in patients at risk for renal impairment.

The prognosis for recovery from bacterial pneumonia is generally considered favorable for horses that have been managed appropriately in a timely fashion. Horses with severe disease that have not responded or incompletely respond to antimicrobial therapy may subsequently develop pleuroneumonia, which may worsen the prognosis for complete recovery and return to previous level of athletic function.

### Pneumonias

#### Pleuropeumonia

**Etiology and Epidemiology**
Pleuropeumonia is a condition in which infection associated with bronchoneumonia has spread to involve the pleura and the pleural space.89 This disorder most often occurs in performance horses, frequently after long-distance transport.82.71.80 Although apparently spontaneous cases of pleuropeumonia may occur in some horses, most affected horses have experienced one or more predisposing risk factors, such as long-distance transport, recent viral or bacterial respiratory tract disease, or a recent episode of generalized anemia.87,88,91

Most cases of equine pleuropeumonia result from bacterial infection, but reports also demonstrate that *Mycoplasma* spp.,71 viral agents,31 and mycotic agents134 may be isolated, or the disease may occur as a complication of septic thrombophlebitis.86 Rarely, pleurocutaneous cellulitis may be a cause of equine pleuropeumonia39 (see Chapter 61). Bacterial pleuropeumonia can be associated with a single pathogen but more often results from a mixed infection that may include aerobic and anaerobic organisms.87.31.32.94 The most important factor for the development of transport-associated pleuropeumonia is head position during long-distance transport.87.70.95-97

The most compelling evidence for this claim is the observation that horses transported long distances without restraint of head position do not develop changes in lower airway cytologic findings. In contrast, horses without other stress had an estimated 75% increase in likelihood of developing lower airway accumulation of bacteria and inflammatory debris after a minimum of 24 hours of head restraint.5,87,88,91 High-intensity exercise in combination with long-distance transport further contributes to development of lower airway inflammation and impaired immune clearance mechanisms.1,12

Striving to prevent equine pleuropeumonia is important because the prognosis for return to previous level of athletic function may be guarded to poor in severe cases.87,91 Complications associated with pleuropeumonia, such as laminitis and chronic abcess formation, may negatively influence the future athletic performance of affected individuals.87

**Clinical Findings**
Horses with pleuropeumonia may demonstrate a variety of clinical signs. However, disease should be suspected in horses with an appropriate history and that demonstrate lethargy, pyrexia, cough (may be a quiet cough because of pleural pain), nasal discharge (unilateral or bilateral, may be bloody), shallow breathing pattern, increased laryngeal excursions, and painful, stilted gait. During the acute stage of the disease, horses are likely to have signs referable to pleurodynia. Pain may be demonstrated by pawing, reluctance to move, abducted elbows, stiff gait, guarded breathing pattern, or shallow respiration. Ballottement or percussion of the thorax typically reveals reduced or absent resonance and may elicit a painful grunt. Differential diagnoses for such cases include exertional rhabdomyolysis, laminitis, and colic.

Thoracic auscultation usually reveals abnormal pulmonary auscultatory sounds. When pleural effusion is present, the most common finding is attenuation of audible bronchovesicular sounds over the ventral lung fields. In the dorsal lung fields, normal pulmonary sounds may be heard; more often, however, increased bronchovesicular sounds are heard, accompanied by crackles or wheezes. Before significant pleural fluid accumulation, abnormal pulmonary sounds may be heard diffusely.98,99 With chronicity, friction rubs are common, reflecting fibrin accumulation along the parietal and visceral pleural surfaces.
Tachycardia and tachypnea are common findings in horses with pleuropneumonia. Jugular pulsation and severe respiratory distress may occur. Nasal discharge is often present and can vary from serous to mucopurulent to mucopurulent or mucopurulent hemorrhagic in character. A fetid odor associated with nasal discharge, breath, or pleural fluid should increase the clinicians’ suspicion of anaerobic infection. Mucous membrane color may be dark red to injected, depending on whether the horse is experiencing significant toxemia or ventilatory compromise (Fig. 1-6). Horses with subacute to chronic pleuropneumonia often demonstrate weight loss, which may be dramatic.

Diagnosis

History and physical examination findings are often highly suggestive of pleuropneumonia. Definitive diagnosis is made on the basis of identification of septic fluid within the pleural space. Ultrasonographic examination (3.5- to 5.0-MHz transducer) will reveal evidence of pleural effusion. Ultrasonographic examination is superior to radiography to confirm a diagnosis of pleuropneumonia because fluid accumulation within the thoracic cavity (Fig. 1-7). Ultrasonography may also reveal evidence of pleural irregularities or changes within the pulmonary parenchyma, such as atelectasis, abscess formation, consolidation, and pulmonary hypertension. "Comet tail" artifacts on pleural surfaces denote foci of inflammation or fibrosis on the visceral pleura. The ultrasonographic character of pleural fluid in horses with pleuropneumonia may range from anaerobic to hyperechoic, depending on the relative cellularity and fibrin accumulation. Evidence of bright gas echoes within the pleural fluid indicates anaerobic organisms within the pleural fluid. Other possible explanations for gas accumulation within the pleural space include previous thoracocentesis or severe parenchymal disease resulting in a bronchopleural fistula, with communication between the pleural space and conducting airways. Fibrin accumulation can be detected with ultrasound examination, typically visualized by strands or loculated cavitations. Familiarity with pleural ultrasonographic examination is important, because in some cases the pericardio-diaphragmatic ligament may be confused with fibrin accumulation.

Thoracocentesis is required to determine specific characteristics of pleural fluid, such as leukocyte cell count and differential and total protein concentration. Fine-needle aspiration of parenchymal lesions may be indicated in horses with suspected pulmonary abscess formation. Samples of pleural fluid, pulmonary abscess aspirates, and transtracheal wash samples should be submitted for bacterial culture (aerobic and anaerobic) and sensitivity testing and cytologic analysis. Because pleuropneumonia in most horses begins as severe bronchopneumonia, culture of transtracheal wash samples is particularly important for identification of primary bacterial pathogens (Fig. 1-8). Early in the course of disease, pleural fluid may be inflammatory but sterile, and an etiologic diagnosis would be missed if only pleural fluid samples were cultured. If the pleural sepsis results from a traumatic, penetrating wound, however, transtracheal wash analysis is not indicated, and the primary etiologic agents are best identified by culture and sensitivity testing of pleural fluid samples.

Cytologic examination of pleural fluid is important diagnostically and may influence prognosis. Normal pleural fluid is an ultrafiltrate of plasma and is appropriately classified as a transudate. It is transparent, straw colored, and nonfetid. The total nucleated cell count should be less than 10,000 cells/μL, and the protein concentration less than 2.5 g/dL. Differential analysis of normal pleural fluid reveals the majority of cells to be neutrophils, with few monocytes and mesothelial cells. Additional analysis may include measurement of glucose, lactate, and pH. Pleural fluid samples from horses with pleuropneumonia are usually acidic, with low glucose concentrations and increased lactate concentrations.

Pleuritis is the potential complication of pleuropneumonia, with a reported incidence of up to 43%. Clinical evidence of pneumothorax may include dyspnea, tachypnea, loss of auscultable pulmonary sounds in the dorsal thorax, depression, anxiety, and cough. Radiography and ultrasonography are useful aids in the diagnosis of pneumothorax. When pneumothorax occurs as a complication to pleuropneumonia, it is usually unilateral. In general, horses with pneumothorax secondary to pleuropneumonia have a more guarded prognosis for recovery and survival as compared to horses with uncomplicated pleuropneumonia.

Pleuroneumonia with secondary hemorrhagic pulmonary infarcts has been described in thoroughbred racehorses shortly after a bout of strenuous exercise. Affected horses showed evidence of acute respiratory distress with serosanguineous
nasal discharge shortly after strenuous exercise. Thoracic radiography and ultrasound revealed evidence of pulmonary consolidation and pleural effusion in affected individuals; in contrast to many cases of pleuropneumonia, thoracocentesis revealed serosanguineous to hemorrhagic effusion. Although an underlying bacterial etiology was demonstrated in most affected horses, conventional management with antibiotic and antiinflammatory therapy was unsuccessful in resolving most cases. Therefore, although various manifestations of pleuropneumonia may occur, individuals with a history and clinical evidence of pulmonary infarction should receive a more guarded prognosis.107

**Therapy**

The primary goals of therapy in horses with pleuropneumonia include resolution of sepsis, clearance of effusion from the pleural space, and provision of excellent nursing care to avoid or manage the onset of complicating factors associated with the primary disease.

Antimicrobial therapy is generally aimed at broad-spectrum coverage for a wide variety of bacterial pathogens including gram-positive and gram-negative aerobes and anaerobic organisms.98 Combination therapy with β-lactam (e.g., penicillin, 22,000 IU/kg body weight intravenously [IV] every 6 hours [q6h]) and aminoglycoside (e.g., gentamicin, 6.6 mg/kg IV q24h) antibiotics are the mainstay of antimicrobial therapy in horses with pleuropneumonia. Metronidazole (15-25 mg/kg q6-8h) is added to the treatment regimen if anaerobic infection is suspected. Identification of all bacterial species present is an important component of clinical diagnosis because the presence of obligate anaerobic organisms will influence patient prognosis.97,98 Anaerobic organisms frequently isolated from horses with pleuropneumonia include Bacteroides, Peptostreptococcus, Clostridium, and Fusobacterium species (see Chapter 48). Although most of these anaerobic pathogens are sensitive to penicillin, some strains of Bacteroides are resistant to β-lactam therapy because of elaboration of β-lactamase enzymes that inactivate this class of antimicrobial.

Metronidazole is a nitroimidazole antibiotic that is metabolized to its active form in the reducing environment produced exclusively by anaerobic organisms and is highly efficacious against this class of organisms.108

Supportive care for horses with pleuropneumonia frequently includes intravenous (IV) fluid therapy, especially during the acute stages of disease, when affected horses are typically depressed, anorectic, and dehydrated. Dehydration results from reduced voluntary fluid intake as well as a redistribution of fluid to the pleural space. IV fluid therapy aids in controlling pyrexia and maintaining secretions that can easily be removed by the mucociliary escalator rather than remaining inspissated within the pleural cavity. Nonsteroidal antiinflammatory therapy is indicated in the euvolemic patient to aid in management of pain, endotoxemia, and pyrexia associated with infection.109

Drainage of pleural fluid is required in patients with moderate to severe pleural fluid accumulation. Without appropriate removal, development of severe respiratory distress may ensue. If large volumes of pleural fluid exist within the pleural
Surgical intervention is indicated in horses that do not recover after thoracic drainage through an indwelling tube. A thoracotomy may be performed between rib spaces or may necessitate removal of a portion of rib. Surgical drainage is typically reserved for patients that have not fully recovered from pleural disease but are clinically stable. Description of the entire surgical procedure is beyond the scope of this discussion, but it should be performed over the area of chronic septic accumulation (identified by ultrasonographic examination). In some horses a surgical entry site needs to be reopened because of rapid closure, or bilateral procedures are required for horses with severe involvement of both hemithoraces.

Supportive care is focused on prevention of secondary complications, which may include pulmonary abscess formation, bronchopleural fistula, pneumothorax, cranial mediastinal abscess, restrictive pericarditis, laminitis, colic, antibiotic-associated colitis, and jugular vein thrombosis.

The prognosis for horses with pleuropneumonia depends on the inciting pathogen and the duration of disease before seeking veterinary assistance. Infarctive pleuropneumonia, described earlier, is associated with an especially severe prognosis.

**Interstitial Pneumonia**

Interstitial pneumonia is a pulmonary condition that may affect horses of various age groups. Interestingly, adult horses with interstitial pneumonia are given a guarded to poor prognosis for recovery and survival, whereas foals and weanlings provided with appropriate therapy and supportive care have a good prognosis for complete recovery.

**Etiology and Pathogenesis**

Most cases of interstitial pneumonia are thought to result from a primary toxic or infectious insult, but at presentation determining the exact etiology can be challenging. Toxigenic pulmonary disease has been associated with ingestion of Croton weed, pyrrolizidine alkaloids (Crotolaria, Tribulus, and Senna), perilla ketones, sarsosil, and prolonged oxygen therapy. Hepatic metabolites of pyrrolizidine alkaloids cause cellular damage and death in the pulmonary endothelium. Inhaled irritants or toxins may contribute to direct pulmonary damage, such as occurs after inhalation of smoke or agricultural chemicals. Silicosis is a highly specific, chronic granulomatous pneumonia of horses and should be considered in horses with compatible clinical signs that originate from the Carmel Valley in California.

The initial infectious or toxic agent causes alveolar damage, resulting in cell death and increased permeability at the level of the alveoli. Pulmonary congestion, interstitial edema, erythrocyte extravasation and alveolar edema occur during the exudative phase of the disease. Subsequently, alveolar infiltrates with inflammatory leukocytes and fibrin and increased permeability lead to fluid accumulation, impairing normal gas exchange mechanisms; hyaline membrane formation; and clinical respiratory distress. Acutely affected patients typically demonstrate respiratory distress, injected mucous membranes, and impaired pulmonary function. Subacute to chronic disease results in alveolar regeneration with alveolar type II pneumocyte proliferation to replace damaged type I pneumocytes. Fibroplasia leads to cellular proliferation and septal thickening, fibrosis, and ultimately reduced pulmonary compliance.

**Clinical Findings**

Horses presenting with interstitial pneumonia are typically in severe respiratory distress, with labored breathing,
dark mucus membranes, poor pulse quality, and tachycardia. Some patients are mistakenly considered to have an obstructive disease such as heaves, but interstitial pneumonia is characterized by a restrictive rapid, shallow breathing pattern. Additional clinical features of disease include hypoxemia, a stress or inflammatory leukogram, hyperfibrinogenaemia, and hypoxemia that may be severe. More chronic disease may be observed in mildly affected individuals with exercise intolerance and chronic cough.

**Diagnosis**

Definitive diagnosis of interstitial pneumonia in horses is based on histopathologic evaluation of a pulmonary biopsy (Fig. 1-10). Thoracic radiographs can be helpful in establishing a preliminary diagnosis of interstitial pneumonia. Two patterns of interstitial disease have been described in horses with interstitial pneumonia: discrete or diffuse nodules suggestive of neoplasia or mycotic disease and a diffuse increase in the radiographic interstitial pattern (Fig. 1-11). Serum titers may indicate recent exposure or infection with viral respiratory disease. Histopathologic evaluation of lung biopsies or specimens obtained postmortem will confirm the diagnosis of interstitial pneumonia. If silicosis remains a possibility, differential diagnosis is based on X-ray diffraction techniques on lung tissue preparations.

**Therapy**

The prognosis for adult horses with interstitial pneumonia is guarded. In horses that present with mild to moderate disease, treatment should be aimed at improving oxygenation. Intranasal insufflation of oxygen is warranted for patients that are severely hypoxic. Antiinflammatory therapy should initially include systemic corticosteroids (e.g., dexamethasone, 0.05-0.1 mg/kg IV daily), with transition to aerosolized corticosteroids (e.g., beclomethasone, 1500 μg intranasally two or three times daily) as clinical improvement is observed. Corticosteroid therapy should be continued until clinical resolution is observed or no further improvement is noted with therapy. Prolonged corticosteroid therapy of several weeks to months should be anticipated because of the severity of lower airway inflammation associated with this condition. Bronchodilator therapy is indicated when severe bronchoconstriction exists. Beta-2-adrenergic receptor agonists are the drugs of choice for immediate bronchodilation and subsequent improvement of air movement to the lower airways (albuterol, 360-720 mg/kg q3-12h). After initial stabilization, an additional therapeutic option is the use of a parasympatholytic agent (ipratropium, 360-470 μg/kg q6-12h) combined with a β2-adrenergic receptor agonist (albuterol). This combination (Combivent; 3M Pharmaceuticals and Boehringer Ingelheim, Canada) improves oxygen delivery to the lower airways, with the added advantage of an increased half-life, compared with β2-adrenergic agonist therapy alone.

**Prognosis**

The prognosis for return to function is guarded for adult horses with interstitial pneumonia and favorable for foals that are managed appropriately. Supportive and antiinflammatory therapy may improve clinical status, but high-level athletic activity may be impaired.

**Parasitic Pneumonia**

**Etiology**

Parasitic pneumonia is a condition that may affect foals or adult horses. Parasites associated with this condition include *Parascaris equorum* larvae or the adults of *Dictyocaulus arnfieldi* (see Chapter 62). Clinically affected horses have obvious evidence of respiratory disease, including exercise intolerance and coughing that may be accompanied by nasal discharge, fever, and depression, particularly when secondary bacterial infection has occurred. *P. equorum* infection is most common in foals and weanlings, particularly those raised on breeding farms where the parasite resides in the environment and soil. *D. arnfieldi* infection may occur in horses of any age, but this parasite requires a donkey as a primary host to complete its life cycle.

**Clinical Findings**

Chronic coughing, mucoid to mucopurulent nasal discharge, respiratory distress, and poor overall body condition provide nonspecific evidence of parasitic disease in foals. Poor body condition and abnormal pulmonary sounds marked by increased bronchovesicular sounds, crackles, and wheezes are common findings on thoracic auscultation of horses with
parasitic pneumonia. Poor body condition is a common finding because of intestinal involvement of parasitic infection. Colic may be a component of the history or may follow therapeutic antihelmintic treatment in severely affected individuals. Frequently, the history also includes a poor response to appropriate antimicrobial therapy for suspected bronchopneumonia.

Diagnosis
Hematologic evaluation often reveals an inflammatory leukogram consisting of a mature neutrophilia, hyperfibrinogenemia, and hyperglobulinemia. In some patients, particularly early in the course of disease, hematologic evaluation may reveal few abnormalities. Hepatic parasitic migration (P. equorum) may result in mild to moderate hepatic enzyme elevation. Thoracic radiography is a useful diagnostic test in affected individuals. A moderate to severe bronchointerstitial pattern is a common finding, whereas granuloma or abscess formation may be detected by radiographs in horses with advanced disease. Thoracic ultrasonographic examination will allow the clinician to detect the presence of pleural fluid or peripheral pulmonary consolidation.

Cytologic examination of a sterile tracheobronchial aspirate will often reveal abundant eosinophils (5%-50%, normal <2%); neutrophilic inflammation may be present concurrently, particularly with a secondary bacterial infection. Microorganisms are apparent with significant bacterial infection; culture is recommended to determine the presence of infection and to determine the antimicrobial sensitivity pattern for pathogens of concern. Fecal flotation is indicated to determine the presence of parasite ova being shed from the host. D. arnfieldi requires a donkey or mule host for life cycle completion; therefore, parasite eggs will only infrequently be detected in adult horses with lungworm infection. It is difficult to diagnose P. equorum infection on fecal flotation because tissue migration occurs during the prepatent period. Therefore, diagnosis is based on clinical signs, lack of evidence of bacterial infection, and tracheal wash cytology indicating eosinophilic pneumonia. Response to therapy is supportive of the diagnosis, although antibiotic therapy may be required in combination with antihelmintic therapy.

Therapy
Severely hypoxemic patients may require oxygen insufflation. Severe pulmonary inflammation is induced by eosinophilic infiltrates necessitating bronchodilator and potentially aerosolized corticosteroid therapy (see previous recommendations on aerosol therapy). Oral anthelmintic agents used to treat P. equorum infection include fenbendazole at an initial low dose of 5 mg/kg. Careful monitoring for approximately 24 hours is recommended to observe the foal for evidence of deterioration or gastrointestinal distress. Laxative therapy may be required if gastrointestinal ascariid impaction is suspected. After the foal has received the low dose of fenbendazole without complication, the oral dose can be increased to 10 mg/kg daily and repeated for 5 days. This therapy is effective in killing adult and migrating larvae. Because this is a farm problem, other individuals on the same property of similar age should be managed appropriately, even if clinical evidence of disease is not apparent. Other anthelmintics used to treat P. equorum include pyrantel pamoate (6.6 mg/kg) and ivermectin (200 µg/kg). D. arnfieldi infection can be successfully treated with ivermectin (also 200 µg/kg), moxidectin (adult horses only, 400 µg/kg), thiabendazole (440, mg/kg/day twice), or levamisole (10 mg/kg).

Benznidazole anthelmintic agents inhibit microtubule formation, which impairs the parasite’s ability to move and ingest food. Energy metabolism is also impaired because of the inhibition of fumarate reductase. Although many benznidazoles are efficacious against intestinal larvae, they are not uniformly effective at killing migrating parasite larvae; however, at higher doses, fenbendazole is safe and effective at killing intestinal and tissue larvae. Anecdotal and personal observations suggest that this anthelmintic is highly efficacious, particularly when ivermectin resistance is suspected.

Pyrantel pamoate is an acetylcholine agonist that results in parasite paralysis. At the recommended dose, this agent is effective at killing intestinal larvae, but not migrating larvae. Avermectins are effective because of their ability to bind glutamate-gated chloride channels, and this class is effective against both P. equorum and D. arnfieldi adults and migrating larvae. Ivermectin has a reported efficacy of 76.9% for removal of intestinal P. equorum and 100% for removal of tissue larvae. Overall, ivermectin and moxidectin have similar efficacy as effective anthelmintics in horses for many gastrointestinal parasites other than Anoplocephala perfoliata. Based on these reports regarding anthelmintic efficacy, recommendations include combining therapeutic agents to maintain maximal efficacy. Initial treatment with fenbendazole (10 mg/kg PO daily for 5 days), followed in 14 days with an avermectin product at the appropriate dose, should clear the individual of both intestinal and pulmonary parasites.

Prognosis
Foals or adult horses with primary parasitic pneumonia and secondary bacterial infection will require concurrent antibiotic and anthelmintic therapy. The prognosis is excellent for recovery from parasitic pneumonia. It is important to emphasize the need for complete deworming, including donkeys and mules, because they harbor the adult Dictyocaulus parasites that serve as a source for parasitic contamination to horses in the immediate environment.

GUTTURAL POUCH

David E. Freeman and Joanne Hardy

Guttural pouches are paired extensions of the eustachian tubes that connect the pharynx to the middle ear. They are found in perissodactyls, such as equids, tapirs, some species of rhinoceros (except the white rhinoceros), some bats, a South American forest mouse, and hyraxes.

Anatomy
The guttural pouches are separated from each other on the midline by the rectus capitis ventralis and the loopus capitis muscles and the median septum. Each pouch is in close contact rostrally with the basioccipital bone; ventrally with the retropharyngeal lymph nodes, pharynx, and esophagus; caudally with the atlanto-occipital joint; laterally with the diaphragm muscle and the parotid and mandibular salivary glands; and dorsally with the petrous part of the temporal bone, tympanic bulla, and auditory meatus. Each guttural pouch is divided ventrally into a medial and a lateral compartment by the stylohyoid bone, and it communicates with the pharynx through the pharyngeal orifice of the eustachian tube. The pharyngeal orifice is a funnel-shaped opening in the dorsolateral aspect of the pharynx that forms an oblique slit, rostral and ventral to the dorsal pharyngeal recess. The small end of the funnel opens into the guttural pouch. The medial lamina of each opening is composed of fibrocartilage directed in a rostroventral-to-caudodorsal direction. The capacity of guttural pouches in adult horses is 472 ± 12.4 mL, and the lateral compartment is approximately one third of the capacity of the medial compartment.
**Pathogenesis**

Clinical signs of important guttural pouch diseases are referable to injury of specific nerves and arteries in the guttural pouch and acoustic system. The internal carotid artery (ICA), cranial cervical ganglion, cervical sympathetic trunk, and the vagus, glossopharyngeal, hypoglossal, and spinal accessory nerves are all contained in a fold of mucous membrane along the median wall of the medial compartment (Fig. 1-12). The cranial laryngeal nerve and the pharyngeal branch of the vagus nerve lie beneath the mucosa on the floor of the medial compartment. The external carotid artery (ECA) lies along the wall of the lateral compartment and gives off the cervical and superficial temporal artery, and it continues as the maxillary artery (MA) along the roof of the guttural pouch. The facial nerve (cranial nerve [CN] VII) passes for a short distance over the caudal dorsal aspect of the lateral compartment after it emerges from the styloglossus muscle. The vestibulocochlear nerve (CN VIII) enters the internal acoustic meatus in the facial nerve and divides into vestibular and cochlear branches that innervate components of the middle ear. CN VIII does not enter the guttural pouch but can become involved in guttural pouch diseases that affect the middle ear (e.g., temporal bone osteomyelitis). The mandibular nerve, a branch of the trigeminal nerve (CN V), emerges from the foramen lacerum, passes close to the muscular process of the petrous part of the temporal bone, and continues rostrally along the roof of the lateral compartment of the guttural pouch.

The guttural pouch is lined with pseudostratified ciliated epithelium containing goblet cells in both adults and foals. The guttural pouch mucosa has the ability to clear foreign substances, but this ability varies among different regions of the epithelium. In a study on the distribution of various immunoglobulin (Ig) isotypes and subisotypes in the guttural pouch mucosa of healthy horses, IgM was found in the guttural pouch mucosa, mucosal lymph nodules, and submucosal lymph nodules. IgM was scattered in the mucosal lymph nodules and in the germinal centers of the submucosal lymph nodules. IgG was recognized only in the submucosal lymph nodules, and IgA was detected in glandular epithelial cells and the surface layer of the mucosal epithelium.

Possible functions of the guttural pouches include air equilibration across the tympanic membrane, contribution to air warming, a resonating chamber for vocalization, and a flotation device. A more recently proposed role is brain cooling, based on measurement of lower arterial temperatures in the cerebral side of the internal carotid artery compared with the cardiac side. As shown by cadaver studies, opening of the pharyngeal orifice of the guttural pouch involves the levator and tensor veli palatini muscles and the pterygopharyngeus and palatopharyngeus muscles. Passive opening of the auditory tube involves a reduced tone in the stylopharyngeus and pterygopharyngeus muscles, accompanied by increased inspiratory pressure. Although guttural pouch filling was previously reported to occur on expiration, the latter study demonstrated that filling occurs on inspiration.

**Clinical Examination**

The guttural pouches are examined by external palpation, endoscopy, and radiography. Enlargement caused by empyema (purulent material in the pouches), but particularly by tympanocele (air engorgement), can be palpated externally. Guttural pouch endoscopy provides the most information regarding guttural pouch disease. Non-specific evidence of guttural pouch disease, such as collapse of the pharynx and blood or pus draining from...
the pharyngeal orifice, can be found on endoscopic examination of the pharynx. However, blood or pus from other respiratory sources may be aspirated into the gullet pouch opening and appear to drain from it, so that direct endoscopic examination of the pouches must be performed (Fig. 1-13). With the horse mild sedated, the biopsy instrument is passed through the larynx channel of the endoscope and used to guide the endoscope into the gullet pouch. The endoscope is placed so that the biopsy forceps is as close as possible to the lateral wall of the pharynx until successful insertion into the gullet pouch is achieved. Both pouches can be entered in this manner with the endoscope in the same nostril. Alternatively, the pharyngeal opening can be levered open with a Chamber's catheter to allow the endoscope to enter the pouches.

Lateral radiographic projections of the gullet pouches can demonstrate fluid lines, fractures and exostoses of the stylohyoid bone, radiopaque foreign bodies, and space-occupying masses (Fig. 1-14). Air distention, in particular, can increase dimensions of the affected gullet pouch, sometimes beyond the second cervical vertebra. A dorsoventral or ventrodorsal projection is best used to image the stylohyoid bones and temporomandibular articulation. CT can provide an alternate imaging modality, especially for imaging of the stylohyoid bone, inner ear, and petrous temporal bone in cases of temporomandibular osteoarthropathy. Ultrasoundography can be used to demonstrate soft tissue lesions in the gullet pouches, such as tumors or muscle damage and associated submucosal hemorrhage. A percutaneous cæsarean technique through Vibe's technique has been described for gullet pouch lavage and collection of samples for cytologic and microbiologic examinations. The normal cytologic pattern is less than 5% neutrophils, a large proportion of ciliated columnar epithelial cells, a few nonciliated cuboidal epithelial cells, and less than 1% monocytes, lymphocytes, and eosinophils. The proportion of neutrophils

is important, with less than 5% considered normal and greater than 25% considered abnormal. A high correlation exists between high cytologic score and presence of pathogenic bacteria such as Streptococcus equi subsp. equi. The cytologic gradings and neutrophil concentrations of gullet pouch washings are increased in horses whose heads are restrained for more than 12 hours, as during long-distance transport. Wushings from these horses are more likely to contain bacteria and yield potentially pathogenic bacteria.

Empyema

Empyema of the gullet pouch is defined as the presence of purulent material (Fig. 1-15) or chondroids within one or both gullet pouches. Chondroids consist of inappressed purulent material, usually numerous individual round balls (Fig. 1-16). Empyema can affect horses of any age but usually occurs in young animals.

Etiology

Upper respiratory tract infections (especially those caused by Streptococcus), abscessation and rupture of retropharyngeal lymph nodes into the gullet pouch, infraction of irritant drugs, fracture of the stylohyoid bone, congenital or acquired stenosis of the pharyngeal orifice, and pharyngeal perforation by a nasogastric tube may cause empyema. Persistence of gullet pouch infection in an infected long-term carrier could be responsible for recurrent outbreaks of asthma.

Clinical Findings

Clinical signs of gullet pouch empyema include intermittent nasal discharge, swelling of adjacent lymph nodes, paresis swelling and pain, extended head carriage, excessive respiratory noise, and difficulties in swallowing and breathing. In rare cases, gullet pouch empyema can cause pharyngeal and laryngeal paresis. In one study of 91 horses with gullet pouch empyema, 21% had chondroids, and the horses with chondroids were more likely to have retropharyngeal and pharyngeal swelling than those without this complication. The number of chondroids present is variable, ranging from one to many, and both gullet pouches can be affected.
Duration of infection does not appear to correlate with development of chondroids.

**Diagnosis**

On endoscopic examination, a purulent discharge can be seen at the pharyngeal orifice of the affected side, with pharyngeal collapse in some horses. Fluid accompanied by masses seen within the gullet pouch on standing lateral radiographs suggests chondroids. Fluid aspirates or saline washings can be obtained from the gullet pouch for culture and sensitivity testing; however, results should be interpreted with caution because microorganisms can be retrieved from the normal gullet pouch and upper respiratory tract. Horses that are carriers of, or infected with, *S. equi* subsp. *equi* in the gullet pouches can be identified by culture and PCR tests with repeated swabs (see Chapter 28).

**Medical Therapy**

In acute cases, daily irrigation with physiologic saline solution is usually effective. An indwelling catheter, devised from polyethylene 240 tubing with heat-formed coils at one end, can be used for this purpose. Alternatively, a commercially available gullet pouch catheter (Cook Veterinary Projects, Bloomington, Ind; Mila International, Florence, Ky) or one made from a polypropylene canine urinary catheter can be used. Coiled catheters can be straightened to facilitate insertion by inserting a coaxial wire or by passage through a larger, curved catheter. The coiled end of the catheter is placed under endoscopic guidance within the pouch, and the free end is secured by a suture to the alar fold. A Foley catheter can also be used, but it should be advanced until the end is completely in the pouch because distention of the balloon within the pharyngeal opening could cause pressure necrosis. In larger horses, standard Foley catheters are not long enough to reach the gullet pouch. Alternatively, the pouch can be flushed through the biopsy channel of the endoscope, which has the advantage of delivery of the flush solution to areas coated with purulent material. After 7 to 10 days, irrigation should be interrupted briefly to assess the response, with the awareness that this treatment can cause some inflammation.

In horses that are severely dyspneic because of gullet pouch distention, a tracheotomy should be performed. If the response to medical treatment is poor or if the purulent material becomes inspissated or forms chondroids, surgical drainage of the gullet pouch should be considered (see later discussion). Chondroids can also be removed by maceration, followed by saline lavage or extraction by endoscopically guided grabbing forceps, a basket snare, or a memory-helical polyp retrieval basket (Cook, Bloomington, Ind). Another technique involves repeated section of each mass by a diathermic snare (Olympus Optical, Irving, Texas) or a wire loop, with removal by suction, lavage, or extraction by basket-type endoscopic forceps (Gomco Equipment, Chelmeron Medical Products, Buffalo, NY). In one study, 44% of horses with chondroids were treated successfully by these noninvasive methods, although removal by these methods can take a long time. If empyema is the result of occlusion of gullet pouch openings by adhesions, this occlusion may be relieved by blunt division through a surgical approach to the gullet pouch interior. Chronic empyema of the gullet pouches, possibly unresponsive to medical therapy because of poor drainage through the pharyngeal ostia, can be successfully treated by using a laser to establish a permanent pharyngeal fistula into the gullet pouch.

Response to medical treatment is usually satisfactory, and surgery is rarely indicated. Neurologic signs usually resolve once the infection is brought under control by medical or surgical treatment.

**Surgical Therapy**

Surgery of the gullet pouch through any approach should be a last resort because of risks of istrogenic nerve damage. Identification of the gullet pouch lining and underlying nerves is difficult, especially in horses in which there is no distention, and can be facilitated by a lighted endoscope inserted into the medial compartment. A fixed structure, such as the stylohyoid bone, should be used as a guide for deep dissection. The mucosa should not be incised with sharp instruments, and retractor should be applied with care to avoid nerve damage. Because all approaches enter the pouch...
cavity in the same approximate area, none provides less risk of nerve damage than the others. Several approaches can be used to open the gullet pouch for removal of pus, myxomatous plaques, and foreign bodies and to establish drainage. These include hyoideobronchoscopy, approach through Viborg’s triangle (tendon of sternocephalic muscle, linguofacial vein, vertical ramus of mandible), Whitehouse approach, and modified Whitehouse approach. Advantages of both Whitehouse approaches are direct access to the roof of the gullet pouch, digital access to the lateral compartment, excellent ventral drainage, and simultaneous access through the septum to both pouches. Although both approaches involve deep dissection, they do not appear to have a higher rate of complications than other approaches.

Open incisions in the gullet pouch are cleaned daily, and the gullet pouch cavity should be flushed daily with a nonirritating solution. Open incisions close spontaneously within 14 days, and the infection should also resolve within this time. Postoperative antibiotics can be given.

Guttural Pouch Mycosis

Etiology

Guttural pouch mycosis is usually unilateral, but rarely it may affect both pouches. There is no apparent age, gender, breed, or geographic predisposition to this disease. The cause of gullet pouch mycosis is unknown, although Aspergillus spp. can frequently be identified in the lesion. The typical lesion of gullet pouch mycosis is a diphtheritic membrane of variable size, composed of necrotic tissue, cell debris, a variety of bacteria, and fungal mycelia. Aneurysm formation does not appear to precede or follow arterial invasion consistently and therefore is not essential to the pathogenesis of arterial rupture.

Clinical Findings

The most common clinical sign of gullet pouch mycosis is moderate to severe epistaxis, which is caused by fungal erosion of the ICA in most cases138-143 (Fig. 1-17) and of the ECA and MA in approximately one third of cases142,143 (Fig. 1-18). However, any branch of the ECA, such as the caudal auricular artery, can be affected. Several bouts of hemorrhage usually precede a fatal episode. Mucus and dark blood continue to drain from the nostril on the affected side for days after acute hemorrhage ceases.

The second most common clinical sign is dysphagia caused by damage to the pharyngeal branches of the vagus and glossopharyngeal nerves.139 Aspiration pneumonia may develop in severe or protracted cases. Abnormal respiratory noise can arise from pharyngeal paresis or from laryngeal hemiplegia, which results from recurrent laryngeal nerve damage.139 Horner’s syndrome may develop from damage to the cranial cervical ganglion and postganglionic sympathetic fibers. The classic signs associated with this denervation are ptosis, miosis, and enophthalmos; patchy sweating; and congestion of the nasal mucosa. The reason equine sweat glands increase their activity when denervated is unclear.144 Equine sweat gland myoepithelium is predominantly under α1-adrenergic control, with additional α2-adrenergic input from receptors. However, sweating after neuroectomy may be caused by increased peripheral vasodilation, which increases blood flow and skin temperature. Ptosis is caused by a decreased tone of the superior tarsus muscle, and it is assessed by observing eyelash angles from a frontal view. Papillary response to decreased sympathetic tone in horses is variable, and the maximal difference in pupil size is usually slight. Enophthalmos, which is the result of decreased smooth muscle retraction and unopposed activity of the striated retractor bulbi muscle, is rarely obvious and usually evident as a slight protrusion of the nictitating membrane.144

Less common signs of gullet pouch mycosis are parotid pain, nasal discharge, abnormal head posture, head shyness, sweating and shivering, corneal ulcers, colic, blindness,
Diagnosis
Endoscopy is critical for diagnosis of guttural pouch mycosis and should be combined with the history and clinical signs. On endoscopic examination of a horse with epistaxis, blood can be seen draining from the pharyngeal orifice. In horses with dysphagia the roof of the pharynx can be collapsed, the soft palate can be displaced, and the nasopharynx may contain food material. The lesion appears as a white, tan, and black diphtheritic membrane on the roof of the affected guttural pouch, and its size can vary but bears no relationship to the severity of clinical signs. Part of the diphtheritic membrane can coat the stylohyoid bone and the bone can be thickened, but clinical signs usually do not develop from this change. Fistulas may form into the opposite guttural pouch and pharynx. The presence of serum antibodies to Aspergillus fumigatus detected by ELISA cannot distinguish between horses with guttural pouch mycosis and healthy horses.

Medical Therapy
The response to topical treatment is generally slow and inconsistent. Daily direct lavage through the endoscope can macerate the diphtheritic membrane, and the biopsy forceps or cytology brush of the endoscope can be used to detach it, provided any eroded artery was occluded beforehand. Topical povidone-iodine or thiabendazole, with or without dimethyl sulfoxide, has been used with mixed results. Nystatin, natamycin, and miconazole are effective against this organism, although its use is limited by its toxicity.

Successful treatment of dysphagia from guttural pouch mycosis has been reported with a combination of oral triazole (5 mg/kg) and topical enilconazole (50 mL of 33.3 mg/mL solution per day) in one horse, and with topical enilconazole alone in another. Itraconazole at 3 mg/kg twice a day in the feed can be effective against Aspergillus and other fungi in the nasal passage of horses, but treatment may be required for up to 4 or 5 months. Bioavailability of another triazole antifungal agent, fluconazole, can be sufficiently high after oral and IV administration in horses to suggest a potential value in treatment of fungal infections. The response to any treatment method that is measured solely by disappearance of the mycotic lesion should be interpreted with caution because spontaneous regression of the lesion over a variable time course is typical. Horses with blood loss should be treated with polyionic fluids and, if necessary, with blood transfusions, and horses with dysphagia should be fed by nasogastric tube or by esophagostomy and should receive nonsteroidal antiinflammatory drugs to reduce neuritis.

Surgical Therapy
The diphtheritic membrane can be detached by gentle swabbing and lavage through a modified Whitehouse approach. This treatment does not eliminate the risk of hemorrhage completely; and it does not slow or reverse progression of neurologic signs, but it does carry the risk of intracranial nerve damage and hemorrhage. In horses with epistaxis the affected artery should be identified by endoscopy and surgically occluded. Anecdotally, but widely accepted evidence indicates that occlusion of the affected artery hastens spontaneous resolution of the mycotic lesion and thereby renders medical therapy unnecessary.

In a horse with hemorrhage caused by guttural pouch mycosis, the involved artery or arteries should be occluded by one of the following procedures, or a combination, as soon as the diagnosis is made. The vessel to be occluded is determined by endoscopy. If accurate identification is impossible because landmarks are obscured by blood and diphtheritic membrane, all arteries in the pouch should be occluded. Arteriography may be used to identify the affected vessel and to identify unusual anatomy. It is not required in all cases but in all cases, however, it does allow more precise and selective occlusion.

In horses with guttural pouch mycosis, fatal or severe hemorrhage has followed ligation of the affected ICA and could be attributed to occlusion of the wrong vessel or to retrograde flow from the cerebral arterial circle (circle of Willis). Complications likely occur because ligation of the ipsilateral common carotid artery in a horse bleeding from the ICA would increase flow in the affected artery and would be contraindicated. However, the same procedure may provide some immediate benefit in horses bleeding from the ECA and its branches, although any such benefit could be temporary. Ligation of the affected ICA would decrease flow but not pressure, so bleeding could persist or recur. However, if access to definitive occlusion procedures is not immediate during a severe bleeding crisis, induction of general anesthesia to quiet the horse and ligation of the affected internal carotid artery could be attempted as a temporary measure.

Success with ICA ligation can be attributed to thrombosis and early ligation at some time after surgery. To prevent backflow, an additional ligature has been placed distal to the mycotic infection; however, this is difficult because the artery must be ligated deep within the guttural pouch, where it is likely to be obscured by the diphtheritic membrane. The site for ligation of the ICA is immediately distal to its origin, outside the guttural pouch, using a similar but more ventral approach to a hyovertroptomy. The ICA is identified on the cardiac side of the occipital artery and deep to that vessel. In some horses, both arteries arise as a single trunk. If necessary, both ICAs can be ligated simultaneously without any apparent risk.

The ECA can be ligated distal to the origin of the lingual arterial trunk through an incision similar to that used for the ICA ligation; however, after extensive rostral dissection, this procedure is generally unsuccessful because the ECA and MA have numerous collateral channels that allow retrograde flow to the affected segments. Although ligation of the major palatine artery could prevent retrograde flow, a combination of this procedure with ligation of the ECA and ICA can cause ischemic optic neuropathy and permanent blindness.

The balloon catheter technique allows immediate intravascular occlusion of the artery and prevents retrograde flow from the cerebral arterial circle. Risk of retrograde flow is not diminished immediately by ligation alone, because this does not decrease blood pressure in the distal segment of artery. Complications associated with this procedure are rare. The catheter rarely penetrates the defect in the artery, and if it does, it can be withdrawn and redirected. Failure to prevent fatal hemorrhage in one case was caused by inadvertent catheterization and occlusion of an aberrant branch from the ICA, which left the affected segment of artery open to retrograde blood flow. To prevent this mishap, approximately 6 cm of the ICA should be exposed to locate any aberrant branch. Such a branch should be ligated so that the catheter can be maintained in the ICA.

Approximately 50% of horses with hemorrhage die from this complication, but this risk can be eliminated or greatly reduced by occlusion procedures. These procedures must be
performed as soon as possible after the first bout of hemorrhage to prevent subsequent bouts that could render the horse a poor candidate for anesthesia and surgery. Although the myotic lesion disappears with time, neurologic signs can persist. Laryngeal hemiplegia is usually permanent, but recovery has been reported. Some horses with dysphaia do eventually recover, but 6 to 18 months may be required and recovery may be incomplete. Horses can recover from Horner’s syndrome and facial nerve paralysis.

Balloon catheter occlusion has been fraught with failure because of inappropriate placement. Balloon occlusion of the MA is more effective than ligation. In addition, blindness associated with MA ligation (resulting in loss of flow to the parotid gland) does not occur. However, the owner should still be warned of the risk of blindness.

A detachable, self-sealing, latex balloon can be used to occlude the ICA successfully, without the need for catheter removal, as required in some patients treated with the non-detachable balloons. Combined with angiography, the detachable system can also be used to occlude aberrant vessels that originate at a distance from the origin of the ICA. A transcorterial balloon embozilization technique can selectively occlude the arterial segments involved in a myotic lesion in horses with gullet pouch mycosis. The embozilization technique combines angiographic studies to image the affected vessels and identify any unusual vessels and sites of bleeding, followed by a selective embozilization or occlusion of the affected vessels. Compared with the balloon catheter technique, transcorterial balloon embozilization allows visualization of affected vessels throughout the procedure because it is performed under fluoroscopic guidance. This is critical because aberrant vasculature has been described in horses with gullet pouch mycosis, and failure to identify and occlude such aberrant branches may result in fatal hemorrhage. It is less invasive than the original balloon catheter procedures and requires shorter anesthesia and shorter hospitalization. Transcorterial embozilization can be performed during active bleeding. The surgical approach for all arteries in the gullet pouch is the common carotid artery exposed through a single incision. The disadvantages of this technique are the need for fluoroscopy (and the specialized equipment and expertise involved), positioning of the horse’s head for fluoroscopy, and apparel and equipment for radiation shielding.

**Temporohyoid Osteoarthropathy**

Etiology

Temporohyoid osteoarthropathy is a progressive disease of the middle ear and componentes of the temporohyoid joint, such as the stylohyoid bone, the cartilaginous tympanohyoid, and squamous portion of the temporal bone. Horses of a wide age range and of any breed or either sex can be affected. The cause is thought to be an inner or middle ear infection of hematogenous origin that spreads to the bones listed, causing them to thicken and the temporohyoid joint to fuse. Other possible causes range from extension of otitis media/externa or gullet pouch infection to a nonseptic osteoarthropathy. Although gullet pouch mycosis can involve the same bony structures and temporohyoid articulation, clinical signs of temporohyoid osteoarthropathy are rare with this disease.

Once the temporohyoid joint fuses and the associated bones thicken, forces generated by movement of the tongue and larynx during swallowing, vocalizing, combined head and neck movements, oral or dental examinations, and teeth floating may induce fractures of the petrous part of the temporal bone, resulting in facial nerve (CN VII) and vestibulocochlear nerve (CN VIII) dysfunction. Severe new bone production and inflammation can damage the glossoptaryngeal and vagus nerves where they leave the medulla caudal to the vestibulocochlear nerve. After fracture of the petrous temporal bone, middle or inner ear infection could extend around the brain stem and involve additional cranial nerves and hindbrain structures.

**Clinical Findings and Diagnosis**

Early clinical signs include head tossing, ear rubbing, refusing to take the bit, refusing to position the head properly when under saddle, resistance to digital pressure around the base of the ears or on the bony prominence, and other nonspecific behavior changes. The disease can cause an acute onset of signs consistently referable to facial and vestibular nerve deficits, including asymmetric ataxia, head tilt with the poll to the affected side, and spontaneous nystagmus with the slow component to the affected side. These signs can be revealed or exacerbated by blindfolding. Signs of facial nerve damage, including paresis or paralysis of the ear on the affected side, deviation of the upper lip away from the affected side, decreased tear production, and inabiity to close the eyes, are evident in most cases. Decreased tear production and inability to close the eyes may cause corneal ulcers, keratoconjunctivitis sicca, and exposure keratitis. Dysphagia is rare but can result from damage to the glossoptaryngeal and vagus nerves.

Radiographs of the skull may depict proliferation and osteitis of the affected bones; however, endoscopy of the gullet pouch is in most cases a more sensitive method for detection of stylohyoidal bone and temporohyoid joint involvement and thus for making the diagnosis. CT or MRI can precisely demonstrate bony and soft tissue changes in the middle and inner ear.

**Therapy**

Medical treatment includes broad-spectrum antibiotics for infection, nonsteroidal antinflammatory drugs to relieve pain and inflammation, and dimethyl sulfide to relieve inflammation. Unilateral partial osteotomy of the stylohyoid bone has been used to create a pseudoarthrosis between the cut ends of the bone, which decreases the forces on the ankylosed temporohyoid and thereby prevents skull fractures (Fig. 1-20). In this procedure, approximately 2 to 3 cm

![Fig. 1-19 Thickened stylohyoid bone with involvement of temporohyoid articulation in horse with clinical signs of damage to vestibulocochlear and facial nerves. (From Freeman DE, Hardy J: Cuttural pouch. In Auer JA, Stick JA, editors: Equine surgery, ed 3, St Louis, 2006, Elsevier, p 599.)](image-url)
of the midbody of the stylohyoid bone is removed. Although this procedure appears to have merit as a prophylactic measure against more severe bone damage and associated neurologic consequences, it may cause transient dysphagia or injury to the hypoglossal nerve. When performed as a bilateral procedure, it causes permanent problems with prehension. An additional complication of partial ostectomy is regrowth of the stylohyoid bone approximately 6 months after surgical resection, with recurrence of clinical signs. Because of this complication, a cartilageostectomy has been recommended as a safer, easier, and more permanent surgical alternative. Although the prognosis is good according to one report, neurologic signs may persist, especially if treatment is delayed. In general, the prognosis for stylohyoid arthropathy is dependent on the severity of clinical signs. Some degree of facial and vestibulocochlear nerve paresis can persist. The cornual ulcers are difficult to treat, because there is an underlying problem with lid closure and tear production. A temporary tarsorrhaphy may help to manage the ocular complications until facial nerve function returns.

REFERENCES

See the CD-ROM for a list of references linked to the abstract in PubMed.

SUGGESTED READING

Guttural Pouch


CHAPTER 2  •  Cardiovascular Infections

Celia M. Marr

All components of the cardiovascular system, from cardiac tissues to blood vessels, are susceptible to infection. Fortunately, these conditions are relatively uncommon in the horse, but they can be devastating when they occur. Viral or bacterial infection can also act as a trigger for immunemediated disorders, such as pericarditis and myocarditis. Fever is a common clinical feature of cardiovascular infections, and specific localizing signs will vary depending on the specific site of infection. In general, successful treatment relies on appropriate antimicrobial therapy. In many cases, however, systemic inflammatory response syndrome is a prominent feature, and supportive therapy is important and challenging in these severely compromised individuals.

INFECTIVE ENDOCARDITIS

Etiology and Pathogenesis

Infective endocarditis (IE) is an uncommon but frequently fatal disorder in horses. Endocardial lesions have been reported in association with Lyman borreliosis and infection with Shigella equi. However, review of clinical and pathologic reports of equine IE published since 1980 (34 cases) together with an additional six cases seen at the author's clinic, has demonstrated that a range of microorganisms may be implicated in equine IE. Actinobacillus equuli, Pasteurella multocida, Actinobacillus spp., Pseudomonas spp., Escherichia coli, Corynebacterium spp., Bacillus spp., Staphylococcus spp., and Streptococcus spp. are reported as causes of IE in horses, with no one organism emerging as distinctly more prevalent than the others. Actinobacillus equuli (6 of 32 reported cases, 18.8%; 95% confidence intervals [CI] 5.2%-32.3%) and Pseudomonas spp. (3 of 32 cases, 9.4%; CI 0%-19.5%) occur more than once in this literature series, whereas the other organisms were each identified in one case only.

Rhodococcus equi was isolated from synovial and bony material removed surgically from a foal with septic osteoarthritis and mural IE, but blood culture from that foal yielded Escherichia coli. A blood culture from a 14-year-old mixed-breed gelding with aortic IE in the author's clinic also yielded R. equi. That horse had no apparent immunosuppression or other reason to have become infected with R. equi and recovered after 6 weeks of treatment with trimethoprim-sulfonamide and rifampicin. Although not a typical skin commensal, R. equi may have been a contaminant introduced during the blood collection. Fungal IE has been attributed to Aspergillus species in a horse with disseminated aspergillosis affecting the lungs, intestine, and peritoneal cavity, as well as the mitral valve and left ventricular wall. In another report, Candida species affected the aortic valve and right atrial wall in an 11-year-old Thoroughbred. In many cases of IE the causative microorganisms cannot be determined. Neither blood nor post-mortem cultures allowed identification of a causative organism in 7 of 32 horses (22%, CI 7.6%-36.2%) in which culture was attempted.

A combination of endothelial damage and bacteremia are prerequisites for the development of IE. Frequent heart disease is present in 42% to 58% of human IE patients, and 4% to 13% have congenital defects such as ventricular septal defect (VSD), with preexisting valvular regurgitation in most of the remaining patients. Endothelial damage caused by the effects of high-velocity jets and turbulence leads to deposition of complexes of platelets and fibrin, which in turn are susceptible to colonization by bacteria or fungi during bacteremia or fungemia. In horses the structures on the left side of the heart are most likely to be affected by IE, with the mitral valve affected slightly more often than the aortic valve, despite that preexisting valvular lesions are most likely to be present on the aortic valve (Table 2-1). Mural endocarditis occurs less often in horses, possibly because an association between IE and VSD, which is an important predisposing factor in human IE, has not been identified in the horse, although this is a fairly common congenital abnormality in certain breeds, such as the Standardbred, Arabian, and Welsh Mountain pony.

The portal of entry of the causative microorganism is often not apparent. In humans, potential routes include dental infection and procedures, surgery, endoscopy, intravenous (IV) catheters, drug abuse, and infection of the skin, lungs, bowel, and urinary tract. No established association exists between bacteremia and dental procedures in horses, but IE has occurred after repulsion of the first molar by traumatization of the maxillary sinus in a case of endocarditis infection caused by Fusobacterium necrophorum. A 13-year-old mixed-bred mare at the author's clinic had concurrent temporomandibular osteoarthropathy and garticular pouch empyema from which β-hemolytic Streptococcus spp. were isolated, although blood culture was negative. Septic jugular thrombophlebitis is considered a risk factor for tricuspid IE in horses. Two of six reported cases of tricuspid IE had recent jugular thrombophlebitis; a third case had an inactive thrombosis related to treatment for an unrelated condition 1 year earlier. Permanent IV devices, such as transvenous pacing devices, are rarely used in horses but can predispose to IE. IE has also been reported in foals with concurrent septicaemia, umbilical infection, and osteoarthritis, but in most adult cases the route of infection remains unclear.

Once a critical mass of bacteria has been deposited on an area of damaged endothelium, vegetations consisting of platelets, fibrin, microorganisms, exopolysaccharides, inflammatory cells, and associated necrotic debris begin to develop. Mitrail and tricuspid vegetations typically occur on the atrial surface of the valve (Fig. 2-1), whereas aortic vegetations are more likely to develop on the ventricular surface. However, vegetations may occur on any endocardial surface, including the valve leaflets, ventricular or atrial endocardium, and the intimal surface.
**Table 2-1**

**Location of Lesions in 40 Cases of Infective Endocarditis**

<table>
<thead>
<tr>
<th>Location</th>
<th>Number Affected</th>
<th>Prevalence (%)</th>
<th>Lower Confidence Limit (%)</th>
<th>Upper Confidence Limit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases with Single Site Involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral valve only</td>
<td>11</td>
<td>27.5</td>
<td>13.7</td>
<td>41.3</td>
</tr>
<tr>
<td>Aortic valve only</td>
<td>9</td>
<td>22.5</td>
<td>9.6</td>
<td>35.4</td>
</tr>
<tr>
<td>Tricuspid valve only</td>
<td>5</td>
<td>12.5</td>
<td>2.3</td>
<td>22.7</td>
</tr>
<tr>
<td>Pulmonic valve only</td>
<td>1</td>
<td>2.5</td>
<td>0</td>
<td>7.3</td>
</tr>
<tr>
<td>Mural: left atrium</td>
<td>11</td>
<td>27.5</td>
<td>0</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Cases with Single or Multisite Involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral valve</td>
<td>21</td>
<td>52.5</td>
<td>37.0</td>
<td>68.0</td>
</tr>
<tr>
<td>Aortic valve</td>
<td>15</td>
<td>37.5</td>
<td>22.5</td>
<td>52.5</td>
</tr>
<tr>
<td>Tricuspid valve</td>
<td>8</td>
<td>20.0</td>
<td>7.6</td>
<td>32.4</td>
</tr>
<tr>
<td>Pulmonic valve</td>
<td>2</td>
<td>5.0</td>
<td>0</td>
<td>11.8</td>
</tr>
<tr>
<td>Mural sites</td>
<td>4</td>
<td>10.0</td>
<td>0.7</td>
<td>19.3</td>
</tr>
<tr>
<td>&quot;Left heart&quot; structures</td>
<td>26</td>
<td>65.0</td>
<td>50.2</td>
<td>79.8</td>
</tr>
<tr>
<td>&quot;Right heart&quot; structures</td>
<td>7</td>
<td>17.5</td>
<td>5.7</td>
<td>29.3</td>
</tr>
<tr>
<td>Both sides of heart</td>
<td>5</td>
<td>12.5</td>
<td>2.3</td>
<td>22.7</td>
</tr>
</tbody>
</table>

*With 34 cases from references 3-18, 29, 31, and 32, plus 6 cases from the author’s clinic.*

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**Fig. 2-1** Pathologic specimen from 8-year-old Thoroughbred stallion with infective endocarditis. Vegetations are attached to both the ventricular (white arrows) and the aortic (black arrowhead) aspects of the aortic valve. An additional small vegetation is attached to the intimal surface of the aorta (black arrow). The tear in the left coronary cusp was created postmortem.

**Fig. 2-2** Pathological specimen from 4-year-old Thoroughbred colt with infective endocarditis. Vegetations are attached to both the ventricular (white arrows) and the aortic (black arrowhead) aspects of the aortic valve. An additional small vegetation is attached to the intimal surface of the aorta (black arrow). The tear in the left coronary cusp was created postmortem.

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of the great vessels (Figs. 2-2 and 2-3). Vegetations usually form at the line of valve closure.21 "Kissing lesions" develop by spreading between adjacent cusps21,28 (Fig. 2-4). IE can extend to involve adjacent structures, such as the chordae tendineae7,12,29 and papillary muscles,28 or can form myocardial abscesses through metastatic infection or direct extension.6,30,31 Infected areas may perforate, leading to defects in the septum or aorta31 or septic pericarditis.38 Valve cusps32 and chordae tendineae7,12,29 can rupture, causing catastrophic regurgitation.

The hemodynamic consequences of IE involve the combined effects of regurgitation and the systemic inflammatory response syndrome (SIRS). Severe mitral regurgitation results in pulmonary hypertension and pulmonary congestion and may lead to right-sided heart failure.32 In acute cases, there may be clinical and radiographic signs of pulmonary edema. Horses that survive the initial episode of acute mitral IE may develop signs of congestive heart failure (CHF), and resultant chronic pulmonary hypertension can lead to pulmonary artery rupture.15
Fig. 2-3  Right (A) and left (B) long-axis echocardiograms of the left ventricular outflow tract (LVOT) and right short-axis (C) echocardiogram of the ascending aorta (AO) from 5-year-old Thoroughbred mare with infective endocarditis diagnosed 6 days earlier. Large, heterogenous vegetations (arrows) are attached to upper and lower aspects of the aortic valve and to the intimal surface of the aorta. TV, Tricuspid valve; LA, left atrium; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

Fig. 2-4  Right long-axis echocardiograms from 8-year-old polo pony gelding with infective endocarditis diagnosed 2 days earlier. Vegetations (arrows) are visible on adjacent aspects of the septal and nonseptal cusps of the mitral valve, and rupture of a chorda tendinea is allowing a portion of the septal cusp (arrowhead) to prolapse into the left atrium (LA). RA, Right atrium; RV, right ventricle; LV, left ventricle.
In general, aortic regurgitation appears to be better tolerated in horses than in humans, in whom severe hemodynamic collapse occurs more often with aortic IE or myocarditis than with mitral IE.

Regardless of the site of the vegetation, bacteremia is likely to induce SIRS and, consequently, distributive shock. The self-amplifying cascade of inflammatory mediators that is triggered in SIRS dysregulates hemodynamic control mechanisms. The pathogenesis of SIRS is described in Chapter 37. In brief, widespread vasodilation produces vasodilatory blood pooling, decreased venous return, and decreased cardiac output. This is exacerbated by a direct myocardial suppression, and when these changes are superimposed on mitral or aortic insufficiency, the situation worsens synergistically.

Once IE is established, in addition to valvular pathology, local infection, bacteremia, and related hemodynamic consequences, embolic complications and immunologic events contribute to disease progression. Myocarditis results from microabscesses, coronary vasculitis, immune complex deposition, and injury from microbial toxin production. Myocardial infarcts, coronary artery thrombosis, and pulmonary artery thrombosis may further compromise cardiac function. Embolic pneumonia occurs secondary to tricuspid IE. Testicular, adrenal, and pancreatic infarcts have been described in a horse with aortic IE and a history of testicular torsion. Renal infarcts are found in two-thirds of horses who succumb to IE and were present in 8 of 28 horses (28.6%; CI 11.8%-45.3%) at postmortem examination. All the equine cases of renal infarct involved IE in the left side of the heart; however, renal infarcts are occasionally associated with right-sided IE in humans, in whom the presumed source of emboli is thrombosed pulmonary vessels resulting from embolic pneumonia.

Immunologically mediated glomerulonephritis, prerenal azotemia, and disseminated intravascular coagulation are also potential sequelae to IE. The compromised individual with IE is at increased risk of developing acute tubular nephropathy in association with use of antimicrobials, such as the aminoglycosides. Lameness and synovial effusion are common. Multiphasic synovial distention is generally immunologic in origin, however, septic embolism can lead to synovial sepsis, particularly in the digital sheath. Various forms of neuropathology occur in approximately 30% of humans with IE, about half of whom have associated clinical signs and a high mortality rate. These complications are relatively rare in horses, but their prevalence may be underestimated (3 of 28 reported cases, 10.7%; CI 0%-22.25%) because of the lack of large, high-quality case series. Meningeal infarcts were described in two horses with IE, one of which had neurologic signs. An additional horse with mitral and aortic IE developed unilateral blindness, optic neuritis, uveitis with endophthalmitis, and multifocal suppurative meningoencephalitis in association with Actinobacillus equuli infection.

**Clinical Findings**

IE has been described in horses ranging from 2 months to 15 years of age, with a median age of 5 years and interquartile range of 10 months to 9 years. Thus, IE appears to be a disease of younger adults, although the demographics of the populations from which these cases were derived are unknown. There is no apparent breed predisposition, but the ratio of males to females is 1.85:1, which is similar to that described in humans. Fever is the most common presenting sign in horses with IE (Table 2-2).

Cardiac murmurs were present in all animals with left-sided involvement but in only three of six horses with tricuspid IE. In the sole reported equine case of pulmonic IE, no murmur was detected. Therefore, it is important to remember that absence of a cardiac murmur does not exclude a diagnosis of IE. Murmurs are most likely to be absent in IE caused by a virulent microorganism that induces rapid, severe disease, and interestingly, two of four equine reports include horses that died shortly after the onset of signs. When present, the murmur of tricuspid regurgitation has its point of maximal intensity (PMI) over the right fourth intercostal space and is usually holosystolic. Mitral regurgitant murmurs are also holosystolic, with their PMI over the left fifth intercostal space. Aortic regurgitant murmurs are holodiastolic, with their PMI over the left fourth intercostal space, high in the axilla. Mitral IE and aortic IE are usually associated with very
## Table 2.2

<table>
<thead>
<tr>
<th>Major Clinical Findings in 35 Cases of Infective Endocarditis*</th>
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<tr>
<td><strong>CLINICAL SIGN</strong></td>
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<td>--------------------</td>
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<tr>
<td>Fever and depression</td>
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<tr>
<td>Cardiac murmur†</td>
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<td>Cardiac arrhythmia</td>
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<td>Ventral edema</td>
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<td>Lumeness</td>
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<td>Joint and/or tendon</td>
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<td>Smooth distention</td>
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<td>Weight loss</td>
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<td>Respiratory signs</td>
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*With 20 cases from references 3, 18, 29, 31, and 32, plus 6 from the author's clinic.

†Not reported = 1.

‡Not reported = 3.

lead murmurs that radiate over a wide area. Aortic IE murmurs, as with the murmur caused by severe degenerative aortic valve disease, typically have a squeaking or buzzing quality. A mitral regurgitant murmur with a honking quality should raise the suspicion of rupture of one or more chordae tendineae.

Additional signs of cardiovascular compromise that are not specific for IE include tachycardia, weak pulses, congested or pale mucous membranes, and petechiation. Affected horses are usually depressed, lethargic, anorexic, and weak.

Cardiac arrhythmias occur in approximately one third of horses with IE (Table 2-2). Ventricular arrhythmias may involve isolated ventricular depolarizations or monomorphic or polymorphic ventricular tachycardias (Fig. 2-5). Episodic collapse or distress can be associated with arrhythmic episodes in both acute and chronic stages. Although no statistical association has been documented, horses with aortic IE appear to be most likely to develop ventricular arrhythmias in humans, these patients are most likely to develop coronary thrombosis and myocardial microabscesses. Supraventricular premature depolarizations and atrial fibrillation may occur, particularly in horses with mitral or left-side atrial mural IE. Signs consistent with CHF, including ventral edema, pleural and peritoneal effusion, and venous congestion, may be detected on presentation or develop as disease progresses.

Lameness is a frequent presenting complaint for horses with IE (Table 2-2). This is often shifting in nature and may be associated with distention of one or more synovial structures. IE should be considered as a potential source of hematogenous synovial sepsis. Right-sided IE generally presents with clinical and radiographic signs relating to embolic pneumonia in humans. Other clinical signs reported in horses with IE include ataxia or other neurologic abnormalities, blindness, laminitis, guttural pouch empyema, sinusitis, umbilical infection, and physisis.

### Diagnosis

Hematologic and blood biochemical abnormalities are not specific for IE but include leukocytosis (18 of 20 reported cases, 90%; CI 76.9%–100%), hyperbilirubinemia (13 of 14 reported cases, 93%; CI 79.4%–100%), anemia (12 of 17 reported cases, 71%; CI 56.8%–87.2%), and less often, thrombocytopenia (1 of 13 reported cases, 7.1%; CI 0%–28.6%). C-reactive protein (CRP), an acute-phase protein that increases in response to infection and inflammation, is considered particularly useful in diagnosis of IE in humans and is used to monitor therapy. Suitable alternatives in the horse may be serum amyloid A and fibrinogen concentrations. Increases in serum concentrations of creatinine and blood urea nitrogen warrant a guarded prognosis because they may indicate renal infarct. Measurement of cardiac troponin I and the cardiac isoenzyme of creatine kinase (CK-MB) can be useful in identifying myocardial lesions. Cardiac arrhythmias should be characterized; ambulatory electrocardiographic (ECG) monitoring may be useful in detecting paroxysmal arrhythmias that are not evident on a short rhythm strip.

The Duke diagnostic criteria for IE in humans, based on laboratory and echocardiographic findings, were developed to categorize patients as definite, possible, or rejected IE cases. Major criteria are (1) persistent positive blood cultures (the specific number of cultures required is defined by the specific organism in question) and (2) echocardiographic evidence of endocardial involvement. Minor criteria include (1) fever, (2) predisposition (e.g., preexisting heart condition), (3) vascular phenomenon (e.g., renal infarcts), (4) immunologic events (e.g., glomerulonephritis, positive rheumatoid factor), (5) positive blood cultures that fall short of the definitions of persistent bacteremia, and (6) suspicious but not definitive echocardiograms. Cases are rejected when (1) a firm alternative diagnosis is made, (2) the clinical signs resolve with antimicrobial therapy in 4 days or less, or (3) pathologic evidence is lacking at surgery or autopsy. The Duke criteria are primarily a tool to allow comparison of patient groups in clinical research but serve to emphasize the importance of blood culture and echocardiography in the diagnosis of IE. Echocardiography achieves improved sensitivity and equivalent specificity when these criteria are compared with older classification systems based on clinical and laboratory findings alone. Similarly, in horses the majority of premortem diagnoses of IE are based on echocardiographic findings combined with laboratory findings.

Blood culture is extremely important in the diagnostic evaluation of horses with IE because it may allow identification of a specific microorganism that will help define therapy. In IE there is continuous bacteremia, and therefore timing culture with fever spikes has no advantage. The optimal number of cultures is not known, but at least three and ideally five blood samples obtained at hourly intervals using aseptic technique should be submitted. Prior antimicrobial therapy limits
the likelihood of positive cultures. Microorganisms were identified in 13 of 20 horses (68.4%; CI 47.5%-89.9%) when one to four cultures were submitted (median of two). In all cases, samples were obtained before antimicrobial therapy was initiated by the attending veterinarian, although almost all these horses had received antimicrobial medication before admission to the hospital where they were investigated. Passage of the blood sample through a device designed to remove antimicrobials before inoculation of blood onto culture media may enhance bacterial recovery rates. Cultures should be incubated for a minimum of 4 days before they are classified as negative because prior antimicrobial therapy may delay the growth of microorganisms. Additional reasons for negative blood culture include extended course of illness, mural endocarditis, and infection with a fastidious microorganism or an obligate intracellular pathogen.

The introduction of molecular techniques for the identification of microorganisms has led to the recognition of a wide spectrum of causal organisms in culture-negative IE in humans, and similar progress can be expected in veterinary medicine in the future. In such culture-negative infections, however, antimicrobial sensitivity testing is not possible, so the therapeutic advantage of identifying the specific causative organism is lost.

Echocardiography has a pivotal role in the diagnosis of IE. The presence of an oscillating soft tissue mass attached to the valve cusps, endocardial surfaces of the cardiac chambers, or the intimal surface of the great vessels represents definitive evidence of a vegetation (see Figures 2-3 and 2-4). Many disease processes can cause thickening of the valve cusps, and it can be difficult to distinguish vegetations from other forms of nodular pathology. Recognition of oscillatory movement of a mass independent of movement of the valve confirms that it is a vegetation. In humans, the use of transesophageal imaging provides superior resolution and has superior sensitivity to transthoracic echocardiography in detection of vegetations. Currently, transesophageal imaging in horses is limited to a small number of veterinary hospitals and requires general anesthesia. Because conventional transthoracic echocardiography requires transducers of relatively low frequency, vegetations may go undetected in some cases of equine IE.

Differentiating severe degenerative valvular disease from IE can be difficult. When severe nodular changes are detected in younger animals at low risk of severe degenerative valvular disease, particularly if the nodules are located on the low-pressure side of the valve (ventricular surface for aortic valve, atrial surfaces for mitral and tricuspid valves) and are accompanied by clinical and laboratory evidence of infection, a diagnosis of probable IE should be considered, with appropriate treatment instituted (at least until this diagnosis can be rejected after reaching an alternative diagnosis). In the early stages of the disease, vegetations tend to be fairly homogenous (see Figures 2-3 and 2-4), and as they become more organized, they become more echogenic and heterogeneous. Additional structural changes may be visible, such as ruptured chordae tendineae, which cause portions of the valve (flail cusp) or chordae to prolapse into the atrium (see Figure 2-4).

Doppler echocardiography allows identification of regurgitation and permits semiquantitation of its degree, which is usually moderate to severe with IE (Fig 2-6). Jet dimensions provide only a subjective impression of the degree of regurgitation, and these measurements are not very repeatable. Limitations are created by several factors: suboptimal image angulation leads to underestimation of jet size, particularly in the mitral valve, where regurgitant jets are often running at right angles to the image plane, and variation of the image plane is difficult because of anatomic constraints. Additional Doppler echocardiographic findings indicative of severe regurgitation include proximal flow convergence and velocity characteristics. Proximal flow convergence is recognized where nonturbulent, retrograde flow can be seen to speed up as it is approaching the regurgitant orifice, represented by bands of color on the proximal aspect of the regurgitating valve (Fig 2-6). The velocity of flow across a regurgitant orifice or other intracardiac shunt is determined by the pressure difference between the two chambers in question. With severe aortic regurgitation, flow early in diastole will have high velocity but as left ventricular pressures rapidly increase resulting from the entry of the additional regurgitant volume, there will be a rapid deceleration of the regurgitant jet. In the presence of normal left atrial pressures that would be expected with mild mitral regurgitation, regurgitant flow between the left ventricle and left atrium is fast (usually greater than 5 m/s²), whereas with severe regurgitation, the jet velocities are lower. However, accurate flow velocities also depend greatly on the operator, machine, and angle, and these velocities should be interpreted with extreme caution because they have not been validated as indices of severity of regurgitation in the horse. A useful rule of thumb is that if Doppler echocardiographic findings suggest that there is severe regurgitation, this is probably true. However, if Doppler echocardiography fails to demonstrate severe regurgitation in a horse in which clinical findings suggest otherwise, the clinician should remember that the Doppler echocardiographic findings may be misleading.

Two-dimensional and M-mode echocardiography are also useful in assessing the hemodynamic impact of valvular regurgitation. In long-standing degenerative valve disease, the most accurate assessment of severity is gained by measurement of the diameter of the left ventricle, and these M-mode measurements correlate with heart failure score better than Doppler echocardiographic indices. Because IE is an acute severe condition, however, cardiac remodeling will not have occurred, and often the ventricular dimensions are normal despite the presence of severe regurgitation, although due to volume overload the ventricle may be hyperkinetic with

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**Fig. 2-6** Left long-axis color-flow Doppler echocardiogram from 13-year-old mixed-breed mare with aortic infective endocarditis and concurrent myocarditis of 12 weeks' duration. Two large (yellow and turquoise) jets of aortic regurgitation occupy most of the left ventricular outflow tract (LVOT), and proximal flow convergence is present [between arrows]. RV, Right ventricle; RA, right atrium. (See also Fig. 2-5.)
exaggerated movement of the septum and the free wall (Fig. 2-7). Fractional shortening* may be increased provided that myocardial function is maintained, but it may be decreased if there is concurrent myocardial failure. With reduced cardiac output, the diameter of the aortic root may be decreased and the movement of the aortic root depressed on M-mode echocardiography (Fig. 2-7). Dilation of the pulmonary artery is a sensitive indicator of pulmonary hypertension; it can be identified by comparing the diameter of the pulmonary artery in a long-axis image of the right ventricular outflow tract with the diameter of the aorta in a long-axis image of the left ventricular outflow tract (Fig. 2-8). In longstanding cases, signs of ventricular remodeling can be expected. As it enlarges, the left ventricle will typically take on a rounded or globoid shape at the apex, and M-mode measurements of the ventricular dimensions and septal-mitral E-point separation will increase.55,56

Therapy
The first goal of therapy is sterilization of the vegetations.30,57 Successful treatment of IE requires bactericidal therapy over a prolonged period. It is extremely important to attempt to isolate the organism and determine antimicrobial sensitivity patterns if possible.50 In the absence of specific culture results, broad-spectrum antimicrobial therapy should be instituted. Penicillin and gentamicin are the most common choices, but previous reports have also described using ampicillin, trimethoprim-sulfonamide, metronidazole, oxytetracycline, cefotaxime, and rifampicin, with no antimicrobial regimen emerging as superior to the others. Bactericidal drugs are preferable to bacteriostatic drugs in this life-threatening bacteremia.50,58 It is difficult to predict the causative organism, although as noted previously, Pasteurella and Actinobacillus species represent about 20% of cases, and Psuedomonas spp. were isolated from about 10%. Consequently, penicillin with an aminoglycoside or a fluoroquinolone such as enrofloxacain can be predicted to have an appropriate spectrum of activity. Serum bactericidal titers can be used to monitor therapeutic efficacy. Serial dilutions of the patient's serum, collected at the end of dosing, are tested for their ability to inhibit growth of the bacteria previously isolated from the patient. Serum bactericidal titers of 1:16 or higher have been associated with successful outcomes in human IE.57

Drug efficacy may be compromised by poor penetration of the vegetation, high bacterial numbers and slow growth of deep-seated organisms.57 The diffusion of antimicrobials within vegetations varies; ceftriaxone and penicillin generate a concentration gradient with decreasing levels towards the center, whereas others, such as fluoroquinolones, permeate the vegetation homogeneously, which, at least theoretically, should confer a therapeutic advantage. However, studies relating specifically to the pharmacokinetics and pharmacodynamics of common antimicrobials used in equine IE are lacking. Rifampin has excellent tissue penetration and should be effective against gram-positive organisms but should not be used in isolation because of concerns over the development of resistance. Rifampin also has potential to induce drug interactions with phenylbutazone and digoxin.58 The clinician should

*References 4, 7, 11, 12, 14, 16, 17.
consider the possibility of concurrent renal pathology and prerenal azotemia and should use therapeutic drug monitoring with aminoglycosides to minimize the risk of renal toxicity.

Successful treatment of fungal IE has not been described in horses, although successful treatment of systemic candidiasis in foals with IV amphotericin B and oral fluconazole has been reported. In humans, amphotericin B, possibly combined with rifampin, is used to treat IE caused by candidiasis. Fluconazole is less successful but avoids the nephrotoxic effects of amphotericin.

Repeat blood cultures do not differentiate between complete and incomplete healing because vegetations may contain dead or lived organisms. On the other hand, repeat cultures may be useful in identifying treatment failure. In human medicine, serum concentrations of acute-phase CRP are used most often to monitor response to therapy and should begin to decrease within 24 hours of initiating effective therapy. In horses, antimicrobial therapy should be continued until the white blood cell count, serum fibrinogen, and serum amyloid A concentrations have returned to normal. This may involve many weeks of treatment. After treatment is discontinued, these laboratory parameters as well as clinical signs (e.g., rectal temperature) should be evaluated frequently to ensure that any relapse can be detected early. The echocardiographic appearance of vegetations alters over time, becoming denser and more echogenic, but this does not necessarily provide any information on the sterility of the lesion.

Specific measures to combat SIRS are important in the early stages of therapy (see Chapter 37). All serum and plasma products containing antibodies to the lipopolysaccharide molecule, polymyxin B, pentoxifylline, fluvinic meglumine, low-molecular-weight heparin, and aspirin are potentially useful. However, renal function must be monitored carefully when polymyxin B and nonsteroidal antiinflammatory drugs (NSAIDs) are used in patients that may have preexisting renal pathology.

Provision of cardiovascular support presents a particular problem in horses with IE. In conditions involving SIRS, high volumes of IV crystalloid and colloid fluids together with inotropic agents are advocated. With severe regurgitation, however, increased preload and consequently increased stroke volume are likely to result in an increased regurgitant fraction, and therefore it is difficult to improve cardiac output with volume replacement. In left-sided heart failure from other causes, vasodilators are used to support forward flow and cardiac output. The decrease in systemic vascular resistance (SVR) induced by SIRS may temporarily have a similar beneficial action in maintaining forward flow, and forward flow may decrease as SVR is restored when treating SIRS. Drugs such as dopamine should be used cautiously because their beneficial effects in producing vasodilation of the renal, mesenteric, coronary, and intracerebral vasculature are present only when low doses (1-3 μg/kg/min) are used, whereas dopamine stimulates α1-adrenoreceptors at higher doses, causing vasoconstriction. Similarly, because of its α1-adrenoreceptor activity, norepinephrine is likely to be counterproductive in IE. The vasoconstrictive effects of dopamine and dobutamine mediated through β1-adrenoreceptor are unlikely to be beneficial in many horses with IE. These drugs increase forward stroke volume by decreasing end-systolic volume; in acute mitral IE with normal left ventricular function, however, the afterload reduction created by the regurgitant pathway already allows for ejection to the point of minimum end-systolic volume.

The arteriovenous dilatator sodium nitroprusside along with diuretics is used to stabilize humans with left-sided IE, provided the arterial pressure is adequate for organ perfusion. Angiotensin-converting enzyme (ACE) inhibitors such as enalapril have a similar effect, and if arteriovenous dilatation fails, the arterial dilator hydralazine is considered. The pharmacokinetics of hydralazine have been established in the horse, with a dose of 0.5 mg/kg IV recommended. Unfortunately, the oral bioavailability of enalapril in the horse is extremely low. Sodium nitroprusside, hydralazine, and alternative ACE inhibitors have yet to be critically evaluated in equine patients with acute heart failure. It is mandatory that the arterial pressure be monitored if such agents are employed. Furosemide is indicated if pulmonary edema is present and should be administered intravenously in the critically ill patient (1 mg/kg IV tid). Oral bioavailability is poor, and the clinical response with oral administration is often disappointing.

Prognosis

The prognosis for equine IE is extremely guarded. Thirty-two of 40 horses (fatality rate 80%; CI 67.5%-92.4%) died or were euthanized (7 died, 19 euthanized, 6 not specified). Even if the vegetation can be sterilized with antimicrobial therapy, unfortunately the structural damage to the heart valves is often so severe that CHF ensues. Clinical and laboratory signs of renal insufficiency and rupture of chordae tendineae warrant a poor prognosis. Examination of the associations between survival and age, gender, affected cardiac sites, presence of arrhythmias, and clinical and laboratory findings has shown that horses with IE of the mitral valve, either alone or in combination with other sites, have an increased risk of not surviving (proportion of cases affecting mitral valve in nonsurvivors, 62.5%; in survivors, 12.5%; p = 0.0174; odds ratio 12.09; CI 1.27-106.9). No other factor was significantly associated with survival. This demonstrates that horses with mitral vegetations are less likely to survive, although clearly with such a small study group, the magnitude of the increased risk is difficult to quantify.

INFLAMMATORY VALVULITIS

Inflammatory valvulitis is an uncommon cause of valvular regurgitation in horses, occurring much less frequently than degenerative valvular disease. Its pathologic features have not been documented rigorously, and detailed clinical descriptions are lacking. Early work on equine valvular pathology demonstrated inflammatory cell infiltrates in valvular lesions, and it was proposed at that time that this might represent a parallel condition to human rheumatic heart disease, but this hypothesis has not been explored critically. Acute rheumatic fever and its chronic sequel, rheumatic heart disease, remain a significant human health issue in developing countries. The pathogenesis involves an exaggerated immune response to streptococcal epitopes in a susceptible host and probably involves molecular mimicry between epitopes on the pathogen and host tissues resulting from structural similarities between streptococcal M protein and myosin (α-helical, coiled molecules). Valvular tissue does not contain myosin, and the involvement of the valve results from the presence of laminin, which has a similar molecular structure to myosin and M protein.

Inflammatory valvulitis is difficult to diagnose with certainty. It should be considered in horses with valvular regurgitation and echocardiographically visible valve thickening, for which the main alternative differential diagnoses are degenerative valvular disease, congenital valvular dysplasia, and IE. In particular, inflammatory valvulitis should be suspected in individuals with concurrent mild ventricular dysfunction when the regurgitation improves or resolves after a period of rest, with or without corticosteroid therapy, because the other forms of valvular disease are unlikely to respond in this way. It is important for the clinician required to offer a prognosis for horses presenting with cardiac murmurs of valvular regurgitation.
to remember that occasionally, valvular regurgitation may be reversible if caused by inflammatory valvulitis. Further studies are needed to define this condition and its pathogenesis, management, and prognosis.

**MYOCARDITIS**

**Etiology and Pathogenesis**

Infection with bacteria, viruses,\(^6\) and fungi\(^66\) can cause myocarditis. Clinical signs consistent with myocarditis may also occur as sequelae to viral or bacterial respiratory infection.\(^6\) However, detailed reports of such cases are rare, and specific information on the pathogenesis is minimal.

**Clinical Findings**

Horses with myocarditis can present with signs of varying severity depending on the extent of the pathology. With focal myocarditis, horses may display fairly mild signs (e.g., impaired performance) only on maximal exercise, whereas horses with generalized myocarditis will present with signs of acute heart failure (Fig. 2-9). In more severe cases, respiratory distress, weakness, ataxia, collapse, weak pulses, tachycardia, arrhythmias, cardiac murmurs, and pulmonary and ventral edema occur.

**Diagnosis**

All forms of cardiac arrhythmias can occur with both generalized and focal myocarditis. Ambulatory ECG monitoring is useful in identifying intermittent arrhythmias and assessing response to therapy. Radiotomographic techniques are invaluable for identification of exercise-induced arrhythmias. Ventricular dilation and abnormal wall movement are the echocardiographic hallmarks of severe myocardial dysfunction. The ventricles may be subjectively enlarged with a goboid appearance at the apex (Fig. 2-10). Global myocardial dysfunction leads to reduction in movement of the ventricular walls (Fig. 2-11) and reduction in the fractional shortening. Focal myocardial disease may produce regional wall movement abnormalities, but often the echocardiogram is unremarkable. With ventricular dilation the septal-mitral E-point separation increases (Fig. 2-11, B), and reduced cardiac output leads to flattening of the aortic root on M-mode echocardiography, prolongation of the pre-ejection period, and decreases in the left ventricular ejection periods.

Cardiac troponin I is considered the most specific biochemical marker of myocardial disease,\(^41\) and increases in the serum concentration of CK-MB or lactate dehydrogenase (LDH) also suggest myocardial injury.\(^66\) Marked increases in cardiac troponin I should prompt further investigations; however, minor increases are often encountered in biochemical profiles performed at the in-house laboratory at the author’s clinic, and these horses rarely have any other evidence of myocardial disease when investigated with echocardiography or exercising and 24-hour ambulatory ECG monitoring. Evaluation of seven horses with myocardial pathology presenting to the author’s clinic suggests that cardiac troponin I is not more sensitive than CK-MB for detection of myocardial disease in horses. Increases in CK-MB, but not in cardiac troponin I, were found in horses that had myocardial disease of more than 2 weeks’ duration.\(^*\) Further work is required to determine the sensitivity and specificity of biochemical markers of myocardial injury.

**Therapy**

Treatment of myocarditis has not been well defined. If an infective origin is suspected, broad-spectrum antimicrobials are indicated. With other forms of myocardial pathology, treatment with corticosteroids is often prescribed. Dobutamine (1-5 μg/kg/min) may improve cardiac output.\(^6\) Furosemide may relieve pulmonary congestion, and digoxin has potentially beneficial positive inotropic effects and negative chronotropic effects. Digoxin can be associated with ventricular arrhythmias (or dysrhythmias), and phenytoin is recommended for treatment of digoxin-induced arrhythmias.\(^79\) In the horse, supraventricular premature depolarizations are often prevented from reaching the ventricles by the action of the vagus nerve on the atrioventricular (AV) node, such that the ventricular rate remains fairly stable in their presence, rendering specific anti-dysrhythmic therapy unnecessary. Digoxin may be used concurrently to suppress conduction at the AV node if necessary. Ventricular arrhythmias are much more likely to require anti-dysrhythmic therapy. Accepted guidelines suggest that anti-dysrhythmics should be considered when the heart rate is rapid (>100 beats/min), the arrhythmia is polymorphic, and R-on-T phenomenon is present. However, the clinical status of the animal is the most important factor to consider, and the decision to use anti-dysrhythmic drugs should be based on the presence or absence of signs of low cardiac output (e.g., weakness, cold extremities, pallor, hypotension, azotemia). Procainamide, lidocaine, and quinidine gluconate are popular first choices for emergency treatment of unstable ventricular tachycardia. Magnesium sulfate is inexpensive and readily available and can be efficacious alone or in combination with other anti-dysrhythmic agents.\(^71\) Phenytoin may be effective in cases refractory to therapy with other anti-dysrhythmics.\(^72\) (See Table 2-3.)

**Prognosis**

The prognosis for myocarditis is variable. Horses with suspected focal myocarditis, manifested by cardiac arrhythmias

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*Courtesy J. Sento and C. Marr (unpublished data).
PERICARDITIS

Etiology and Pathogenesis
Pericarditis can be effusive, noneffusive, or constrictive. Effusive pericarditis is most often fibrinous and neutrophilic in nature. Much less often, nonfibrinous, eosinophilic and histiocytic effusions have been described. Constrictive pericarditis occurs when fibrin matures to fibrous tissue or when pericardial or myocardial injury results in fibrosis.

Noneffusive pericarditis is not well described in horses but should be considered in individuals presenting with signs consistent with pericardial disease in which no effusion is identified. Rarely, pericarditis may be associated with Mycoplasma felis infection and with trauma arising from external thoracic injury, penetrating foreign bodies entering through the gastrointestinal tract, and intravenous penetration during bone marrow aspiration.

However, pericarditis appears to be of two major types: (1) idiopathic or immune-mediated infection and (2) septic pericarditis, caused by bacterial infection. Until recently, the vast majority of reported cases were classified as idiopathic. In humans, idiopathic pericarditis is viral in origin and is attributed to direct cytopathic effects, infiltration of tissues in which virus is evidenced by cytotoxic lymphocytes, and immune-mediated processes. Similar mechanisms likely...
occur in the horse. Horses with pericarditis often have a recent or current history of respiratory disease, and rising titers to equine herpesvirus type 1 (EHV-1) have been observed on paired serology in 2 of 18 cases in one study. Nevertheless, the evidence for a viral etiology, whether directly or through immune-mediated mechanisms, remains scant. Idiopathic pericarditis has also been observed as a sequela to pleuritis and peritonitis, and occasionally there is evidence of concurrent immune-mediated disorders, such as vasculitis and hemolytic anemia.

Bacterial infection is the other major cause of fibrinoeffusive and constrictive pericarditis. In an epidemic of equine pericarditis that occurred in association with early and late fetal losses in Kentucky (mare reproductive loss syndrome), bacteria were isolated from 13 of 32 pericarditis cases, with *Actinobacillus* spp. identified in 11 of 13 horses and in three of four and one of four horses in other reports. *Escherichia coli*, *Enterococcus faecalis*, *Streptococcus equi subsp. zooepidemicus*, *Streptococcus bovis*, and *Corynebacterium pseudotuberculosis* have been reported in individual cases, and β-hemolytic *Streptococcus* spp. were isolated in one of six and 2 of 18 reported cases of equine pericarditis. Of 85 cases reported in the literature since 1980, bacterial infection accounts for approximately one third of cases (27.1%; CI 17.6%-36.5%). *Actinobacillus* species are the most common isolate from pericardial fluid of horses with bacterial pericarditis (65.2%; CI 45.8%-84.7%). *Actinobacillus* spp. are commensal bacteria of mucosal surfaces that appear to be pericardiotrophic in the horse. In the outbreak of pericarditis in Kentucky, exposure to *Eastern tent caterpillars* was the greatest risk factor for the development of pericarditis, and the temporal distribution of cases was consistent with a point-source epidemic. Thus, some unidentified mechanism most likely led to a breakdown of mucosal barriers, facilitating opportunistic infection in these horses.

The hemodynamic effects of effusive pericarditis depend on the volume of fluid within the pericardial sac and its rate of accumulation. Fibin tends to accumulate in a villonodular arrangement on both inner surfaces of the pericardial sac (Fig. 2-12). Fluid and fibrin restrict diastolic filling of the

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Table 2-3

| Antidysrhythmic Agents Used In Horses |
|--------------------------|-------------------------|------------------|
| **DRUG**                | **INDICATIONS**         | **DOSE**         |
| Atropine                | Bradycardia             | 0.005-0.01 mg/kg IV |
| Bretyllium tosylate     | Ventricular fibrillation| 3-10 mg/kg IV     |
| Digoxin                 | Supraventricular tachycardia | 0.0022 mg/kg IV  |
| Lidoceaine              | Ventricular tachycardia | 0.011 mg/kg PO, q12h |
| Magnesium sulfate       | Ventricular tachycardia | 0.25 mg/kg IV bolus, can repeat in 5-10 minutes |
| Phenytoin sodium        | Ventricular and supraventricular tachycardia | 0.004 mg/kg IV boluses, q5min intervals to 0.05 mg/kg |
| Procainamide            | Ventricular and supraventricular tachycardia | 20-22 mg/kg PO q12h for 3 or 4 doses followed by 10-15 mg/kg PO q12h |
| Propranolol             | Ventricular and supraventricular tachycardia | 1 mg/kg/min IV to 20 mg/kg |
| Quinidine gluconate     | Ventricular and supraventricular tachycardia | 0.03-2 mg/kg IV |
| Verapamil               | Supraventricular tachycardia | 25-35 mg/kg PO, q12h |

*IV, intravenously; PO, orally; q12h, every 12 hours.*
heart and have the most impact on the low-pressure right side of the heart. With larger amount of fluid and fibrin, all cardiac chambers may be reduced in volume. Venous return is compromised, and diastolic myocardial perfusion and contractility are decreased, resulting in decreased stroke volume and cardiac output. With constrictive pericarditis, the initial phase of diastolic filling is unimpeded, but when a critical diastolic volume is reached, filling ceases rapidly as the limit of the noncompliant pericardium is reached. Ventricular preload is decreased, leading to decreased stroke volume. In both situations, there is a compensatory tachycardia to maintain cardiac output, and signs of right-sided failure predominate.

Clinical Findings

No specific breed predispositions for pericarditis have been identified. Younger horses may be at increased risk, although in the sole case-control study that has examined this risk factor, the study design may have biased this result. Intact males were overrepresented and geldings underrepresented compared with the general hospital population in another study. Common presenting complaints include fever, anorexia, and lethargy. Specific cardiovascular signs include tachycardia, weak peripheral arterial pulses, muffled heart sounds, cardiac murmurs, and pericardial friction rubs, which are usually biphasic or triphasic sounds that coincide with the heart rate and that may not become apparent until the pericardial effusion is removed. Pericarditis cannot be excluded in the absence of these signs, and horses often present with signs relating to concurrent respiratory disease. Right-sided heart failure is manifested by ventral edema, venous distention, and pleural and peritoneal effusions evident on ultrasonography.

Diagnosis

Echocardiography

Echocardiography is the most important tool for diagnosis of pericarditis. Pericardial fluid creates an anechoic space between the parietal pericardium and the epicardial surface of the heart, and a subjective assessment of its volume can be made. Fibrin typically appears as tags of tissue that are slightly more echogenic than the myocardium (Fig. 2-13). Echocardiographic findings suggestive of cardiac tamponade include right atrial collapse, right ventricular early-diastolic collapse, overall decreases in chamber size, reduced fractional shortening, and decreased opening and slowing of the closure of the anterior leaflet of the mitral valve. The main alternative differential diagnoses for fluid within the pericardial sac are hemopericardium and neoplastic effusion; neither is typically associated with the accumulation of large amounts of fibrin. In hemopericardium the fluid is usually slightly echogenic, and diagnostic ultrasonography may reveal the source of hemorrhage, such as fractured ribs or a ruptured sinus of Valsalva aneurysm. Therefore, these structures should be examined carefully when fluid is detected within the pericardium. With neoplastic effusion, masses within the pericardial sac or heart may be visible, and cytologic characterization of the pericardial fluid may be diagnostic.

In constrictive pericarditis, pericardial thickening may or may not be evident. Characteristically, there is abrupt cessation of ventricular filling during early diastole, diastolic flattening of the left ventricular free-wall, and abnormal increases in tricuspid flow with abnormal decreases in mitral flow during inspiration.

Electrocardiography, Thoracic Radiography, and Cardiac Catheterization

The most common ECG findings in horses with pericarditis are decreased QRS amplitude and electrical alternans (variations in amplitude). Decreased QRS amplitude is caused by fluid dampening and short-circuiting of the electrical signal (Fig. 2-14). This QRS decrease is not specific to pericarditis and can also be seen in horses with obesity, chronic respiratory disease, diaphragmatic hernia, and thoracic masses.

Thoracic radiography adds little to the information obtained with echocardiography. Enlargement of the cardiac silhouette may be present (Fig. 2-15), but in many cases, pleural effusion obscures the heart.
Cardiac catheterization provides the definitive diagnosis of constrictive pericarditis. There is equalization of the right atrial and right ventricular pressures, and a dip-and-plateau configuration of the right ventricular pressure curve reflects the abrupt termination of diastolic filling when the limit of compliance of the pericardium is reached.\textsuperscript{86}

**Laboratory Investigations**

Leukocytosis, neutrophilia, and hyperfibrinogenemia are common but nonspecific findings in pericarditis. Paired serology for influenza, equine herpesvirus, and equine viral arteritis may be useful. Renal function should be assessed because prerenal azotemia is often present.

Box 2-1 lists guidelines for collection of pericardial fluid. Pericardial fluid should contain less than $1500 \times 10^6/L$ total nucleated cells and have a protein content less than 2.5 g/dL.\textsuperscript{89} Samples of pericardial fluid should be submitted for bacteriologic culture, and culture of mycoplasmal species may also be useful. Ideally, culture should be performed before antimicrobial therapy is instituted. The diagnosis of septic pericarditis is based on the identification of increased

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**Box • 2-1**

**Technique for Pericardiocentesis**

1. **Location for pericardiocentesis**
   - Left 4 to 6 intercostal spaces, approximately 6 cm ventral to point of shoulder.
   - Selection of site is facilitated by echocardiography.
2. **Sedation for pericardiocentesis**
   - May not be necessary depending on the horse's clinical status.
   - If necessary, use with caution; these drugs may exacerbate cardiovascular compromise.
3. **Monitoring for pericardiocentesis**
   - Monitor the cardiac rhythm for ventricular arrhythmias.
   - Have appropriate doses of procainamide, quinidine, or lidocaine at hand (see Table 2-3).
   - If ventricular arrhythmia occurs, the needle should be retracted immediately.
   - If ventricular arrhythmia persists, antidysrhythmic drugs are necessary (see Table 2-3).
4. **Preparation of site**
   - Clip and surgical scrub.
   - Infiltration of lidocaine in skin, subcutaneous layers, and intercostal muscles.
5. **Selection of catheter and drain**
   - For small sample collection: over-the-needle intravenous catheters (14 g, 15 cm) or blunt-ended teat cannulae.
   - For lavage: chest drains (16-24 French).
6. **Insertion of catheter and drain**
   - Stab incision.
   - Insert catheter and drain carefully using the minimum force while observing the ECG continuously.
   - Withdraw trocar promptly once pericardial sac has been penetrated.
   - Be prepared to seal the catheter with an artery forceps or similar instrument if air enters.
7. **Maintenance of drain**
   - Secure drain using purse-string suture.
   - After lavage, flush with a small volume of heparinized saline.
   - Seal drain with a clamp or sterile syringe.
   - Clean drain entry site twice daily.
   - Cover with gauze, tape, and bandage material to keep the site clean.
numbers of degenerative neutrophils, with or without cytologic evidence of bacteria. Idiopathic or immune-mediated pericarditis is characterized by the presence of increased numbers of well-preserved neutrophils. Monitoring glucose concentrations in the pericardial effusion may be helpful as an immediate assessment of sepsis. Glucose concentrations of less than 2.2 mmol/L (40 mg/dL) suggest sepsis, and concentrations greater than 3.3 mmol/L (60 mg/dL) probably indicate a sterile effusion.79

Therapy
Pericardial drainage and possibly lavage should be considered for horses with moderate to severe pericardial effusion.76,82 Echocardiographic signs of cardiac tamponade, particularly marked right atrial collapse (see Fig. 2-13), should prompt emergency pericardiocentesis to restore cardiac function (see Box 2-1). During the procedure, ECG monitoring can identify ventricular arrhythmias and facilitate prompt treatment (see Fig. 2-14). After drainage, 1 to 2 L of 0.9% saline may be infused and left in place for 30 to 60 minutes before removal. Another liter of saline solution is then inserted and left in place until the next drainage-lavage cycle. Drainage-lavage may be repeated twice daily until the amount of fluid removed at the beginning of a drainage session is less than the amount infused at the end of the preceding session.78

Broad-spectrum antimicrobial therapy is indicated for horses with documented sepsis and while awaiting pericardial fluid culture.77 Antimicrobials are also often used prophylactically in horses with suspected nonseptic immune-mediated pericarditis.78 Antimicrobial therapy is ideally based on pericardial fluid culture results, but these are often negative. Given the high prevalence of infection with Actinobacillus and Streptococcus species, appropriate empiric choices include penicillin and an aminoglycoside or cephalosporin. Experimental studies in dogs suggest that these drugs should penetrate the pericardium effectively.76 Sodium penicillin G (10 x 10^6 units in a 420-kg mare)76 and gentamicin (no dose reported)77,78 can be instilled at the end of drainage as adjunctive antimicrobial therapy.

Corticosteroids have been advocated for treatment of idiopathic or immune-mediated pericarditis.74,76 Decision making in these cases is complicated by the concern of possible active viral infection, but the majority of affected horses apparently are not viremic. Supportive therapy includes NSAIDs, and if the patient has prerenal azotemia, the cautious use of IV fluids is warranted. In this horse it is helpful to monitor central venous pressure so that fluid therapy can be closely titrated.

Prognosis
The prognosis for idiopathic or immune-mediated pericarditis appears to be very favorable.74,76 Similarly, there are several reports of successful treatment of septic pericarditis using drainage or drainage-lavage techniques.76,78,79 Constrictive pericarditis warrants a poor prognosis. A partial pericardiectomy technique has been reported but was ultimately unsuccessful because the pericardial fibrosis returned.80 Chronic pericarditis has been associated with chronic lameness resulting from hypertrophic osteopathy in one horse.80

**THROMBOPHLEBITIS**

Etiology and Pathogenesis
Thrombophlebitis is defined as vein thrombosis accompanied by mural inflammation and is a common complication of IV catheterization.81 The prevalence of jugular thrombosis in horses being treated for a variety of gastrointestinal (GI) diseases has ranged from 6% to 22%. Combining data from these studies suggests that the prevalence in this patient group is approximately 18% (CI 13.0%-22.8%).92-94 Many proven and putative positive risk factors exist for thrombopithritis. Use of home-produced fluid solutions, fever, diarrhea, and duration of IV treatment increase risk.79 Foals and horses with colic or diarrhea are more likely to have bacteria isolated from catheters after removal.95 Horses with GI disease are at risk of developing coagulopathies, which contribute to the propensity to develop jugular thrombophlebitis during treatment. Putative but unproven risk factors for thrombophlebitis include administration of antimicrobials and NSAIDs, which irritate the vascular endothelium; rapid IV fluid infusion rates; and standing with the head down for prolonged periods. These latter two factors may predispose to thrombophlebitis because they promote turbulent blood flow.95

Studies investigating catheter types and materials have lacked statistical power, but both catheter material and design are likely to be important. Flexible polyurethane over-the-wire catheters are assumed to have less risk than the more rigid polyurethane over-the-needle catheters, and Tetlon or polytetrafluoroethylene catheters are likely to carry the greatest risk.96 Jugular thrombophlebitis may be septic or nonseptic. Microorganisms most often isolated from the tips of IV catheters are coagulase-negative Staphylococcus spp., Corynebacterium spp., Enterobacter spp., and Streptococcus spp.93

Clinical Findings
Swelling or palpable thickening of the jugular vein is characteristic of thrombophlebitis. There may be variable degrees of

Fig. 2-16 Longitudinal ultrasonogram of jugular vein from 3-year-old Thoroughbred colt that developed jugular thrombosis after surgery to correct colon torsion. A small, homogenous, nonseptic thrombus is visible (arrows).
perivenous swelling. Heat, pain, fever, and discharge from the site of venipuncture suggest sepsis. Acute-onset, severe thrombophlebitis may result in obstruction to venous drainage of the head, and swelling may occur in the supraorbital area, muzzle, and cheek on the affected side. Bilateral thrombosis may be associated with swelling of the tongue and airway obstruction. Chronic thrombophlebitis can lead to distention of the facial veins and discharging abscesses.

**Diagnosis**

**Diagnostic Ultrasonography**

Diagnostic ultrasonography is useful to characterize the nature and extent of thrombophlebitis. Nonseptic thrombi are usually uniformly echogenic and fairly small (Fig. 2-16). Septic thrombophlebitis has a heterogeneous appearance, and in the early stages there may be numerous anechoic areas representing areas of fluid accumulation or necrosis (Fig. 2-17, A)

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**Fig. 2-17** Transverse (A, B, and C) and longitudinal (D) ultrasonograms of jugular vein from 5-month-old Thoroughbred filly that developed jugular thrombosis associated with colitis. An anechoic pocket (arrows in A) and echogenic gas echoes (arrows in B) are visible within a thrombus, confirming sepsis. The thrombus has an "onion ring" appearance in the transverse image (C), and in the longitudinal image (D) the blood that is stationary proximal to the thrombus (arrows) is swirling and creating movement patterns within the vein (arrowheads).
and hyperchoic areas with reverberation artifacts representing gas formation (Fig. 2-17, B). The thrombus will often have an onion-layer appearance on transverse images (Fig. 2-17, C). This layering is also evident on longitudinal images, reflecting the layers of platelets and fibrin that are deposited on the thrombus (Fig. 2-17, D). Variable degrees of thickening of the vessel wall are apparent. Pernicious swelling can readily be distinguished from thrombophlebitis, and perivascular edema typically has a honeycomb appearance. As thrombophlebitis resolves, the thrombus usually becomes more echogenic because of fibrosis and eventually contracts into irregular shapes as it shrinks away from the vessel wall (Fig. 2-18).

Generally, it is possible to assess patency of the vein and visualize flow with conventional B mode images; however, color-flow Doppler imaging may depict this more elegantly (Fig. 2-18). Because jugular flow is sluggish and acute thrombi can be hypoechoic, in early thrombosis the blood may be more echogenic than the thrombus (see Fig. 2-17).

**Laboratory Investigations**

As in pericarditis, leukocytosis, neutrophilia, and hyperfibrinogenemia are common but nonspecific findings in septic thrombophlebitis. If disseminated intravascular coagulation (DIC) is suspected, platelet count, prothrombin time, activated partial thromboplastin time, fibrinolytic degradation products, and antithrombin III should be measured. Abnormality in four of five of these coagulation variables is considered indicative of DIC. The tips of catheters removed from an affected vein should be sterilely inserted into thioglycolate broth for bacterial culture. Blood cultures, swabs of discharging tracts at the catheter insertion site, and aspirates of fluid pockets obtained in a sterile manner may also be submitted for bacterial culture and antimicrobial sensitivity testing.

**Therapy**

Intravenous catheters should be removed at the first sign of potential problems. If possible, further IV therapy should be avoided. If continued IV therapy is needed and unilateral jugular thrombosis is present, it is prudent to place a catheter at an alternative site, such as the lateral thoracic or cephalic vein rather than the opposite jugular vein. Penicillin with an aminoglycoside, enrofloxacin, cephalosporins, and trimethoprim-sulfonamides are appropriate choices for antimicrobial therapy while awaiting results of microbiologic sensitivity testing. The presence of gas echoes may indicate anaerobic infection, and in these cases, metronidazole therapy should be considered. Generally, parental administration of antimicrobials is preferred in the acute stages of thrombophlebitis. Some horses with chronic septic thrombophlebitis require several weeks of antimicrobial therapy and oral administration of enrofloxacin, with or without metronidazole, or a combination of trimethoprim-sulfonamide and rifampin may be more practical. Horses with head swelling should be tied with the head elevated, ideally with the option of resting the head on straw bales or another suitable support. Oral aspirin (18 mg/kg every other day) and topical treatments, such as hot packing and application of dimethyl sulfoxide (DMSO) gel, may be helpful. Reconstructive surgery using saphenous vein grafts has been effective in horses with permanent thrombophlebitic stenosis.

**Prognosis**

Jugular thrombophlebitis resolves uneventfully in most affected horses but can occasionally prolong treatment and delay hospital discharge for patients with primary GI disorders. Septic jugular thrombosis can be associated with a variety of serious complications (including IE) temporary or permanent damage to the sympathetic and recurrent laryngeal

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Fig. 2-18 Transverse (A) and longitudinal (B) ultrasonograms of jugular vein from 5-year-old Warmblood gelding that developed jugular thrombosis after severe colitis. Eight days after the onset of signs, as the thrombus begins to resolve, it contracts to an irregular shape with attachments to the vessel wall (arrows). Color-flow Doppler imaging confirms that the vein is patent.
ners, and upper airway edema that affects the horse’s athletic performance. In most individuals, even with complete loss of the jugular vein, collateral circulation will develop to allow adequate venous drainage of the head.

Prevention
Thrombophlebitis can be minimized with (1) early identification and appropriate treatment of the coagulation disturbances associated with GI disease and SIRS (see Chapter 37); (2) careful selection, insertion, and use of IV catheters; (3) avoidance of homemade IV fluid solutions; (4) appropriate dilution of irritant drugs; and (5) avoidance of needlesticks in veins that are, or recently have been, catheterized. Catheters should be flushed frequently with heparinized saline (1 IU/mL) when not in continuous use, and Teflon over-the-needle catheters should be left in place for no more than 72 hours. Polyurethane over-the-needle catheters can be maintained for up to 5 days. Fluid lines should be changed every 24 hours in high-risk patients. It may be helpful to cover the catheter with bandage material in foals or horses that are frequently recumbent, although this is not done routinely in adult horses in most veterinary hospitals.90

**ARTERIAL THROMBOSIS, ARTERITIS, AND AORTITIS**

Horses with *aortoiliac thrombosis* are typically adults presenting for evaluation of hindlimb lameness, difficulty in breeding, or acute pain. Affected horses have cold extremities and reduced arterial pulses in the affected limbs. The condition can be diagnosed with ultrasonography or nuclear scintigraphy. The etiology is unknown but is not thought to involve infection.

*Arterial thrombosis* associated with sepsis is rare but has been documented in association with neonatal septicemia affecting the aortoiliac quadrification ("saddle thrombus").98,99 in the digital,100,101 metacarpal, and metatarsal arteries101; and in the major vessels of the metatarsal and metacarpal regions in older animals with enterocolitis.101 In an additional case of brachial artery thrombosis in a foal with an atrial septal defect, it was suggested that the condition may have arisen following embolism from an atrial thrombus.102 In septicemia and endotoxemia, abnormalities of hemostasis and fibrinolytic pathways may lead to arterial thrombosis. Thrombocytopenia and deficiencies in antithrombin III, caused by either extensive consumption or loss through the GI tract in protein-losing enteropathy, have been observed in affected patients.103 Activation of procoagulants by endotoxin, dehydration, hypoxia, and acidosis may also contribute to the pathogenesis.104 Clinical examination reveals that the affected limbs are cold, and there may be partial or complete sloughing of the hoof. Arterial thrombosis can be documented using Doppler ultrasonography, nuclear scintigraphy,105 and contrast angiography.106 Attempts to remove the thrombus by surgical embolectomy and use of tissue plasminogen activator107 and urokinase108 have yet produced successful results.

*Cranial mesenteric arteritis* is associated with migrating strongyle species. It has been documented in foals as young as 3 months.109 As it migrates through the mesenteric arteries, *Strongylus vulgaris* induces thrombosis, inflammation, and intimal and adventitial fibrosis, and the accumulation of collagen leads to decreased arterial elasticity.104 Affected animals present with recurrent or persistent colic, and a firm mass can sometimes be palpated at the mesenteric root. The condition is no longer common, presumably as a result of the widespread use of anthelmintics that are effective in reducing the burden of *S. vulgaris*. The diagnosis can be confirmed with transrectal ultrasonography,105; typically a complex solid mass is visualized, representing fibrous tissue surrounding the mesenteric blood vessels (Fig. 2-19). Appropriate anthelmintic regimens should minimize the risk of cranial mesenteric arteritis (see Chapter 62).

*Aortitis* and *aortic root abscess* are rare conditions described in a horse with concurrent aortic valve IE109 and also reported

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**Fig. 2-19** A, Pathologic specimen from a grey Coonawarra mare with pyrolizidine alkaloid toxicity. A mass in the area of the mesenteric root was detected as an incidental finding. B, Transrectal abdominal ultrasonogram shows thick-walled blood vessels surrounded by fibrous tissue in longitudinal (arrows) and transverse (arrowheads) planes resulting from mesenteric arteritis.
CARDIAC COMPLICATIONS IN SYSTEMIC INFLAMMATORY RESPONSE SYNDROME AND SEPTICEMIA

Cardiac Arrhythmias

Arrhythmias (or dysrhythmias) occurring secondary to other systemic diseases, particularly GI diseases accompanied by SIRS, are encountered more frequently in horses than rhythm disturbances associated with primary myocardial pathology. In a group of 67 horses with duodenitis or proximal jejunitis, six (9%) CI 2.1%-15.8% had arrhythmias, and ambulatory electrocardiograms (ECCs) obtained from 50 horses within 3 days of exploratory celiotomy demonstrated that 11 horses (22.5%; CI 10.5%-33.5%) developed isolated supraventricular premature depolarizations and eight horses (16%; CI 5.8%-26.2%) developed isolated ventricular premature depolarizations, including four (8%; CI 0.5%-15.5%) with idioventricular rhythms or paroxysmal monomorphic ventricular tachycardia. These arrhythmias are often self-limiting, requiring no specific treatment, and often the arrhythmia is not recognized on physical examination. Occasionally, more clinically significant arrhythmias are encountered in critical care patients, and concurrent clinical signs of reduced cardiac output and marked tachycardia are recognized. Such arrhythmias can occur in other systemic diseases and conditions associated with SIRS, such as IE and pancreatitis (see Fig. 2-5).

In these horses, arrhythmogenesis is likely caused by multiple confounding factors, including the direct effects of endotoxin on the myocardium, autonomic imbalance resulting from GI distention, and metabolic, electrolyte, or acid-base imbalances. Overall electrolyte balance is more important than isolated disturbances, although the electrolytes usually associated with arrhythmias are potassium, calcium, and magnesium. With potassium, hyperkalemia leads to decreased P-wave amplitude and increased T-wave amplitude. Hypokalemia is associated with ventricular arrhythmias in humans and horses and has been implicated in the development of atrial fibrillation in horses. Calcium principally affects the ST segment, and both hypocalcemia and hypercalcemia are associated with fatal cardiac arrhythmias. Magnesium is an important cofactor in the sodium-potassium ATPase pump that regulates action potentials; hypomagnesemia is associated with ventricular arrhythmias.

In addition to electrolyte imbalances at the intracellular or extracellular level, metabolic and acid-base disturbances and alterations of the autonomic nervous system play a role in the genesis of arrhythmias. Addressing underlying and contributory factors are the main therapeutic goal. Strong evidence to support decisions on which specific antiarrhythmic agent to use in equine patients is lacking, and the decision to institute specific antiarrhythmic therapy is generally based on an assessment of whether it is likely that the arrhythmia will destabilize to a life-threatening state. Guidelines for treatment of arrhythmias are provided earlier in the section on myocarditis (see Table 2-3).

Cardiac Involvement in Multiple Organ Dysfunction

The distributive shock that occurs with endotoxemia and SIRS is principally caused by dysregulation of systemic vascular function and is accompanied by microthrombosis. However, a direct myocardial depressant mechanism may also come into play. Compared with measurement of cardiac output by thermodilution or lithium dilution techniques, echocardiography is not a particularly useful tool in critical care monitoring. However, horses and foals with endotoxemia or septicemia often have echocardiographic signs of global cardiac dysfunction, such as reduced fractional shortening, spontaneous contractions, and poor ventricular wall movement. Hypovolemic patients may have reduced cardiac chamber size, and in septicemic patients, mild pericardial effusions are fairly common. Thus, in addition to primary myocardial or pericardial diseases, endotoxemia and septicemia should be considered as major differential diagnoses when these echocardiographic findings are observed.

Mild fibrous pericarditis, right atrial and ventricular enlargement, myocardial depression, and ventricular tachycardia have been observed in streptococcal toxic shock with multiple organ dysfunction in a horse. Treatment of streptococcal shock consists of supportive care and symptomatic therapy. Maintaining adequate tissue perfusion with IV crystalloid and colloidal fluids and pressor agents is critical. Antimicrobial therapy is important and should be guided by the results of blood culture and antimicrobial sensitivity tests. In humans, fluoroquinolones are not recommended because these agents have a poor spectrum of activity against streptococci. Interestingly, in the single reported equine case, clinical deterioration was noted when initial treatment with cephalosporin, penicillin, and metronidazole was changed to enrofloxacin, although the microorganism that was identified on blood culture, Streptococcus mitis, was sensitive in vitro to enrofloxacin. Streptococcal toxic shock was previously associated specifically with Streptococcus pyogenes infection in humans, but it is now recognized in association with a wide range of Streptococcus spp. in both humans and dogs. In the last 20 years, this condition has been increasingly diagnosed in humans, and streptococcal toxic shock may become more important in horses in the future.

REFERENCES

See the CD-ROM for a list of references linked to the abstract in PubMed.
CHAPTER 3 • Gastrointestinal and Peritoneal Infections

L. Chris Sanchez

The common infectious diseases of the gastrointestinal (GI) tract and their pathogenesis are covered in detail individually in other chapters of this text. The primary goals of this chapter are to identify the normal microflora throughout the GI tract and briefly discuss an approach to the diagnosis and management of the primary clinical syndromes associated with these infectious processes.

ORAL CAVITY

Normal Flora
Most information regarding the normal flora of bacteria in the equine pharynx relates to upper respiratory tract infection and lower respiratory tract infection attributed to aspiration. Comparatively few studies have examined the normal flora of the equine oral cavity. Several aerobic and facultatively anaerobic organisms have been isolated from various locations throughout the pharynx, most notably Streptococcus equi subsp. zooepidemicus.1,2 Anaerobic bacteria isolated from the normal equine pharyngeal tonsillar area include bacteria from the genera Bacteroides, Eubacterium, Fusobacterium, Clostridium, and Veillonella.3

Infectious Disorders
Unlike in small animals, infectious diseases of the oral cavity are relatively rare in horses. Primary problems with a possible infectious etiology include periodontitis and tooth root abscesses, pharyngitis, and dysphagia. Anaerobic organisms are frequently associated with tooth root abscesses.4 Other infectious problems with potential impact on the oral cavity include infection from Actinobacillus lignieresii, the organism associated with swollen or “wooden” tongue5,6 (Fig 3-1); various fungal organisms such as Candida spp., which can cause thrush in foals (see Chapter 53); viral diseases such as vesicular stomatitis7 (see Chapter 24); and infectious causes of dysphagia such as Clostridium botulinum8,9 (botulism, see Chapter 46), equine protozoal myeloencephalitis (see Chapter 59), and West Nile virus (see Chapter 21).

ESOPHAGUS AND STOMACH

Normal Flora
The esophagus and stomach are not sterile environments. In one study, 2.8 x 10^5 total and 2 x 10^6 viable bacteria per gram of ingesta were recovered from the fundic region of normal ponies, with 1.9 x 10^9 total (but only 10 x 10^6 viable) bacteria/g recovered from the pyloric region.10 In both regions, gram-positive organisms (rods and cocci) predominated, and very few cellulolytic bacteria (100-300/g) were isolated,10 suggestive of the capacity for fermentation but minimal ability to utilize forage. Colonization of and attachment to the gastric squamous mucosa by several indigenous Lactobacillus spp. were recently described.11

Infectious Disorders
Infectious diseases of the esophagus mainly occur secondary to perforation and involve a mixed population of aerobic and anaerobic bacteria. Although polymerase chain reaction (PCR) fragments unique to gastric-dwelling Helicobacter spp.
have been identified in horses, an association between H. pylori and ulceration has not been established in adult horses or foals.\textsuperscript{12,13} One case of emphysematous gastritis from Clostridium perfringens has been reported.\textsuperscript{14}

**SMALL INTESTINE**

**Normal Flora**
Few studies have evaluated normal microbial populations in the equine small intestine. Total bacterial counts and proportion of gram-positive bacteria recovered from the ileum were similar to those seen in the stomach,\textsuperscript{10} but viable bacteria numbered $3.6 \times 10^7$. In a study analyzing only anaerobic bacteria, increasing numbers of both culturable and proteolytic bacteria were identified in the duodenum, jejunum, and ileum.\textsuperscript{15} Proteolytic bacteria comprised a high proportion of the total bacteria in all regions, but accounted for almost all bacteria in the duodenum. Numbers of bacteria identified from the GI lumen outnumbered those recovered from the mucosa in all segments.\textsuperscript{15}

**Infectious Diarrhea in Foals**
Most infectious causes of diarrhea in foals, unlike those in adult horses, affect the small intestine either alone or in combination with the large colon.

**Bacterial Disorders**
Clostridial organisms can act as primary pathogens in foals, causing disease in individual animals or as outbreaks on affected farms (see Chapter 44). Clostridium perfringens typically affects foals under 10 days of age. Types A and C are most often implicated, with type C resulting in more severe disease, hemorrhagic diarrhea, and higher mortality than type A.\textsuperscript{16} Type A C. perfringens is typically isolated from the feces of normal foals, but the organism in general is more often isolated from foals with diarrhea.\textsuperscript{17} A diagnosis is usually confirmed with the combination of clinical signs and culture of the organism from feces, preferably with genotyping of the obtained isolate. Observation of large, gram-positive rods on a fecal Gram stain should prompt the clinician to consider clostridial enteritis\textsuperscript{18} (Fig. 3-2).

Clostridium difficile has also been implicated as a cause of diarrhea in foals. Disease severity can vary from mild to hemorrhagic diarrhea. As with C. perfringens, C. difficile can be isolated from asymptomatic foals, and thus toxin detection in feces is useful for confirmation of a diagnosis.\textsuperscript{18}

Commercial immunoassays are available for the detection of toxins A and B in feces as well as the enterotoxin of C. perfringens (CPE). Treatment is supportive, with the addition of directed antimicrobial therapy, typically with metronidazole. In some geographic locations, documented metronidazole resistance in C. difficile isolates has prompted therapy with vancomycin in select cases.\textsuperscript{19}

The other predominant bacterial cause of enterocolitis in foals is salmonellosis (see Chapter 38). In addition to diarrhea, affected foals typically display clinical signs of sepsis. Diagnosis is confirmed by aerobic culture of blood and feces. Treatment is supportive and should include directed systemic antimicrobial therapy. Foals with systemic sepsis may develop diarrhea in association with their primary disease, with a reported incidence between 16% and 38%.\textsuperscript{20-23} Although Escherichia coli is the most common etiologic agent associated with sepsis (see Chapter 6), it is not typically recognized as a primary cause of enteritis or enterocolitis in foals. There is an increased probability of diarrhea in foals with Actinobacillus sepsis compared with foals from which other organisms are isolated.\textsuperscript{20}

**Viral Disorders**
Infection of older foals with Lawsonia intracellularis, an obligate intracellular pathogen, results in proliferative enteropathy\textsuperscript{24-27} and should be considered in weanling-age foals with severe hypoproteinemia (see Chapter 36). Clinical signs include weight loss, ill thrift, depression, colic, peripheral edema, and variable fecal consistency, ranging from soft, normal stool to watery diarrhea. Protein loss can be severe. Diagnosis is based on clinical signs in combination with results of fecal PCR and serum antibody testing. Treatment includes supportive care, predominantly with colloid replacement, and directed antimicrobial therapy with erythromycin estolate and rifampin or chloramphenicol.\textsuperscript{28,29}

Infection of foals with Rotavirus is an acute diarrheal disease of foals under 35 days of age (see Chapter 17). Typically, rotavirus affects foals between 5 and 35 days of age, with most foals at the younger end of this spectrum.\textsuperscript{30} The most common and obvious clinical sign is diarrhea, and fecal consistency can vary greatly. Other signs relate to disease severity, including depression, anorexia, dehydration, and similar findings. The virus causes blunting of the small intestinal microvilli, with malabsorption and malnutrition. Diagnosis can be confirmed with fecal electron microscopy, which has a significant time, or commercial immunoassays, also performed on feces. Treatment is principally supportive, with extracellular fluid administration. Prognosis is good with supportive care, and mortality is typically low in uncomplicated cases.

Other viral causes of diarrhea occur much less frequently and include coronavirus\textsuperscript{30,31} and adenovirus\textsuperscript{32,33} (see Chapters 18 and 16, respectively).
Protozoal Disorders

Cryptosporidium spp. are the major protozoal cause of diarrhea in foals (see Chapter 61). These organisms are generally regarded as less significant relative to the major bacterial and viral diseases discussed previously.

Infectious Small Intestinal Disease in Adult Horses

Etiology and Pathogenesis

Proven infectious disorders of the small intestine of adult horses are rare. Horses do not appear predisposed to small intestinal bacterial overgrowth, which is common in dogs and humans. One equine disorder that has a suspected, but to this point unsubstantiated, infectious origin is duodenitis/proximal jejunitis (DPJ, also known as anterior enteritis or proximal enteritis), a syndrome of small intestinal inflammation characterized by copious quantities of gastric reflux (Fig. 3-3). In most affected horses, an underlying etiology cannot be determined and the syndrome of DPJ may include a wide variety of inflammatory small intestinal disorders resulting in a similar clinical presentation. In some horses, Salmonella spp. or Clostridium spp. are isolated from gastric reflux samples (see Chapters 38 and 44). Recently, toxicogenic strains of Clostridium difficile were isolated from the reflux in five of five horses with DPJ and from none of six control horses with other causes of nasogastric reflux. Mycotoxins of Fusarium moniliforme may also play a role in some cases of DPJ.

Regardless of the initiating cause, intestinal inflammation results in changes in secretory activity and motility that contribute to a functional obstruction. Intestinal inflammation can change normal sensory-motor function, mucosal function, ion transport, and transepithelial permeability.

Clinical Findings

The most characteristic clinical signs in horses with DPJ include moderate to severe pain, which improves after gastric decompression; large volumes of gastric reflux; clinical signs of endotoxemia (see Chapter 37); and small intestinal distention evident on rectal palpation and ultrasonographic examination (Fig 3-4).

Abnormal clinicopathologic findings in horses with DPJ include hemoconcentration, neutropenia, acidemia, prerenal azotemia, hypernatremia, hypochloremia, hypokalemia, and increased hepatic enzyme activities. Typically, peritoneal fluid has a mild to moderate increase in total nucleated cell count (TNCC, up to 20,000/μL), with a moderate to marked increase in total solids (up to 5 g/dL). However, the nucleated cell count may vary widely. These findings may help to differentiate horses with DPJ from horses with strangulating small intestinal disease, which tend to have higher numbers of red blood cells as well as a higher TNCC. However, the wide fluctuation in results obtained with these disorders may make differential diagnosis difficult in many horses, necessitating exploratory celiotomy.

Therapy

Treatment of DPJ consists primarily of supportive care, with an emphasis on fluid therapy and gastric decompression. Particular care should be taken to administer maintenance fluid requirements and replace the fluid volume lost through gastric reflux. Therapy should also include nonsteroidal anti-inflammatory therapy for analgesic and antiinflammatory effects,
as long as renal function remains normal, and directed therapy to combat endotoxemia. If the affected horse's condition either deteriorates or fails to improve with medical therapy, surgical exploration can be considered.\textsuperscript{30} Surgical exploration can offer manual decompression of the small intestine and rule out any physical obstruction. In protracted cases or in horses with increased serum triglyceride concentrations, intravenous (IV) parenteral nutritional support should be considered. Prokinetic therapy with erythromycin lactobionate, metoclopramide, bethanechol, or lidocaine may also be considered.\textsuperscript{30,40}

With prompt medical therapy, horses with DJP generally have a good prognosis for survival. Factors associated with a decreased risk of survival include increased peritoneal fluid protein concentration, increased anion gap,\textsuperscript{41} and failure to respond to prokinetic therapy within 24 hours.\textsuperscript{30} Potential complications of DJP include laminitis, thrombophlebitis, peritonitis, adhesions, pharyngitis or esophagitis, and cardiac arrhythmias.

LARGE INTESTINE

Normal Flora
Much more is known about the resident microflora in the equine large intestine than the small intestine or the more oral portions of the GI tract. The cecum and colon have a large capacity and the capability for extensive fermentation by bacteria and protozoa. Total proteolysis in the large intestine appear to increase in horses fed a diet high in fiber, relative to a diet high in concentrate.\textsuperscript{42} The colon has concentrations of both total and cellulosolytic fungi more than 10 times greater than those found in the cecum.\textsuperscript{42} At least two species of anaerobic phycobilisomes capable of digesting plant cellulose and hemicellulose have been isolated from the equine cecum.\textsuperscript{43} Ruminococcus flavefaciens has recently been identified as the predominant cellulosolytic cecal bacterial species.\textsuperscript{43} At least two types of spirochetes have been identified in the equine cecum.\textsuperscript{45} Bacteriophages infecting spirochetes within the equine cecum\textsuperscript{45} and bacteriophage-like particles have been demonstrated in various regions of the large intestine by electron microscopy.\textsuperscript{46}

Acute Diarrhea in Adult Horses

Etiology
The principal infectious agents associated with colitis in horses include Salmonella spp. (see Chapter 38), Neorickettsia risticii (see Chapter 43; equine monocytic encephalitis, Potomac horse fever), Clostridium difficile, and Clostridium perfringens (see Chapter 44). Aeromonas spp. are often isolated from horses with diarrhea, but their significance has not been fully determined. Parasites are not typically associated with acute diarrhea in adult horses, with the exception of larval cyathostomiasis in Europe and the northern part of the United States and Canada (see Chapter 62). The most common cause of outbreaks of colitis in horses is salmonellosis. Outbreaks of Potomac horse fever (PHF) and clostridial colitis are rare, although the latter may occur as a clustering of foals or hospitalized horses. Because each of these agents is covered in depth in other chapters, this chapter focuses on a diagnostic and therapeutic approach to an individual horse presenting with acute diarrhea.

Diagnostic Approach
In all horses with acute diarrhea, a minimum database includes complete blood count (CBC) with fibrinogen and a biochemical profile. If available, venous blood gas analysis is desirable. Additional diagnostic tests to identify a specific etiologic agent can be performed on blood and feces. The clinician should remember the potential for co-infections within the same patient.

Diagnostic Tests on Whole Blood or Serum.
Although an enzyme-linked immunosorbent assay (ELISA) has been described for diagnosis of N. risticii infection in horses, an immunofluorescent assay (IFA) for detection of specific antibody or polymerase chain reaction (PCR) assay for detection of organism is the preferred test. IFA utilizes serum, and PCR is performed on buffy coat or feces. Most laboratories that perform PCR use buffy coats isolated from standard ethylenediaminetetraacetic acid (EDTA)-treated whole-blood tubes. Infected horses develop high IFA titers (>1:640) within days of infection, often before clinical signs are apparent. Paired serum samples (acute and convalescent) should be collected within 5 to 7 days rather than the conventional interval of 2 to 4 weeks because infected horses rapidly develop high titers. It is generally believed that horses with PHF should have a titer of 1:80 or greater at the onset of signs; consequently, a negative titer indicates this disease is unlikely. Vaccination for PHF results in positive titers that usually disappear by 6 to 9 months. PCR offers the advantage of excellent sensitivity without the potential for interference from vaccination.\textsuperscript{47,48}

Diagnostic Tests for Feces.
Fresh fecal samples from horses with diarrhea should be submitted for aerobic culture, with a specific request for Salmonella spp. identification. These cultures require special media and antigens for serogroup identification and are readily available through most, if not all, commercial laboratories. Multiple cultures are preferable. Recovery of pathologic organisms can be difficult when feces are very watery, and thus the most productive cultures are performed on feces with at least some substance. Culture of a rectal mucosal biopsy sample may also improve the recovery rate.\textsuperscript{49} PCR is reported to be a more sensitive method for detection of salmonella in feces.\textsuperscript{50,51} The diagnostic significance of horses positive by PCR but negative by culture of multiple fecal samples remains to be determined. (Chapter 38 discusses Salmonella spp. diagnostic tests and their interpretation in detail.)

Anaerobic culture of feces should also be requested to facilitate detection of clostridial organisms. Strict anaerobic handling of the feces is critical to successful culture, especially for Clostridium difficile.\textsuperscript{52} Recovery of C. difficile organisms is dramatically reduced after storage for 72 hours in aerobic conditions at 4°C.\textsuperscript{53} Because clostridial organisms can be cultured from the feces of some normal horses, toxin detection is preferred for a diagnosis of clinically relevant disease. Commercial ELISA assays are available for detection of C. difficile toxins A and B, as well as the enterotoxin of Clostridium perfringens (CPE). Genotyping of C. perfringens isolates is also commercially available. Aerobic storage of fecal samples is unsuitable if samples are intended for culture of C. difficile because of the short length of time that organisms remain viable when stored under those conditions. However, toxins remain stable for at least 30 days when fecal samples are stored aerobically.\textsuperscript{54} Many diagnostic laboratories will perform toxin testing, and some will provide packages including both culture and toxin analysis. (Chapter 44 discusses diagnosis of enteric clostridial infections in detail.)

Feces should be examined by sedimentation for sand and microscopically for increased fecal leukocytes. A Gram stain may be useful as an initial screen for clostridial organisms (long gram-positive rods). Cyathostome larvae are best detected by direct examination of feces (see Chapters 58 and 62).

Therapy
The primary goal of therapy for adult horses with diarrhea is restoration and maintenance of fluid, electrolyte, and
acid-base balance. Specific pathogen-directed therapy may be indicated, depending on the etiologic agent identified. For many horses with acute colitis, initial IV fluid replacement is required because of tremendous volume losses. Typically, mild to moderate acidemia is corrected by restoration of plasma volume with an alkalizing solution such as lactated Ringer’s or Normosol-R. Sodium chloride solutions (0.9%) should be avoided because they can be acidifying and may worsen edema. In horses with severe dehydration, initial therapy with hypertonic saline may be used to restore circulatory volume, but must be followed by administration of isotonic fluids. Alternatively, hydroxyethyl starch (Hestarch) can also be used for quick expansion of plasma volume while also inducing a rapid increase in colloid osmotic pressure.

Other goals of therapy include reducing inflammation, pain control, and limiting the effects of endotoxemia (see Chapter 37). Drugs used for these purposes include nonsteroidal anti-inflammatory drugs (NSAIDs), such as flunixin meglumine, which have analgesic, anti-inflammatory, and antientotoxemic properties. As with other NSAIDs, the clinician must take care to avoid use of flunixin in horses with renal compromise, moderate to severe dehydration, NSAID toxicity, or right dorsal colitis. Adjunctive therapy with polymyxin B sulfate and pentoxifylline is suggested to combat the effects of endotoxemia.

Chronic Diarrhea in Adult Horses

Etiology

Chronic diarrhea is usually defined as diarrhea lasting longer than 4 weeks. Fecal consistency can vary widely. Although many specific diseases can result in chronic diarrhea, identification of the inciting cause in a patient frequently remains elusive. Occasionally, problems of a non-GI nature, such as hepatic disease or abdominal abscessation, result in diarrhea. Infectious causes of chronic diarrhea include chronic salmonellosis (see Chapter 58) and parasitism with large or small strongylies (see Chapter 61). Recently, the spirochete *Borrelia pilosus* was implicated in a herd outbreak of chronic diarrhea in weanling-age horses. Noninfectious inflammatory causes of chronic diarrhea include granulomatous enteritis or colitis, neoplasia (predominantly lymphosarcoma), sand irritation, and right dorsal colitis (Fig. 3–5). Noninflammatory causes include a range of problems, with the common theme of disruption in the flora of the large intestine. This may or may not be related to a dietary disruption, and many affected horses have few other clinical signs. Regardless of the inciting cause, horses with chronic diarrhea remain very difficult to treat and have a guarded prognosis.

Diagnostic Approach

A minimum database for the individual horse with chronic diarrhea typically includes CBC with fibrinogen, serum biochemical profile, venous blood gas analysis, rectal examination, abdominal ultrasound, and analysis of peritoneal fluid. Results of all these diagnostic procedures are frequently normal, and further recommended analyses include a comprehensive fecal examination and rectal biopsy.

Comprehensive fecal analysis should include assessment for parasites (grossly and by fecal flotation or McMaster's quantification), aerobic culture for *Salmonella* (five samples at a minimum 12-hour interval, as for acute diarrhea), water suspension for sand, unstained wet mount for protozoa and parasites, new methylene blue stain for fecal leukocytes, and Gram stain to determine the ratio of Gram-positive to Gram-negative bacterial flora.

Rectal biopsy is a simple, relatively noninvasive procedure. Two samples should be obtained and submitted for culture (*Salmonella*) and histopathology. Histopathologic examination

**Fig. 3–5** A, Abdominal ultrasound image from aged pony with liver disease, low white blood cell count, and fever demonstrating greatly thickened right dorsal colon. B, Right dorsal colon of horse with thickened colon and actual granuloma formation in wall of intestine. (Courtesy Dr. Michael Porter.)

is most helpful for diagnosis of inflammatory and neoplastic bowel diseases.

**Therapy**

If a specific diagnosis is achieved, directed therapy should be initiated. (See individual chapters for a more detailed description of directed therapy based on the causative organism.) In all cases, free-choice access to fresh water is critical to maintenance of hydration. Many horses will consume balanced, isotonic electrolyte water; and such a solution should be offered in addition to fresh water. Alternatively, access to a salt or mineral block can serve as a substitute source of electrolyte replacement. Typical feeding recommendations include good-quality grass hay with limited legume hay and concentrate intake. Dietary changes alone are unlikely to provide a cure.

Non-specific therapy for horses with chronic diarrhea may include transfaunation or administration of iodoxchlorhydroxyquin. Detailed descriptions of transfaunation procedures are sparse in the veterinary literature, as are reported benefits. Typically, colic liquor is obtained either from an animal recently euthanized for non-GI reasons or from an animal implanted with a colic cannula. Because these sources are rarely available in proximity to the affected animal, the procedure itself may be a fairly daunting task. After appropriate transfaunation is
obtained, the clinician must decide whether to pretreat the recipient. Frequently, recipients are pretreated with acid-suppressing agents to enhance viability of transplanted bacteria and protozoa as they pass through the gastric environment. The efficacy of such treatment has not been validated in the horse. However, the potential value of transfaunation was recently highlighted during a herd outbreak possibly related to the spirochete *Brachyspira pilosicoli*.  

**Iodochlortetracycline**, an 8-hydroxyquinoline derivative (also called cloquinol) originally recommended for treatment of trichomoniasis, has long been recommended for the treatment of chronic diarrhea.  

Although chronic diarrhea in horses is more likely to result from disruption of the normal intestinal flora than from infection, some horses responded favorably to therapy. The response to treatment with iodochlortetracycline is highly variable; it may worsen diarrhea in some horses. Therapy may result in improvement in fecal consistency, with reversion to diarrhea within a few days of discontinuing drug administration.  

**Prognosis**  
Regardless of the inciting cause, if a horse has diarrhea for at least a month, the prognosis for complete recovery is guarded. The prognosis worsens with the duration of diarrhea.

**PERITONEAL INFECTIONS**

**Peritonitis** refers to inflammation of the serosal lining of the peritoneal cavity and is typically caused by mechanical, chemical, or infectious insult to the parietal peritoneum. In addition to classification based on the causative insult, further classification may include onset (acute or chronic), distribution (localized or diffuse), origin (primary or secondary), and infectious nature (septic or aseptic). Acute, diffuse, septic peritonitis secondary to GI disease is the most common manifestation.

**Etiology and Clinical Findings**  
Most cases of peritonitis occur secondary to a GI event (e.g., perforation of any portion of GI tract), intestinal ischemia, DPJ, colitis, neoplasia, verminous arteritis, intestinal mural abscess, or other causes.  

**Pathologic processes** include mesenteric abscess (including those associated with *Streptococcus equi* subsp. *equi*), cholelithiasis, and others. Causes specific to the young foal include rupture of the urinary bladder or urachus, omphalitis or omphalophlebitis, sepsis, and *Rhodococcus equi* abscessation.  

Organisms associated with GI rupture include a mixed population of gram-positive and gram-negative aerobic and anaerobic organisms, often with no clear predominance of one type. *Enterobacteriaceae*, *Streptococcus* spp., and *Staphylococcus* spp. are most often isolated from peritoneal fluid samples.  

Common anaerobic isolates include *Bacteroides*, *Clostridium*, and *Bacillus* species. In foals, peritonitis is most frequently associated with *Streptococcus* and *R. equi* infections. Several case series describing peritonitis associated with *Actinobacillus equuli* have been reported. Initial reports of *A. equuli* peritonitis originated solely in Australia, but one case was recently reported from the United Kingdom.  

Clinical signs of peritonitis in horses are variable and may include fever, depression, abdominal pain, diarrhea, and weight loss. Depending on severity and localization, signs may also include those of endotoxemia and shock.

Clinical signs in horses with *A. equuli* peritonitis include depression, inappetence, lethargy, and mild to moderate abdominal pain accentuated or weight loss in a chronic form. Postpartum mares with peritonitis secondary to a uterine perforation typically present with fever and depression, with or without abdominal pain.

**Diagnosis**  
Definitive diagnosis of peritonitis is based upon an elevated TNCC in peritoneal fluid (>10,000 cells/μL). Culture of peritoneal fluid should be performed in all suspected cases, but this procedure has a low sensitivity, with only 9.5% to 32.5% of samples yielding positive growth. Total cell count can be increased after enterocentesis, abdominal surgery, or open castration. Thus, additional parameters must be considered in these populations. Abundant hypochromic or variably echogenic peritoneal fluid (evident on abdominal ultrasound examination), fever, depression, and abdominal pain can all support the diagnosis (Fig. 3-6). A decrease in peritoneal fluid pH (<7.3) or glucose (<30 mg/dL) suggests the presence of septic peritonitis. Peritoneal fluid cytology will typically reflect a septic process, with abnormalities ranging from the presence of bacteria or plant material to degenerate neutrophils (Fig. 3-7). If GI contents or plant material are evident, the clinician should take care to differentiate between GI rupture and enterocentesis. At sampling, alterations in TNCC and cytology should indicate peritonitis; enterocentesis can result in an elevated TNCC within 4 hours. If a differentiation cannot be clearly made, a sample should be taken from an alternate location, preferably with ultrasound guidance. In postfoaling mares, the percentage of neutrophils in the peritoneal fluid can be increased for up to 7 days, but the total protein and TNCC should remain within normal limits.

**Therapy**  
Treatment of horses with peritonitis should begin with identification and correction of the underlying problem, if possible. If a GI source is suspected, an exploratory celiotomy is likely indicated. Supportive care is also critical to the treatment protocol.
Fig. 3-7 Photomicrograph of peritoneal fluid from horse with septic peritonitis demonstrating toxic neutrophils with intracellular bacteria. (Courtesy Dr. Michael Porter)

This should include correction of fluid deficits, acid-base and electrolyte imbalances, and colloid oncotic pressure. Anti-inflammatory and antientotoxic therapies are also clearly of benefit (see Chapter 37). Additional analgesic and prokinetic drugs should be provided if necessary.

Antimicrobial therapy is critical to the management of septic peritonitis. Broad-spectrum coverage should be instituted pending results of peritoneal fluid culture and sensitivity. If positive results are obtained, therapy can be adjusted accordingly. A typical initial regimen includes penicillin, gentamicin, and metronidazole to cover gram-positive, gram-negative, and anaerobic spectrums, respectively. Because many *Bacteroides* species are resistant to β-lactam antimicrobials, metronidazole should be included in the antimicrobial therapy plan if anaerobic involvement is suspected. Enrofloxacain may replace gentamicin in the treatment regimen if warranted. The lipophilic nature of enrofloxacain can provide increased penetration into the peritoneal cavity. Neonatal foals with peritonitis should receive an antimicrobial regimen similar to that suggested for adults, although amikacin is frequently substituted for gentamicin because of increased sensitivity of commonly isolated organisms. A combination of azithromycin or clarithromycin plus rifampin provides reasonable coverage for older foals or weanlings, because *Streptococcus* and *R. equi* are often associated with disease in these populations if a primary GI lesion is not suspected. Although *A. equuli* is typically sensitive to either penicillin or trimethoprim-sulfonamide combinations, initial broad-spectrum coverage with penicillin and gentamicin is suggested pending culture results because of the resistance of some isolates.

Abdominal drainage and lavage can help remove excess fluid, foreign materials, fibrin, and bacterial products from horses with peritonitis. Postoperative lavage decreases the incidence of experimentally induced abdominal adhesions in horses undergoing exploratory celiotomy (Fig. 3-8). Open surgical exploration provides the most effective and thorough examination of all peritoneal surfaces and is recommended if GI perforation or ischemia is suspected, as well as in any other horses in which correction of a primary lesion is indicated. A ventral abdominal drain can either be placed at surgery or in the standing horse with sedation and local anesthesia. Techniques are described in detail elsewhere.

Fig. 3-8 A, Abdominal drain placement in most ventral point of abdomen in horse with septic peritonitis. B, Abdominal lavage system using the drain shown in A.

Fig. 3-9 Two-year-old horse with septic peritonitis and orchitis. The initiating cause was unknown; *Streptococcus equi* subsp. *zooepidemicus* was cultured from the abdomen of this horse.
Peritoneal lavage is typically performed by infusion of 10 to 20 liters of a balanced isotonic electrolyte solution (e.g., lactated Ringer's, Normosol-R) into the peritoneal cavity twice a day for 3 to 5 days, until the lavage solution becomes clear, or until the catheter becomes clogged with fibrin or omentum. Hypertonic solutions should be avoided because they may cause fluid shifts into the peritoneal cavity. The addition of povidone-iodine to a balanced solution should be avoided; concentrations as low as 3% may induce peritoneal inflammation. Other agents, such as antibiotics and heparin, have also been suggested as components of peritoneal lavage solution, but data demonstrating their benefit are lacking. Active (or closed-suction) abdominal drains have also been advocated, with similar benefits and potential complications to other methods. Lavage with a plain isotonic solution did not alter the pharmacokinetics of gentamicin administered systemically.

Prognosis
The prognosis is grave for horses with peritonitis secondary to GI rupture. Reported survival rates for horses with peritonitis vary but can be as high as 59.7% (Fig. 3-9). Some of the variability in reported survival percentages may be related to inclusion criteria, mainly whether or not horses with GI rupture were included. Septic peritonitis after abdominal surgery is reportedly associated with high mortality (56%). Peritonitis associated with A. equi and A. abortus carries a very favorable prognosis, and all horses in these reports responded to medical therapy, if attempted.

REFERENCES
See the CD-ROM for a list of references linked to the abstract in PubMed.

CHAPTER • 4

Central Nervous System Infections
Kathy K. Selino

Infections of the central nervous system (CNS) of horses, although uncommon, are some of the most devastating and frequently fatal diseases in horses. Diseases such as equine protozoal myeloencephalitis (EPM) and West Nile virus encephalomyelitis (WNE) have had a significant economic impact on the equine industry in recent years and stimulated investigations into preventive, diagnostic, and therapeutic alternatives for CNS infections in horses.

Viral, bacterial, rickettsial, protozoal, parasitic, and fungal pathogens may cause CNS infections in horses (Table 4-1). In small animals and in humans the causes of meningoencephalitis, in order of decreasing frequency, are viral, bacterial, protozoal, rickettsial, parasitic, and fungal, whereas in the horse the most frequently diagnosed CNS infections are probably of viral and protozoal origin. In an Australian study, 30% of 150 horses with neurologic disease had an infectious or inflammatory disease, and 11 of these 30 had meningoencephalitis. This study may not reflect the emergence of West Nile virus (WNV) in the United States in 1999 or account for CNS diseases that are present in North America, such as Eastern equine encephalomyelitis (EEE) or EPM.

Regardless of the type of etiologic agent involved, CNS infections require an accurate and rapid diagnosis and implementation of an appropriate course of treatment by the attending veterinarian. CNS infection should be suspected in horses with abnormal mentation, seizures, blindness, multiple cranial nerve abnormalities, and general proprioceptive deficits. Infections involving primarily the spinal cord may manifest as limb weakness, incoordination, and stiffness, with or without associated cerebral dysfunction. The reader is referred to chapters on individual diseases for detailed description and discussion of EPM (see Chapter 59), WNV (see Chapter 28), and Anaplasma phagocytophilum (see Chapter 42). This chapter provides an overview of CNS infection, pathogenesis, diagnosis, and treatment, with discussion of miscellaneous CNS infections not covered elsewhere in this text.

The appropriate term for infection and resultant inflammation of the CNS is determined by the specific area of the nervous system affected. Inflammation of the brain, meninges, spinal cord, and peripheral nerves is termed encephalitis, menigitis, myelitis, and neuritis, respectively. Rhinencephalitis and cerebellitis refer to localized inflammation of the brain stem and cerebellum, respectively. Frequently, more than one tissue or anatomic site may be affected. Meningoencephalitis is inflammation of the meninges and brain, and meningoencephalomyelitis is inflammation of the meninges, brain, and spinal cord. Inflammation of the brain and spinal cord, without meningeal involvement, is termed myeloneuropathy.

Infection of the CNS can also result in focal suppuration of the brain parenchyma or spinal cord and formation of abscesses. Localized areas of infection between the outermost meningeal layer (dura mater) and the skull and vertebral column are termed epidural abscesses. Inflammation between the outer two layers of the meninges (dura mater and arachnoid) is termed subdural empyema.

NEUROANATOMY AND DISEASE

Brain and Meninges
Inside the protective barrier of the skull, the brain is surrounded by three layers of meninges: the outermost dura mater, or pachymeninges, and the leptomeninges, consisting of the inner
Table 4-1

Equine Central Nervous System Pathogens

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<td>Equine encephalomyelitis virus</td>
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<tr>
<td>Murray Valley virus</td>
<td>149-151</td>
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<tr>
<td>Louping ill virus</td>
<td>153-157</td>
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<tr>
<td>California group/snowshoe hare</td>
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<td>Semliki Forest virus</td>
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<td>Japanese encephalitis virus</td>
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<td>Aujeszky's disease virus</td>
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<tr>
<td>Equine herpesvirus type 1</td>
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<td>Equine infectious anemia virus</td>
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<tr>
<td>Rabdovirus (rabies)</td>
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<tr>
<td>Kunjin virus</td>
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<td>Borna virus</td>
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<td>Helobronema</td>
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<td>Hypoderma (lineatum, bovis, diana)</td>
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<td>Strongylus vulgaris</td>
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<td>Halicephalobus gingivalis</td>
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<tr>
<td>Draschia megastoma</td>
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<tr>
<td>Trypanosoma evansi</td>
<td>165-169</td>
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</table>

| **Bacterial**                   |                     |
| Escherichia coli                | 9, 62               |
| Actinobacillus equi             | 62, 79              |
| Streptococcus (equi, zoopneumoniae, suis) | 7, 27, 62, 70, 174, 175 |
| Salmonella                      | 62, 63, 88          |
| Pasteurella caballi             | 11, 177-179         |
| Pseudomonas aeruginosa          | 7                   |
| Enterococcus                    | 8                   |
| Actinomyces                     | 190, 191            |
| Rhodococcus equinomycines       | 25, 79, 81, 82, 86, 89, 193 |
| Brucella abortus                | 89                  |
| Mycobacterium bovis             | 11, 196-198         |
| Staphylococcus spp.             | 77                  |
| Actinobacillus lignieresii      | 80                  |
| Klebsiella pneumoniae, type 1   | 68                  |
| Listeria monocytogenes          | 36, 64              |

| **Protozoal**                   |                     |
| Balamuthia mandrillaris         | 111                 |
| Saccoystis neuroloma            | 18, 48, 199-203     |

| **Fungal**                      |                     |
| Cryptococcus neoformans         | 72-74               |
| Aspergillus niger, A. fumigatus | 75                  |

| **Rickettsial**                 |                     |
| Anaplasma phagocytophilum       | 204                 |

1 Denotes vertebral body osteomyelitis.

The dura mater is adherent to the external surface of the brain and spinal cord, forming folds around penetrating vessels and merging with the epidural lining of the fourth ventricle. Cerebrospinal fluid (CSF) occupies the subarachnoid space between the pia mater and arachnoid. Acute bacterial infections within the subarachnoid space typically begin with the leptomeninges of the brain and spinal cord and spread inward through the foramina of the fourth ventricle. Infections between the dura mater and arachnoid (subdural empyema) can spread over the entire cerebral hemisphere. The dura mater adheres to the peristernum of the skull and limits the spread of epidural abscesses (between the dura and skull), except where it invaginates into the cranial cavity to form four rigid septa: the falx cerebri, falx cerebelli, tentorium cerebelli, and diaphragma sella.

The brain rests within the anterior, middle, and posterior cranial fossa, which are associated with the paranasal sinuses. The anterior fossa forms the roof of the frontal and ethmoidal sinuses. The sella turcica is located between the left and right middle fossa and forms the roof of the sphenoid sinuses. Infection in these paranasal sinuses can spread through the respective fossa centrally to the brain, resulting in epidural abscesses and subdural empyema. In the horse, these infections can be either bacterial or fungal. Middle ear infections (otitis media) within the petrous temporal bone may extend into the middle fossa to involve the temporal lobe of the brain or into the posterior fossa to involve the cerebellum or brain stem.

Neuroanatomic localization of brain disease in the horse has been well described. Briefly, infectious neurologic disease in the horse either is diffuse (e.g., viral or protozoal) or can have a single neuroanatomic signal (e.g., brain abscess). Neuroanatomic localization should be defined in terms of the five major regions of the CNS (and the cranial nerves): disease of the cerebrum, basal nuclei, rostral brain stem, caudal brain stem, and cerebellum.

Seizure activity and moderate to severe obtundation are the most common signs of cerebral disease in the horse. Although the cortex controls conscious proprioception, this is difficult to localize to the cerebrum in the horse and in the absence of other clinical signs. Blindness occurs secondary to lesions in the
visual cortex. Cortical blindness presents as decreased normal reactions to visual cues, with normal pupillary light reflexes. A full ophthalmic examination is paramount to assessing cortical blindness. The most common clinical sign of focal disease of the basal nuclei is the inability to chew and form coordinated eating movements with the tongue, teeth, and oropharynx. However, diffuse disease in this area involves the caudate nucleus, globus pallidus, putamen, and substantia nigra and should result in loss of coordination of movement. Extension to the reticular formation may result in abnormalities of the wake/sleep cycle. Clinical signs referable to lesions of the rostral brainstem can be differentiated on the basis of signs of abnormalities of cranial nerve (CN) II through CN IV. Vision, pupillary responses, and eyeball placement can be affected by disease in these areas. Postganglionic Horner’s syndrome (ipsilateral ptosis, miosis, enophthalmos, and localized ipsilateral sweating) can occur if lesions are rostral to the foramen lacerum involving the sympathetic fibers as they course to the sphenopalatine ganglion (see Chapter 10).

The hypothalamus, reticular formation, and pituitary gland are included within the diencephalon and mesencephalon of the brain stem. Hypothalamic and pituitary disease generally result in endocrine dyscrasia. The reticular formation is very important for arousal and coordination of motor function. Lesions associated with the caudal brain stem can be identified based on clinical signs indicating abnormalities of CN V through XII.

Cranial Nerves
All the cranial nerves exit through the meninges at the base of the brain and are susceptible to injury in horses with meningitis because of direct spread of infection or increased intracranial pressure. The clinical signs of multiple versus single cranial nerve abnormalities are important for ruling out specific etiologies. For example, a weak horse with primary dysphagia and slow pupillary light responses has evidence of a multifocal or diffuse disease process such as botulism. Unilateral masseter atrophy consistent with CN V paralysis is a common finding in horses with clinical disease caused by Strepocystis neurona infection.

Spinal Cord
The spinal cord has a central core of gray matter surrounded by the ascending and descending nerve tracts of the white matter. Intramedullary lesions (within the spinal cord) produce neuronal injury at one or more spinal cord segments and then expand laterally to involve motor and sensory nerve tracts. Clinical signs are observed caudal to the site of the spinal cord lesion because of damage to descending motor tracts.

Although clinical signs of spinal cord disease are most often bilateral in horses, severity is frequently asymmetric; a close examination will reveal that most intramedullary lesions, unless extremely focal, will have some degree of abnormality associated with the contralateral limb. On the other hand, extramedullary lesions, or lesions of the peripheral nerves, will involve a single limb. Peripheral or extramedullary lesions can produce signs of nerve root irritation. When a lesion is compressive on the spinal cord, from outward to inward, there is a stepwise loss of proprioception, then weakness. After onset of weakness, further compression results in loss of sensation, followed by loss of deep pain. A typical presentation for a horse with cervical vertebral myelopathy is a young, strong 2-year-old racchorse with spontaneous loss of balance. Diffuse spinal cord disease is often observed in viral infections such as arbovirus infection, neurologic equine herpesvirus syndrome, rabies, and Halicephalobus infection, whereas multifocal, asymmetric disease is observed in horses with EPM. West Nile virus can be highly variable, with either diffuse spinal signs or highly asymmetric clinical signs.

Spread of infectious agents can be limited by neuroanatomic boundaries. The anatomic arrangements of the spinal meningeal layers (pia mater, arachnoid, and dura mater) are the same as described for the brain, and a plane of infection is possible between the arachnoid and dura. The spinal dura and peristeum diverge at the foramen magnum. At the level of the seventh cervical vertebra (C7), they are separated by a fat-filled epidural space that cannot permit longitudinal spread of infection, and thus infection may extend over many segments. In the horse the spinal cord ends as the cauda equina as the cord tapers into the conus medullaris, with distally coursing spinal nerve roots. Unlike in other species, the meninges end caudally between the second and third sacral vertebrae (S2 and S3) in the horse. The cauda equina is a site associated with CNS inflammatory diseases and occasional peripheral neuritis.

Vascularization
The blood supply to the CNS includes an extensive network of intercranial arterial and venous vessels fed by two sources, the basilar and internal carotid arteries, with multiple communications to the external circulatory vessels via the circle of Willis to ensure collateral circulation of the brain. The horse is distinct from other species because the internal carotid artery does not receive any blood from the maxillary artery. The details are beyond the scope of this review; however, some salient features are worth mentioning. The ophthalmic artery is a branch of the internal carotid artery, which is
branch of the main intracranial artery, the basilar artery. Therefore, CNS infection could result in septic emboli to the ophthalmic artery and consequent retinal lesions and loss of some visual fields. The middle cerebral artery has the greatest blood-flow volume and is considered the area of greatest risk for septic embolization and mycotic aneurysms in the brain. Brain infection most likely arises from infections with Aspergillus and mucoraceous fungi in lungs, uterus, and intestine (see Chapters 56 and 57). In descending order of frequency, the internal carotid artery, external carotid artery, and maxillary arteries are the most common equine vessels to be affected with mycotic aneurysm and extracranial (guttural pouch) infection (see Chapter 1).

Despite an extensive network of collateral circulation, three areas of the brain are supplied by only one or two vessels. Highly vulnerable to ischemic injury and abscess formation, these areas include (1) the middle and posterior cerebral arteries at the junction of the parietal, occipital, and temporal lobes; (2) the medial surface of the hemispheres of the cerebrum; and (3) cerebral white matter. No valves are present in the venous supply to the CNS, and the direction of flow may change with hemodynamic changes caused by pressure changes in the CSF and conditions such as cerebral edema. The anterior spinal cord is supplied by the medulla and intercostal arteries from the descending aorta and generally has a higher likelihood of infection than other parts of the spinal cord.13 Data that support this have been evaluated in the horse, although osteomyelitis of the cervical and thoracic spinal column may occur in foals.25,26

### Blood-Brain Barrier and Cerebrospinal Fluid

The capillary system of the CNS is unique in that it consists of endothelial cells with tight junctions and no fenestration, creating an effective blood-brain barrier (BBB).1 The BBB is the primary protective barrier of the CNS and acts as a filter preventing access of large proteins, immunoglobulins, antigens, pathogens, and some antimicrobial agents (e.g., gentamicin, amphotericin B) to the brain. Injury to the BBB by ischemia (e.g., septic emboli), vasculitis induced by inflammation, or increased levels of tumor necrosis factor alpha (TNF-α) can disrupt this protective barrier and predispose to CNS infection. Disruption of the BBB permits the entry of radiodense agents into the CNS for early visualization of abscesses on contrast magnetic resonance imaging (MRI) and computed tomography (CT) studies.7-8 The blood supply to the pituitary gland, choroid plexus, and brain stem does not have tight junctions, and these areas are considered to exist outside the BBB.

Cerebrospinal fluid (CSF) is an ultraltrafiltrate of plasma produced by active secretion from the choroid Plexus in the lateral, third, and fourth ventricles and by diffusion across the meninges.12,30 CSF protects and sustains the CNS.11,12 It circulates outward through the ventricular foramina into the subarachnoid space and is reabsorbed over 3 to 4 hours through cells of the arachnoid villi along the superior sagittal sinuses. Blockage of the villi from inflammation, blood in the subarachnoid space, or occlusion of the superior sagittal or lateral sinuses prevents the reabsorption of CSF, and communicating hydrocephalus develops. Obstructive hydrocephalus results from blockage of CSF circulation at the ventricles caused by inflammation or compression of the ventricles, as might occur with abscess or hemorrhage. Unlike communicating hydrocephalus, redistribution of increased quantities of CSF and cerebral edema into the subarachnoid space is not possible in obstructive hydrocephalus, and there is increased likelihood of brain herniation and death.11,12

### PATHOGENESIS

#### Entry of Pathogens

Most neurotropic viruses gain initial entry to the body through the bite of an infected mosquito or insect (e.g., arboviruses), the respiratory tract (e.g., herpesvirus), or the gastrointestinal (GI) tract. Dendritic cells or phagocytes at the site of initial infection transport virus to local lymph nodes, where it undergoes primary replication with subsequent viremia. Initial infection with bacterial or fungal organisms most often occurs through the respiratory, GI, reproductive, and urinary tracts. Septic emboli from vegetative endocarditis are another potential source of bacteria or fungi for hematogenous spread to the CNS. Regardless of the initial route of infection, the majority of CNS pathogens probably enter the nervous system of the host by a hematogenous route.2,5,6

The exact mechanism by which pathogens cross the BBB and enter the CNS is uncertain for many viruses and bacteria. Several mechanisms have been proposed. Bacterial infections of the CNS frequently involve the meninges. A breakdown in the BBB due to ischemia of meningeal vessels secondary to emboli and inflammation may provide a route of access to the brain parenchyma with subsequent abscessation.33-35 The initial systemic immune response to viral infection in the periphery results in release of cytokines, which stimulate increased expression of adhesion molecules on CNS endothelial cells and increased surveillance of the CNS by activated T cells.5 Some viruses enter the CNS using these cells as a "Trojan horse." Other viruses use endothelial adhesion molecules to gain entry or induce release of TNF-α, with subsequent increased BBB permeability.36 Intracerebral pathogens, such as Listeria monocytogenes and rickettsial species, gain entry into the CNS by penetrating endothelial cells of the BBB or by traveling within phagocytes.36

Other than hematogenous spread, pathogens may access the CNS by direct invasion (trauma or iatrogenic introduction), spread from contiguous structures (e.g., paranasal sinuses, otitis media), or retrograde entry along nerve roots.2,3,12,17,18 Despite the frequency of infections involving the external ear (e.g., sinusitis, tooth root abscesses, guttural pouch empyema), the number of CNS infections resulting from direct spread to the CNS appears to be low in horses.2,12 Rabies virus gains entry into the CNS by retrograde axonal transport along peripheral nerves. Herpesvirus is thought to infect the peripheral trigeminal nerve during latent phases.7 The potential for entry to the brain through the free nerve endings of the olfactory nerve in the nasal cavity has been proposed for rabies virus and arboviruses, especially Venezuelan equine encephalitis (VEE) virus, but has not been proved clinically.36

### Immune Response of Central Nervous System

The response of the CNS to infection plays an important role in the pathogenesis of disease. In bacterial CNS infections, CSF concentrations of complement and immunoglobulin G (IgG) are low compared with concentrations in the peripheral circulation.39 Complement and specific antibody are important for opsonization of bacteria, and a diminution of this function may be a critical factor in the pathogenesis of bacterial infections in the CNS. The presence of bacterial cell wall components in the CSF elicits the release of cytokines (e.g., interleukin-6 [IL-6], TNF-α, macrophage inflammatory protein [MIP]-1α, -1β, -2), which stimulate the entry of neutrophils, increased BBB permeability, and vasculitis; CNS edema; and inflammation of tissues surrounding the meninges.
The peak inflammatory response is observed 72 hours after the start of infection. Degenerating leukocytes release toxins that stimulate vasospasm, local ischemia, and further tissue edema. Inflammation of the arachnoid villi where CSF is absorbed could result in communicating hydrocephalus; inflammation of the ependymal lining and ventricles where CSF is circulated may result in obstructive hydrocephalus. Initially there is redistribution of increased CSF and cerebral edema into the subarachnoid space with communicating hydrocephalus, but with severe edema and obstructive hydrocephalus, this redistribution is not possible. Within the confines of the skull, the increase in intracranial pressure may result in pressure necrosis of the brain parenchyma or death due to herniation of the cerebellum through the foramen magnum. Vasogenic edema of the CNS is now viewed as a potentially fatal consequence of bacterial infection, and treatment of human patients with both antimicrobial and anti-inflammatory medications has dramatically decreased the mortality associated with CNS infection.

When infection occurs, the CNS must mount a controlled adaptive immune response that minimizes damage to brain cells. Initially there is an innate immune response, with production of interleukin-1 (IL-1), TNF-α, and chemokines that stimulate increased expression of endothelial adhesion molecules (e.g., vascular cell adhesion molecule [VCAM-1], intracellular adhesion molecule [ICAM]). By 3 to 4 days after infection, peripheral inflammatory cells that were activated in secondary lymphoid tissues enter the CNS. Unlike in the periphery, nonlytic clearance of viruses and infected cells occurs in the CNS to prevent secondary damage to surrounding neurons and tissues. Viruses that remain latent in neurons are controlled by continued secretion of antibody, IFN-β, and IFN-γ by lymphocytes.

As with bacterial CNS infections, control or elimination of viral infection in the CNS, without inducing unacceptable damage to neural tissue, requires a delicate balance of the CNS immune response. Induction of apoptosis (cell death) of neurons by microglia and stimulation of migration of T cells into the CNS are possible contributing factors to the neurodegeneration observed in degenerative diseases, such as Parkinson's and Alzheimer's disease. Overexpression of C protein, important in the complement system, causes bystander neurodegeneration and oligodendrocyte damage.

The immune response to equine herpesvirus type 1 (EHV-1) may be important in the pathogenesis of the neurologic form of this pathogen. Localization of EHV-1 in the CNS endothelium induces vasculitis. Subsequent CNS damage results from ischemia rather than direct neuronal insult; thus the disease is termed "myeloencephalopathy" rather than "myelonecrosis." The exact pathogenesis of herpesvirus neurologic disease in horses remains unclear. The disease is sporadic and seems to be more common in horses with a previous history of exposure to this ubiquitous pathogen and in pregnant or lactating mares. Evidence of antigen-antibody complexes between EHV-1 antigen and EHV-4 antibody and decreased levels of complement activation have been observed in experimentally infected ponies.

Other factors also play a role in the pathogenesis of viral infections. Nonvaccinated Japanese encephalitis virus (JEV), a flavivirus infection, has increased levels of IL-6, interferon-α, (IFN-α), and interleukin-8 (IL-8). Host genetic factors influencing production of these cytokines may be a factor. Regardless of the immune response, viruses have developed strategies to facilitate evasion of the CNS immune response. For example, WNV may block the signaling pathway for IFN-α.

Understanding of the host response to viral CNS infections is increasing and may explain the seemingly improper or inadequate immune response that allows the establishment of persistent infection. In human patients, certain types of vaccination or viral infection result in a multifocal inflammatory demyelinating process or acute disseminated encephalomyelitis (ADEM). An immune-mediated attack against antigen in brain myelin appears to be the cause of ADEM. The poliomyelitis-like, acute flaccid paralysis observed in some people with West Nile encephalitis may be an example of ADEM.

The old paradigm of the CNS as incapable of mounting an immune response to infection and being "immunologically privileged" has given way to the current recognition of the CNS as a specialized immune organ. The innate and adaptive immune responses of the host play an important role in CNS infections. A better understanding of this role is important for ultimately developing novel therapeutic and preventive strategies.

CEREBOSPINAL FLUID CHARACTERISTICS

Collection Techniques

Cerebrospinal fluid may be obtained autemtom from two sites in horses: the atlanto-occipital (cerebellomedullary) space (Fig. 4-2) and the lumbar (LS) space (Fig. 4-3). The optimal site for sample collection is determined on the basis of the neuroanatomical localization of the suspected lesion and practical considerations regarding patient systemic health status and restraint options. In general, better diagnostic results are achieved if CSF is obtained from the site closest to the suspected lesion. The atlanto-occipital (AO) space is sampled under general anesthesia and may be preferable in nervous horses, horses undergoing anesthesia for another reason, or in horses with conformation preventing successful LS taps (LS subluxation). Conversely, a LS tap performed standing under sedation may be advantageous in an animal where recovery from general anesthesia is considered a risk because of the severity of neurologic disease.

Fig. 4-2 Atlanto-occipital (AO) cerebrospinal fluid collection from recumbent horse. Spinal needle in position with atlanto-removed. Palpable landmarks are the cranial borders of the atlas (+) and the external occipital protuberance (+) on the dorsal midline. (From Mayhew IG: Cornell Vet 65:500-511, 1975.)
Collection techniques for both AO and LS tap have been described in detail. Briefly, atlanto-occipital CSF collection is performed with the horse under general anesthesia and lying in lateral recumbency. An area of the poll and neck (15-20 cm caudal to ears and 8-10 cm on either side of mane) is clipped and surgically prepped. The head is flexed so that the median axis of the head is at right angles to the median axis of the cervical vertebrae. A sterile 8.9-cm, 20-gauge spinal needle with stylet is inserted at the intersection of the cranial borders of the atlas and the external occipital protuberance along the dorsal midline. The needle should be parallel to the ground, perpendicular to the skin, and aimed toward the nose of the horse. The needle is gradually advanced until a “popping” sensation is felt with penetration of the AO meningeal and cortical dura. The stylet is withdrawn, and the appearance of clear CSF at the hub indicates a successful procedure. If no CSF appears when the stylet is removed, the needle is rotated 90 degrees. If fluid is still not obtained, the stylet is replaced, and the needle is advanced carefully. The approximate depth of needle insertion for entry into the subarachnoid space is 5 to 8 cm. If the needle contacts bone at a depth of 2 to 5 cm, it should be withdrawn and repositioned appropriately. If blood appears at the hub of the needle when the stylet is removed and does not clear with CSF in 15 to 20 seconds, the stylet is replaced and the needle removed; a fresh needle is used for the next attempt. When CSF flows freely from the hub of the needle, the sample is collected by free flow or gentle aspiration into an appropriate tube. After the sample has been collected and the needle is withdrawn, the head of the horse is extended to a normal or slightly extended position to prevent leakage of CSF from the puncture site.

Lumbosacral CSF collection in the horse is typically performed with the sedated horse standing as squarely as possible. Landmarks for the LS site are the intersection of imaginary lines joining the caudal borders of the tuber coxae along the dorsal midline or at the highest point of the gluteal region of the horse. In addition to sedation, adequate restraint with a twitch and use of stocks are advisable. In response to penetration of the dura mater, sedated horses may show no reaction, or tail movement and slight flexion of the pelvic limbs, or violent kicking responses that can endanger the patient and the veterinarian. A 10 × 10 cm site is clipped and steriley prepped. A 20-gauge, 1.52-cm spinal needle with stylet is inserted in a sterile manner and advanced carefully a few millimeters at a time. Care should be taken to keep the needle perpendicular to the dorsum and on midline. A “popping” sensation may be felt with penetration of the LS interarcuate ligament, dorsal dura mater, and arachnoid membrane. The stylet is removed to check for CSF at the hub. Gentle aspiration with a syringe may be necessary to initiate flow of spinal fluid. If no fluid is obtained, the needle (with the stylet replaced) is advanced to the floor of the vertebral canal and then withdrawn with slow rotation of the needle a millimeter at a time. A needle depth of 12 to 14 cm is usually required for successful CSF collection. Large-breed horses or obese horses may require longer needles. Queckenstedt's maneuver (bilateral occlusion of the jugular veins) may be performed by an assistant to increase intracranial and intraspinale pressure and facilitate CSF flow up the spinal needle. Rotation of the needle 90 degrees to remove occluding meningeal tissue and nerve roots from the needle point may also be helpful. Indirect aspiration with a syringe through an extension set connected to the spinal needle hub is recommended to minimize hemorrhage from excessive suction pressure and resultant occlusion of the needle with meninges. After adequate CSF is obtained, the stylet is replaced in the spinal needle, and the needle is removed. Collection of CSF from the LS space while the horse is in lateral recumbency (under general anesthesia or in a tetraplegic horse) is possible but is considered more difficult than in the standing horse. Attempts may be facilitated by elevating the upper pelvic limb so that the tuber coxae are perpendicular to the floor or by advancing the pelvic limbs cranially to flex the pelvis and LS joint.

Both AO and LS collection techniques are regarded as safe procedures in the horse. A common complication is blood contamination of the sample with puncture of meningeal or spinal cord vessels. Initial blood contamination of CSF frequently clears after a few milliliters during collection; however, even microscopic amounts of blood in the CSF sample may result in false-positive results in testing for EPM in horses. In humans, cerebellar herniation through the foramen magnum and herniation of the temporal cortex under the tentorium cerebelli are considered potential complications of CSF collection, especially in patients with increased intracerebral pressure, severe meningitis, or brain abscesses with deteriorating condition. This complication has not been reported as a frequent sequel to CSF collection in horses. Evidence of extradural hemorrhage or formation of fibrous adhesions between the LS ligament and dorsal LS dura mater have been observed in experimental subjects postmortem. Penetration of the AO joint is another potential complication. Cellulitis and septic abscesses secondary to CSF collection in horses are rare.

**Analysis**

Analysis of the CSF may include measurement of CSF pressure and examination of sample cytology, total protein concentration, glucose concentration, biochemical alteration, turbidity, and color. CSF pressure is measured by attachment of a manometer to the hub of the spinal needle before collection. Normal CSF pressure in the horse is approximately...
300 mm H₂O (150-500 mm H₂O). Increased opening pressure, when CSF is first obtained, may result from obstructive hydrocephalus. In addition to noninfectious congenital abnormalities, potential causes of obstruction include tumor, abscess, hemorrhage, and edema. An increased opening pressure that decreases by 20% to 50% after removal of 1 to 2 mL of CSF is indicative of an intracranial mass or spinal cord lesion cranial to the site of collection. Because CSF flows caudad from the ventricles of the brain, and because jugular compression causes increased blood volume in the cranial cavity with subsequent increases in CSF pressure, failure of the CSF pressure to increase in the LS site with bilateral jugular vein compression may indicate a compressive thoracic or cervical lesion.

**Appearance**

Normal CSF is clear and colorless and does not clot. Xanthochromia (yellow discoloration) of the CSF after centrifugation is caused by preexisting trauma, vasculitis, increased protein concentration (150 mg/dL), direct bilirubin leakage from high serum concentration, or breakdown of the BBB. Xanthochromia with increased protein concentration is typical of equine encephalomeningocephalopathy caused by vascular inflammation and increased BBB permeability.

Clots may result from increased fibrinogen caused by inflammation. A CSF sample may appear turbid if there is an increase in quantity of white blood cells (>200 WBCs/µL), red blood cells (>400 RBCs/µL), or epidural fat cells, or if significant numbers of bacterial, fungal, or amebic organisms are present.

**Cellular Evaluation**

Cell counts and cytology evaluation performed within 30 minutes of CSF collection are diagnostic. In normal horses and foals, less than 10 WBCs/µL is expected in the CSF. Cells are predominantly small (70%-90%) and large (10%-30%) mononuclear cells. An initial neutrophilic pleocytosis followed by mononuclear pleocytosis is characteristic of EEE infections. However, CSF from horses with Western equine encephalomyelitis (WEE) and WNE is characterized by predominantly lymphocytic cells. The increase in CSF nucleated cell count with viral infections is typically less (100-1000 cells/µL) than with bacterial meningitis. Eosinophilic pleocytosis with xanthochromia and increased protein concentration may be observed in CSF from horses with parasitic meningitis. Infrequently, horses with parasitic meningitis can have a neutrophilic pleocytosis. Fungal organisms may be observed in the CSF of horses with fungal meningitis. Although CSF analysis is useful to confirm the presence of an inflammatory process, to determine antibody titers to specific pathogens, and to monitor for therapeutic response, culture of viral or bacterial pathogens from CSF of horses with infectious neurologic disease is often difficult. Identification of viral etiologic agents in CSF is rare.

**Protein**

Normal protein concentration in equine CSF ranges from 20 to 124 mg/dL and is typically higher in CSF obtained from the LS site (93.0 ± 16.0 [55-124] mg/dL) than from the AO site (87.0 ± 17.0 [59-118] mg/dL). Differences in CSF protein between AO and LS samples that are greater than 25 mg/dL may indicate a lesion closer to the site of origin of the sample with greater CSF protein. CSF IgG and albumin concentrations may be determined by electrophoresis and radial immunodiffusion. These values are compared with serum IgG and albumin concentrations. An increase in the albumin quotient ([IgG CSF]/[IgG serum] × 100) is considered indicative of an increase in BBB permeability, as may be seen with equine herpesvirus myeloencephalopathy. An increase in the IgG index ([IgG CSF]/[IgG serum] × [Alb serum]/[IgG CSF]) may reflect intrathecal IgG production caused by inflammatory disease (e.g., EPM, meningitis, tumors, equine motor neuron disease).

**Biochemical Parameters**

Increased CSF creatine kinase (CK) are an unreliable indicator of neurologic disease in the horse and may be falsely elevated by contamination of the sample with epidural fat or dura during collection. Lactate acid concentrations in the CSF may increase with some CNS diseases (e.g., EEE, head trauma, and brain abscesses).

**Immunologic Testing and Molecular Diagnostics**

Detection of specific antibodies or antigens within the CSF may be helpful for the diagnosis of some viral, fungal, or rickettsial diseases. Use of polymerase chain reaction (PCR) for the diagnosis of viral encephalitis has become an important and sensitive tool. Details of testing for specific diseases are presented in appropriate chapters.

**GENERAL THERAPEUTIC CONSIDERATIONS**

**Antimicrobial Agents**

Antimicrobial selection for treatment of horses with bacterial infections of the CNS is based on initial Gram stain, culture, and susceptibility results whenever possible. Desirable antimicrobial traits include the ability to penetrate the CNS and predicted activity in the low-pH and high-protein environment of infected CSF. Low-molecular-weight antimicrobial agents that are lipid soluble and have a degree of protein binding and ionization at physiologic pH are favored. With inflammation, BBB permeability increases to allow penetration and accumulation of drugs that are normally actively transported out of the CNS (e.g., penicillin, cephalosporins). To allow for maximum peak plasma concentrations, intravenous (IV) administration of antimicrobials is recommended initially. The rapid bacterial killing needed for CNS infections in human patients requires drug concentrations that exceed the minimal bactericidal concentration by 10- to 20-fold. Expected duration of therapy varies depending on the nature of the infection, but generally is 10 to 14 days.

Antimicrobial agents with poor CNS penetration across the intact BBB include penicillins, cephalothin, cepazolin, cefofof, teicoplanin, and ampicillin. Good penetration is observed with fluoroquinolones, third-generation cephalosporins (e.g., cefotaxime, cefazidime, ceftriaxone), sulfamethoxazole, trimethoprim, pyrimethamine, doxycycline, chloramphenicol, rifampin, metronidazole, and macrolides. Enrofloxacin obtains therapeutic concentrations in the CSF for many gram-negative pathogens (e.g., Escherichia coli, Salmonella, Actinobacillus, Klebsiella) but is ineffective for treatment of most streptococcal and anaerobic pathogens. Its association with arthropathies in foals limits its use for treatment of neonatal bacterial meningitis. Potentiated sulfonamides (e.g., trimethoprim-sulfamethoxazole combinations) are attractive therapeutic agents for CNS infections because they have a broad spectrum of activity, are inexpensive, and are administered orally, but unfortunately, antimicrobial resistance is common.

Third-generation cephalosporins are considered the antimicrobial of choice in human patients with bacterial CNS
infection because of their activity against gram-negative bacteria, but these agents may be cost-prohibitive for use in horses. Although ceftiofur sodium is similar to true third-generation cephalosporins, it does not effectively cross the intact BBB in horses. Chloramphenicol is a bacteriostatic broad-spectrum antibiotic with activity against gram-positive, gram-negative, and anaerobic bacteria and is administered orally, but the associated human health risk (i.e., aplastic anemia) must be considered. Rifampicin has activity against gram-positive and anaerobic bacteria and is distributed into the CSF, but it must be used in combination with other antimicrobials (e.g., erythromycin) because of the frequent development of bacterial resistance when used alone. Fluoroquinolones should not be used with rifampicin because it is an inhibitor of ribonucleic acid (RNA) synthesis. Metronidazole is effective against anaerobic bacteria and is used in combination with third-generation cephalosporins for treatment of human patients with bacterial CNS infections.

**Glucocorticoids, Osmotic Agents, and Diuretics**

Increased intracranial pressure (ICP) caused by vasogenic edema or obstructive hydrocephalus is common in patients with bacterial CNS infections, and its control is critical for successful treatment of these patients. The use of corticosteroids in patients with CNS infection is controversial because of their immunosuppressive effects; however, mortality was unaffected with corticosteroid administration to humans with brain abscesses. Moreover, corticosteroids reverse the increased permeability of the BBB induced by inflammatory mediators (e.g., IL-1, TNF, prostaglandins, leukotrienes). Administration of dexmethasone (0.25–0.75 mg/kg) to two horses successfully treated for intracranial abscesses was thought to be beneficial.

Mannitol causes an osmotic shift of water into the vascular space, decreases blood viscosity, and increases cerebral blood flow and oxygen delivery. The net result is vasoconstriction of the cerebral arterioles and a decrease in cerebral blood volume and ICP. A single dose of mannitol (0.15–2.5 g/kg IV) decreases ICP experimentally within 5 minutes, with peak effects at 10 to 40 minutes and lasting 90 to 120 minutes. Adequate hydration of the patient must be maintained. The benefits of dimethyl sulfoxide (DMSO) for reduction of ICP are unclear, and most research has been performed in rodent models. In one clinical trial, DMSO reduced ICP and improved clinical course of neurologic recovery. In another trial, continued therapy was necessary for maintenance of decreased ICP. Objective studies regarding the efficacy of DMSO in horses for reducing ICP are lacking. Furosemide prolongs the effects of mannitol, but its effect as a sole agent for ICP reduction is inconsistent and delayed. Controlled ventilation to prevent hypercapnia and subsequent cerebral arterial vasodilation is advocated in human patients for the control of ICP. Barbiturates reduce cerebral oxygen demand and are neuroprotective against brain injury.

**Supportive Therapy**

Properly trained nursing personnel and facilities equipped to handle horses with CNS dysfunction are essential because the size, strength, and severity of neurologic disease in some horses can render appropriate care extremely demanding and dangerous. Rapid progression of disease is common in horses with CNS infections, necessitating the use of padded stalls and protective head gear, removal of shoes, and placement of leg wraps. Adequate bedding, periodic turning of the patient from side to side, or the use of slings to prevent formation of decubital ulcers is essential in the care of recumbent horses. Control of hyperthermia with ice water, alcohol baths, and fans may be indicated. Supportive care with IV fluids, parenteral nutrition, and electrolytes is necessary in an inappetent animal.

**MISCELLANEOUS BACTERIAL INFECTIONS**

**Bacterial and Fungal Meningitis and Meningoencephalitis**

**Etiology**

Bacterial meningitis most often occurs in septicemic foals, often caused by infection with *E. coli*, *Actinobacillus spp.*, *Klebsiella spp.*, *Streptococcus spp.*, and *Staphylococcus* spp. (see Chapter 6). *Listeria* has been isolated from affected immuno-suppressed foals (see Chapter 30). Bacterial meningitis occurs rarely in older horses and may be caused by a variety of organisms.

**Clinical Findings**

Early clinical signs of bacterial CNS infection include fever, stiff neck, obtundation, malaise, lethargy, anorexia, and photophobia. The stiff neck (meningismus) is not caused by pain but rather by a reflex spasm of the neck muscles due to traction on inflamed cervical nerve roots. In human patients, meningismus is greatest with flexion and less with extension or rotation of the neck and is associated with involuntary flexion of the hip and knee (Brudzinski’s sign). Hyperesthesia resulting in spasmic extension of the legs with touching may also be observed in humans.

Extension of infection from the meninges into the brain parenchyma (meningoencephalitis) via blood supply through the Virchow-Robin spaces occurs rapidly and will manifest as multifocal or diffuse corticidal disease. Forebrain disease is characterized by behavioral and mentation changes and may manifest as hyperexcitability, hyperesthesia, obtundation, and self-mutilation. Blindness, lack of menace, compulsive walking, circling, and anorexia may also be seen. Depressed consciousness, head tilt, loss of balance, ataxia, limb weakness, and cranial nerve deficits (e.g., facial paralysis, nystagmus, tongue paresis, pharyngeal paresis) indicate brain stem involvement. Cerebellar disorders are characterized by ataxia, intention tremor, and nystagmus. With increasing severity of disease, seizures and coma are likely. In human patients, mycotic meningitis is often characterized by a chronic, slower onset of clinical signs than observed with bacterial meningitis.

Clinical signs in foals may be more subtle because meningitis in the foal may be secondary to generalized sepsis. Presentation in foals can vary from the ambulatory foal with increased body temperature and mild hyperesthesia to the fully recumbent and comatose foal. Foals may present with fever of unknown origin and increased irritability. Seizures are likely in foals with meningitis. Foals may or may not have abnormalities of blood work that support clinical signs; CSF analysis is mandatory to confirm meningitis in the foal.

In horses, fungal encephalitis caused by *Cryptococcus neoformans* (see Chapter 57) is associated with immunodeficiency and guttural pouch mycosis (see Chapter 1). Clinical signs are similar to those of bacterial meningitis. In the horse with guttural pouch involvement, signs associated with the primary disease may include epistaxis, dysphagia, laryngeal hemiplegia, facial paralysis, and mydriasis. Aspergillus niger infection with mycotic vasculitis and right cerebral infarction was reported in one horse, associated with acute bacterial typhlocolitis (see Chapter 56). The mare presented with a 10-day
history of watery diarrhea, fever, increased heart rate, dehydration, dysphagia, and depression.

**Diagnosis**

As with any clinical problem, accurate diagnosis of CNS infection depends on obtaining a thorough history and a detailed physical examination of the patient. Neuroanatomic localization of the lesion in the CNS should be emphasized to facilitate development of an accurate list of differential diagnoses. Further diagnostic tests are chosen to support or eliminate specific differential diagnoses for that patient.

Bacterial meningitis should be suspected in a neonate with clinical signs and history of questionable immune status or concurrent sepsis. A history of systemic infection, ethmoidal hematoma, edema media, or guttural pouch empyema in adult horses with bacterial meningitis is common. Diagnostic investigation to identify possible primary systemic infection is warranted in both adult horses and foals. Confirmation of a diagnosis of bacterial meningitis is usually obtained on the basis of clinical signs, CSF analysis, and imaging of the CNS.

Diagnostic evaluation is done to identify underlying systemic infection that may be associated with meningitis. This evaluation may include complete blood count (CBC), serum biochemical profile, urinalysis, thoracic or abdominal imaging, serology, and blood or urine culture, depending on the patient’s clinical signs and presenting complaints. In foals, clinical signs may mirror metabolic encephalopathies associated with septicemia. CBC and serum biochemistry panel are warranted to rule out hypoglycemia, hypernatremia, and hepatic dysfunction.

Analysis of CSF is often invaluable for diagnosis of bacterial meningitis. In human patients, opening CSF pressure on 180 to 600 mm H2O are reported. Increased white blood cell (WBC) count (10^-10,000 cells/μL) with a predominantly neutrophilic profile and the presence of intracellular organisms are the hallmark of supplicative bacterial meningitis. A low WBC count with high numbers of bacteria is considered indicative of a poor prognosis. Decreased CSF glucose concentration, increased lactate concentration, and increased protein concentration are also observed in many patients. CT and MRI are standard in human medicine as aids in the diagnosis of bacterial meningitis and to rule out concurrent space-occupying lesions (e.g., neoplasia, intracranial abscess). CT and MRI become more readily accessible to veterinarians, these scans may assume increasing importance as imaging modalities for diagnosis of horses with bacterial meningitis. Standard radiographic imaging of the skull or vertebral bodies may facilitate identification of predisposing conditions, such as fractures, vertebral body abscess, sinusitis, and otitis media.

Electroencephalography (EEG) is a sensitive tool for the diagnosis of intracranial disease in horses. Abnormal electroencephalograms (EEGs) appear as high-voltage waves with discrete paroxysmal activity. The cold water test, with a 3- to 5-minute application of ice-cold water into the ear and monitoring for subsequent nystagmus, can help rule out central vestibular disease.

Differential diagnoses for bacterial meningitis include metabolic encephalopathies associated with septicemia, Tyzzer’s disease, idiopathic epilepsy, cerebellar atrophy, intracranial abscesses, neonatal maladjustment syndrome, hydrocephalus, hydranencephaly, and hypoxia. In adult horses, differential diagnoses for bacterial meningitis include mycotic meningitis and encephalitis, viral encephalitides, neoplasia, rabies, migrating parasites, metabolic derangement, hepatoencephalopathy, intracranial abscesses, leukoencephalomalacia, endotoxemia, botulism, tetanus, brain trauma, and intoxication with organophosphate, strychnine, metaldehyde, lead, arsenic, mercury, or bracken fern.

Postmortem findings are diagnostic in most horses with bacterial meningitis. Grossly congested, swollen, opalescent meninges with petechiation are observed. Histopathologic lesions include infiltration of the tissues with neutrophils and lymphocytes, choroiditis, bacterial colonies around blood vessels, and meningeal hemorrhage. In foals, evidence of septicaemia and concurrent infection of the joints, umbilical cord, respiratory system, and GI system may be observed. Culture of lesions will identify specific etiologic agents.

**Therapy**

Treatment of bacterial meningitis emphasizes elimination of bacterial pathogens and limiting the severe and often fatal consequences of the immune response within the CNS. Third-generation cephalosporins and metronidazole remain antibiotics of choice in human medicine, administered in combination with nonsteroidal antiinflammatory drugs (NSAIDs) and corticosteroids. The use of antiinflammatory medications with bactericidal drugs has reduced the mortality in children with bacterial meningitis from 30% to less than 5%. Antimicrobials that do not induce cell lysis (e.g., imipenem) rather than traditional β-lactam antimicrobials have been recommended to reduce the amount of inflammatory bacterial debris created. Polymyxin B, which binds the lipid A portion of lipopolysaccharide, intracerebral injection of IgM antibody to lipid A, and intracerebral injection of anti-CD18 antibody to interfere with leukocyte migration into the CSF have also been suggested as novel therapeutic strategies for treatment of bacterial meningitis. In human medicine, there is growing concern about antimicrobial resistance. Resistant forms of *Streptococcus pneumoniae* have necessitated the use of third-generation cephalosporins with vancomycin.
Methicillin-resistant Staphylococcus aureus (MSRA) was isolated in 3% of 163 patients (see Chapter 29).  Prognosis for survival of horses with meningoencephalitis is fair to poor. Early diagnosis is critical, but vague clinical signs in horses early in the disease process often prevent timely medical care.

Prevention
Although chemoprophylaxis with antibiotics is a mainstay in the prevention of bacterial meningitis caused by Neisseria, S. pneumoniae, and Haemophilus influenzae type B in certain human high-risk groups (e.g., infants, military recruits, workers) and in the prevention of infection of neonates during birth from carrier mothers of Streptococcus agalactiae, this type of treatment is not used in horses. Immunoprophylaxis with vaccination for H. influenzae, S. pneumoniae, and Neisseria meningitidis has been described for humans.

Vaccines against bacterial CNS pathogens are not available for horses.

Intracranial Abscesses

Etiology
Brain and spinal abscesses are rare in horses. Evidence indicates that CNS infections may occur secondary to extension of infections involving other structures in the head (e.g., sinuses, otitis media, traumatic injury, tooth root abscesses). Rhodococcus equi was isolated from an intracranial abscess and concurrent occipital osteomyelitis in a 3-month-old colt. The colt had presented for respiratory distress and a mild left-sided head tilt. The intracranial abscess was suspected to have resulted from dissemination of the pulmonary infection. Streptococcus spp. are a common isolate from brain abscesses in adults.

There is one report of iatrogenic spinal epidural abscess secondary to CSF aspiration.

Clinical Findings
Horses with intracranial abscesses are often presented for evaluation of compulsive circling toward the side of the lesion, head pressing, fever, focal neurologic deficits, seizures, mental change, papilledema, and ophthalmic tract deficits. Improved vision has been frequently reported with brain abscesses in horses. Unilateral cortical abscesses result in loss of vision in the contralateral eye because of the high percentage of optic nerve fibers (85%) that cross at the optic chiasm in the horse compared with other species. Although pituitary abscess is considered rare in horses because of the lack of defined nectrin bright vessels, six abscesses involving the pituitary were observed in four of five horses with intracranial abscesses.

Diagnosis
Previous history of a severe purulent infection such as Streptococcus equi subsp. equi ("stangles") and other systemic bacterial infections (respiratory, gastrointestinal, reproductive, urinary, cardiovascular) are frequently reported in horses with intracranial abscesses. Primary infections of the head (sinusitis, pericranial lesions, dental disease, submandibular lymphadenopathy) without concomitant systemic disease are also considered risk factors. In horses, antemortem diagnosis of intracranial abscess is primarily made on the basis of clinical signs, neuroanatomic localization of the lesion, CSF analysis, ancillary diagnostic testing, and imaging of the brain and spinal cord. Human patients with suspected intracranial abscesses are empirically treated with antibiotics before ancillary testing with CT, MRI, and skull radiographs. Involvement of the pituitary gland may result in hyponatremia caused by inappropriate antidiuretic hormone secretion.

CSF changes in horses with intracranial abscessation may be minimal and nonspecific. Increased protein concentration, decreased glucose concentration, and a mononuclear pleocytosis may be observed in affected horses. Culture of the lesion itself through CT-guided stereotactic aspiration is preferred over culture of CSF for identification of a causative organism. Culture of a pathogen from the CSF of human patients with brain abscesses is successful in only 11% to 17% of cases, whereas culture of aspirates from intracranial lesions is 95% successful in untreated patients and 70% to 82.6% successful in patients treated with antibiotics before sample collection. Collection of CSF is contraindicated in neurologically unstable patients because of the risk of brain herniation.

Use of nuclear scintigraphy, CT, and MRI for imaging of the brain and spinal cord are routine for human patients with suspected CNS infection. Radiopharmaceuticals such as [18F]-hexamethylpropyleneamine oxime and [111In]-labeled leukocyte scintigraphy are useful for differentiation of abscesses from tumors. Labeled leukocytes accumulate in areas of active infection and inflammation.

CT is considered superior to standard radiographs for anatomic visualization of brain abscesses. An intracranial abscess is seen as a hypodense area of avascular necrotic tissue and purulent discharge. With injection of iodinated contrast material, the hypodense area appears to be surrounded by an "enhanced rim," representing a region of hypercellularity and hypervascularity encapsulated by fibrous tissue (see Fig. 4-4). Surrounding the ring may be a hypodense area of brain edema. Stereotactic CT-guided techniques are useful for direct aspiration of abscesses, with minimal damage to surrounding tissue.

In humans, MRI is more sensitive and accurate than CT for the diagnosis of brain abscesses. MRI is also more sensitive than CT for detection of cerebritis and cerebral edema, which frequently precede overt abscess formation. With CT, small pathologic changes in the tissue are masked by "hardening artifacts," streaklike artifacts of low density caused by absorption of lower-energy photons in the x-ray beam by large radiodense structures. MR images are generated with T1-weighted, T2-weighted, proton density (PD)-weighted, and inversion recovery (IR)-weighted spin-echo sequences. Intracranial abscesses appear hypointense to isointense, with a hyperintense rim if there is capsule formation. The contrast agent chelated gadolinium is excluded from the normal CNS. Its appearance in neural tissue after systemic injection indicates breakdown of the BBB. The sensitivity of MRI has allowed clinicians to define four stages of intracranial abscess formation: early cerebritis (days 1-3), late cerebritis (days 4-9), early capsule formation (days 10-13), and late capsule formation (day 14 and onward). Initiation of treatment during the early stages of abscess formation before encapsulation of the lesion allows for better penetration of antibiotics and better prognosis for response to therapy.

There are two reports of MRI for the diagnosis of intracranial abscesses in horses. In one horse, comparison of MRI and CT found that MRI demonstrated better spatial resolution and soft tissue contrast in delineating the surrounding tissue edema. MR findings of a chronic brain abscess in a 10-month-old foal correlated with the characteristics of a mature brain abscess and were confirmed by histopathologic changes.

Whether the advantages of MRI will improve the outcome for horses with brain abscesses remains to be determined because treatment was not pursued in all horses in these reports.

References 6-9, 25, 27, 37, 77, 79-85.
Differential diagnostic considerations for intracranial abscesses in horses include otitis media, central vestibular disease, cholesterol granuloma, neoplasia, rabies, tetanus, EPM, equine herpesvirus myeloencephalopathy, polynucleosis equi, meningocerephalitis (viral, bacterial, fungal, protozoal), subdural empyema, aberrant parasite migration, intracranial hemorrhage, brain trauma, cerebral infarction, and intracerebral injection. Intracranial abscesses are usually obvious lesions if the brain is evaluated grossly during a postmortem examination. They are usually focal lesions of encephalomalacia with surrounding dense, fibrous connective tissue and dense aggregates of microglia.

Therapy

Long-term antimicrobial therapy and surgical intervention are recommended for treatment of horses with intracranial abscesses. Surgical intervention with craniotomy has been described in three horses. In all three cases, poor response and/or progression of neurologic signs despite systemic antimicrobial therapy prompted surgical intervention. A 3-month-old colt that developed CNS infection after traumatic injury to the poll required two surgical procedures. The first was performed 7 days after hospitalization to culture and flush the fracture site, and the second was performed at day 20 for removal of a bone fragment and debridement of the matured abscess.

Of the three horses with a reported successful outcome for treatment of brain abscesses, antimicrobial agents initially administered included crystalline penicillin or procaine penicillin intramuscularly (IM) with or without sulfa-trimethoprim. Therapy was switched to procaine penicillin for 10 to 14 days, and then horses were discharged from the hospital with recommendations for treatment with sulfa-trimethoprim for 28 days. Cefazolin was infused into the craniotomy site in one affected horse.

Empiric therapy with antimicrobials is immediately instituted in all human patients with suspected intracranial abscesses. Course of therapy is determined by whether the patient is a surgical candidate. nonsurgical patients include those with stable neurologic condition, multiple abscesses, deep location of abscesses, abscesses in a sensitive area of the brain, concomitant meningitis or ependymitis, lesions less than 3 cm in size, and response to empiric antimicrobial therapy. Surgery is also contraindicated in patients with early cerebritis because of the risk of hemorrhage with aspiration. Surgery is considered in patients with rapidly deteriorating neurologic conditions (likely caused by increased intracranial pressure) or chronic encapsulated lesions that are nonresponsive to prolonged antimicrobial treatment. CT-guided stereotactic aspiration is the preferred technique; however, full-excision craniotomy may be necessary in rapidly deteriorating patients; patients with inaccessible lesions in the brain stem, thalamus, or basal ganglia; and lesions with gas abscesses. Fungal abscesses require direct infusion of antimicrobial drugs into the lesion because of the poor concentrations achieved by systemic administration of most drugs. Use of corticosteroids in patients with intracranial abscesses is controversial because it decreases antibiotic entry into the CNS and decreases collagen formation and glial response, but it may be indicated in rapidly deteriorating patients to reduce ICP.

The veterinary literature suggests that the prognosis for horses with intracranial abscesses is poor. Of 13 affected horses, three horses were successfully treated, but one of the three succumbed to secondary lamiaritis. Use of CT or MRI, long-term antimicrobial therapy, concomitant anti-inflammatory therapy, and surgical intervention were common factors in the horses that survived. In human patients, mortality associated with intracranial abscess is approximately 5%, with 10% to 50% having mild long-term neurologic deficits and 10% to 25% having posttherapy epilepsy. The success rate for treatment of intracranial infections in humans is likely the result of earlier presentation of the patient, rapid diagnosis and early surgical intervention with the use of CT and stereotactic drainage, and long-term antimicrobial therapy.

Spinal Abscessation and Vertebral Osteomyelitis

Etiology and Epidemiology

Spinal abscesses are rare in horses. Most reported cases originate from a preexisting vertebral osteomyelitis (more likely in foals) or diskospondylitis. Common etiologic agents found in vertebral infections in foals include Salmonella spp., Acinetobacter baumannii, Escherichia coli, Streptococcus spp., Rhodococcus equi, and Klebsiella spp. Less common agents isolated from horses include Mycobacterium avium, Actinobacillus lignieresii, A. equi, Stenotrophomonas maltophilia, and Brucella spp. These bone infections are likely the result of hematogenous spread of the pathogen from primary systemic infection sites (lung, heart, GI) or probably secondary to septicemia in neonates.

The unique vascular anatomy of the vertebrae contributes to the pathogenesis of infection. The decreased blood flow of the tortuous metaphyseal arteries as they approach the vertebral physis creates an ideal environment for the embolization of septic thrombi. Furthermore, the metaphyseal vessels communicate with vertebral vascular plexus, which in turn drains into the postcava, the portal vein, and the pulmonary veins. The ventral vascular plexus does not contain valves, and when blood flow reverses with an increase in abdominal or pleural pressure, regurgitated blood from infected sites in the body cavities shows the vertebrae and spinal cord with bacteria. As previously described, the posterior spinal cord blood supply is rarely involved in infections because it is supplied by an irregular portion of articular plexuses, whereas the anterior spinal cord is supplied by the cervical and intercostal arteries from the descending aorta.

Bone lesions may also develop from sequestra broken from fractured vertebrae. Injection of contaminated vaccines or drugs in the proximity of the spinal column is another potential route of infection. Septic arthritis of the AO joint resulting from extension of a mycotic guttural pouch lesion has been reported. Spinal epidural infection secondary to epidural anesthesia is not considered a likely potential complication in horses. There is one report of iatrogenic spinal epidural abscess secondary to CSF aspiration.

Clinical Findings

Clinical signs depend on the anatomic area involved and the extent of infection. Horses with cervical spinal abscesses may appear stiff, may exhibit signs of neck pain, and may be reluctant to eat food from the ground. Additional signs may include pain, heat, swelling, and crepitus over the affected areas and associated signs of bacteremia (e.g., fever, depression, anorexia). Neurologic deficits depend on the degree of spinal cord compression and inflammation and the area of the lesion. Hindlimb lameness, ataxia, weakness, parasthesia, cauda equina syndrome, and urinary incontinence have been described in horses with epidural abscesses, pelvic osteomyelitis, and sacral diskospondylitis. If the infection is extensive and extends through the dura matter, septic meningitis may develop. Extensive bone infection may also
result in vertebral bone fracture and development of acute signs of spinal trauma.

Diagnosis
In horses, anemometric diagnosis of a spinal abscess is primarily made on the basis of clinical signs, neuroanatomic localization of the lesion, CSF analysis, ancillary diagnostic testing, and imaging of the spinal cord. Plain radiographs are considered the most diagnostic for spinal abscesses, with osteomyelitis manifesting as hyperlucency and increased bone density in the affected vertebrae (Fig. 4-5). Myelography may be used to define spinal cord compression further. Nuclear scintigraphy (Tc-99m methylene diphosphonate [MDP] and labeled leukocytes) may be beneficial when bone lesions are not well defined on plain-film radiography, as with extradural abscesses. In foals, CT or MRI may be beneficial.

CBC in affected horses is often consistent with a chronic inflammatory focus and may include hyperfibrinogenaemia, neutrophilia, monocytosis, nonresponsive anemia, and left shift. In necrotics with inadequate colostal immunoglobulin transfer, plasma globulin levels may or may not be increased. CSF evaluation may not be as beneficial because most spinal abscesses do not infiltrate through the dura and into the pachymeninges. Normal or mild increases in protein concentration may be seen. Diagnostic testing to evaluate underlying primary infection is indicated.

Therapy
As with intracranial abscesses, prolonged systemic antimicrobial therapy is indicated for the treatment of vertebral abscesses. Selection of a broad-spectrum antimicrobial is advocated but ideally should be based on results obtained from culture of the primary underlying systemic infection. Access to the vertebral lesion may be difficult because of the large epaxial muscles of the horse. Surgical drainage and curettage of necrotic bone constitutes successful therapy in one horse. Use of NSAIDs may be beneficial to reduce inflammation and musculoskeletal pain. Use of a supportive fiberglass neck cast has been described to stabilize infected cervical vertebrae in smaller and compliant patients. Easier access to water and food by lifting the feed buckets may be beneficial for horses with neck pain.

As with intracranial abscesses, vertebral osteomyelitis and spinal cord abscesses are potentially life threatening, and prognosis is guarded.

MISCELLANEOUS PARASITIC INFECTION

Mourine T. Long

Verminal encephalitis is rare in horses but does occur in the Midwest and Southeast United States. Specific causes to consider include Strongyulus vulgaris, Setaria filariae, Helicobalobus gingivalis, Dracunculus megastoma, and Hyperderma (see Chapter 61). Setaria and Strongyulus cause brain or spinal cord disease. Signs are ipsilateral and sudden, resulting from an infarctive process. Helicobalobus and Hyperderma usually are intracranial.

Helicobalobus gingivalis Eencephalomyelitis
H. gingivalis, previously known as Micronema delitrix and Helicobalobus delitrix, causes sporadic brain infection in horses resulting from an aberrant infection. This parasite was identified and named in 1954. Infection has been identified in humans as well.

Etiology and Epidemiology
Helicobalobus parasites are free-living nematodes of the order Rhabditida (family Rhabditidae) that normally reside in soil and humus. In Florida, infection with H. gingivalis is anecdotally associated with a swampland environment, although stabled horses have developed the disease. Actual species characterization had been limited until recent molecular techniques were applied to analysis of this organism. The nematode identified as H. delitrix is one of seven nematodes that belong to the Helicobalobus genus.

Recent genetic analysis demonstrates several different clades. Isolates from clinical cases and from the environment are not aligned geographically, although there are differences among isolates from cases in Tennessee compared with California. Only one type of Helicobalobus is associated with mammalian infection; all other species have been obtained solely from environmental sampling.

The life cycle of H. gingivalis has not been completely determined; only females have been recovered from tissue sections. Eggs and immature larvae are present in these infections, indicating an asexual reproductive cycle in tissues. Free-living male worms have been recovered from soil, indicating sexual reproduction does occur.

Pathogenesis
Disease in horses infected with H. gingivalis may affect the CNS and the renal, ocular, and reproductive tracts. Little is known about the pathogenesis of this disease in horses. High numbers of organisms are observed in tissue sections. Regardless of infection site, the tissue burden of this organism is dense, and there is an extremely severe tissue reaction with supplicative inflammation and eosinophilic localization within tissue. Abscess and severe, fulminant pyogranulomatous disease is associated with infection.

Site of entry for the parasite is hypothesized to be through breaks in the skin or mucous membranes. Mammary, uterine,
and renal infection has been reported independent of CNS infection. In one horse with CNS infection, a large, oral granulomatous lesion was observed. Breaks in urogenital mucosa may also provide an important pathway for invasion. Two stallions with renal infection, one with concurrent testicular involvement, have been described. Vertical transmission may also occur in horses. Localization to the kidney may occur through ascending infection, resulting in perirenal granulomas. These frequently coincide with CNS infection. Ocular and periocular infections have also been described in horses.

Clinical Findings
Horses with CNS infection usually present with signs of fulminant encephalitis. Rarely, peripheral CNS infection has been described. Most horses have a rapid onset of progressive cerebellar signs, with head pressing, coma, extensive loss of proprioception, recumbency, and death. Onset can be insidious initially, but with cerebral and hindbrain infection, signs rapidly progress. One horse has been described with cauda equina clinical signs consisting of ataxia, flaccid tail, fecal incontinence, and urinary incontinence. Parasitic granulomas were associated only with spinal nerve roots of the cauda equina.

Diagnosis
There is no specific ante-mortem test for diagnosis of H. gingivalis in horses. CBC is usually normal except for possibly an eosinophilia. Hypergammaglobulinemia has been described in the literature and associated with several clinical cases at the University of Florida. CSF that contains eosinophils is highly suggestive of a parasitic infection. CSF total nucleated cell count and total protein concentration are usually significantly increased. Very high numbers of nondegenerate and degenerate neutrophils have been observed cytologically in the CSF of affected horses.

CNS infection with H. gingivalis is usually confirmed by histopathology; however, renal involvement with perirenal granulomas is highly suspicious for H. delarae. Histopathologic identification of the parasite in tissues is the most common way in which the organism is diagnosed. In tissue section the parasite has a smooth, thin cuticle with what is called a "plymianyar-meromyarian" musculature, and the nematode body ends in a tapered tail. The pendocoeleon and rhabditiform esophagus is composed of a corpus, isthmus, and bulb. The parasite has an intestinal tract lined by single, nucleated cuboidal cells. The ovary and uterus can be visualized as a "flexed" structure.

Therapy
Reports are limited on treatment of H. gingivalis infection. A 12-year-old gelding with a granuloma in the orbit was successfully treated with oral ivermectin (0.55 mg/kg every 14 days) and surgical debulking. There was no evidence of infection in any other organ system. Although ivermectin is likely active against systemic infection, it is unlikely that CNS levels obtained after oral therapy are high enough to treat intracerebral H. gingivalis. High-dose treatment with fenbendazole in addition to ivermectin is indicated for neurologic disease caused by H. gingivalis, although the prognosis for survival is exceedingly poor.

Prevention and Control
Because limited information is available regarding the epidemiology of H. gingivalis infection, no specific control measures can be recommended. Good pasture management and restriction of horses from marsh or swamp environments are indicated.

REFERENCES
See the CD-ROM for a list of references linked to the abstract in PubMed.

CHAPTER • 5

Infections of Muscle, Joint, and Bone
W. Wesley Sutter and Alicia L. Bertone

Musculoskeletal infections are a common clinical problem encountered in equine practice. Infections in the adult horse are often associated with trauma. Conversely, musculoskeletal infections in the foal are more likely to be of hematogenous origin. In both foals and adults, musculoskeletal infections are associated with significant morbidity and mortality. A rapid, accurate diagnosis and prompt initiation of appropriate therapy are important for a successful outcome.

MUSCLE INFECTIONS
Infectious myositis may be caused by bacteria, viruses, or parasites as either a primary or a secondary disease process. Primary infectious myositis occurs when inflammation is caused by active infection of muscle tissue with a pathogen. In secondary infectious myositis, muscle inflammation occurs as a response to current or past infection at other body sites, and viable pathogens are not usually present in the affected muscle tissue. Primary infectious myositis may result from direct inoculation of a pathogen (through the skin) or hematogenous localization to a single muscle or multiple muscle groups.

Primary Bacterial Myositis
Etiology
Bacterial infection occurring in association with trauma is the most common form of primary infectious myositis. Streptococcus equi subsp. equi (see Chapter 28), Clostridium spp. (see Chapter 45), and Staphylococcus spp. (see Chapter 29)
are common bacterial isolates from these cases. Mixed gram-negative and anaerobic bacterial muscle infection with abscess can occur secondary to infection of deeper structures. Many different bacterial agents can colonize muscle from a hematogenous route, including S. equi subspp. equi and Clostridium spp. Salmonella can cause localized myonecrosis and infection secondary to septicemia in both adult horses and foals (see Chapter 38).

**Clinical Findings**

In general, clinical signs of primary bacterial myositis reflect whether infection is generalized or localized. Presentation may vary depending on the type of organism and whether signs of systemic toxic insult are present. Clinical findings of localized infection include signs typical of impeding or fully mature abscess formation, such as fever, pain (on palpation), edema, and localized swelling. Localized myositis may be insidious if deep muscular structures are involved. Mild to non-weight-bearing lameness can be the primary clinical sign. Injection site abscesses caused by non-toxin-producing organisms can present with moderately painful swelling and no other signs. Infections with organisms such as S. equi subspp. equi, Corynebacterium pseudotuberculosis, and Staphylococcus aureus can be accompanied by generalized edema, serum leakage, vasculitis, and cellulitis. Signs of systemic toxemia include redness of mucous membranes, tachycardia, tachypnea, poor peripheral pulses, and reluctance to move.

**Diagnosis**

A diagnosis of primary bacterial myositis can be quite obvious if the lesion is localized; however, if generalized myositis or localized myositis without external swelling is present, identification of myositis, let alone infectious myositis, can be problematic. Detailed history of recent injections, trauma, travel, and other systemic complaints should be closely considered. A complete blood count (CBC) may reveal an inflammatory leukogram (neutrophilia with or without a left shift) and hyperfibrinogenemia. If chronic or viral infection is present, these tests may be normal. Increased serum creatine kinase (CK) and aspartate transaminase (AST) activities indicate muscle inflammation or necrosis. Muscle enzymes may not be significantly elevated when localized or occult infection exists.

For localized infection, ultrasound evaluation, radiography, and scintigraphy may assist diagnosis and intervention strategies. Even with an obvious abscess, ultrasound of affected muscle can facilitate evaluation of the extent of the lesion and assessment of response to therapy. Radiographs of the affected area may be indicated if skeletal involvement is suspected. Nuclear scintigraphy has been suggested to aid in localization of abscesses in muscle either by soft tissue phase imaging or by the use of radiolabeled autologous white blood cells.

Diagnostic testing should include efforts to isolate or identify the causative agent. For localized infections, aspiration and culture of soft or fluid-filled swellings is recommended. Culture of samples obtained by deep swab of draining tracts is important. Both these techniques should be performed aseptically. Culture of fine-needle aspirates from swollen, inflamed muscles may yield infecting organisms such as S. aureus and C. pseudotuberculosis. Muscle biopsy may be indicated in some cases to confirm the presence of myositis and obtain diagnostic culture results. Aerobic, anaerobic, and fungal cultures should be requested when indicated. Identification of parasites is usually accomplished with histopathology. Serology can aid diagnosis of C. pseudotuberculosis (see Chapter 30). High S. equi subspp. equi titer may reflect recent exposure or active infection, if vaccination has not been recent.

**Therapy**

Therapy for infectious myositis depends on the etiologic agent, type of presentation (generalized or localized), and other organ involvement. For localized infection without systemic clinical signs, local drainage and flushing with isotonic solution are essential and may be the only indicated treatment. When there is evidence of cellulitis, systemic infection, or septicemia, antimicrobial and antinflammatory therapy is indicated. Antimicrobial therapy should reflect culture and sensitivity results whenever possible. Initial therapy, before receipt of culture results, should be broad spectrum and, with life-threatening infection, administered parenterally.

**Clostridial Myonecrosis**

**Etiology**

Clostridial myonecrosis, gas gangrene, and malignant edema are all terms used to describe a rapidly progressing infection of muscle with Clostridium spp. resulting in severe myonecrosis (see Chapter 45). Clostridial myonecrosis occurs most often after intramuscular (IM) or perivascular injections but may also be associated with traumatic puncture wounds. It may occur in horses after deep IM injection of a variety of substances, including flunixin meglumine, iomeprazole, B-complex vitamins, vitamin E, selenium, synthetic prostaglandins, dipyrone, phenylbutazone, antihistamines, and vaccines. Clostridium septicum and C. perfringens are the species most often cultured from areas of myonecrosis in horses; however, other Clostridium spp., including C. chauvoei, C. novyi, and C. falciformis, have also been isolated from affected horses.

The origin of the bacteria is unknown. Attempts to culture clostridial organisms from external sources have been unsuccessful. Some authors have hypothesized that spores are present in normal muscle, and that colonization occurs after IM injection with an irritating substance provides a suitable anaerobic environment for bacterial proliferation. Clostridial exotoxins play a central role in the massive myonecrosis associated with infection. These exotoxins directly affect the venous endothelium, creating intravascular platelet aggregation and leukostasis. Resultant decreases in tissue pH and oxygen tension impair immune defenses and create an ideal environment for clostridial growth. Clostridial exotoxins can also have a significant systemic effect, causing shock and in some cases hemolytic anemia.

**Clinical Findings**

Clinical signs of clostridial myonecrosis typically develop within 6 to 72 hours of IM injection. Affected horses often show signs of shock and are painful, tachycardic, and dehydrated. It is not unusual for horses with clostridial myonecrosis to present for colic. Horses with cervical muscle infections may be lame in a thoracic limb and may have severe facial swelling. Pulpable subcutaneous crepitation is considered a hallmark of this disease but may be absent early in the disease, especially if deep [gluteal] muscles are involved. Many horses will have localized swelling, heat, and sensitivity at the injection site; as the disease progresses, however, the skin may become cool and discolored. Any anatomic location used for IM injection can be affected; the cranial cervical muscle region may be affected in association with inadvertent perivascular injections. Clinopathologic abnormalities are variable and may be consistent with shock. Increases in serum muscle enzyme activities may be seen, but rarely reflect the severity of the condition, most likely because of poor perfusion of the necrotic area.

Historically, the prognosis for horses with clostridial myonecrosis has been considered to be guarded to poor. More recently, a retrospective study of 37 horses with clostridial
myonecrosis reported an overall survival rate of 73%. Several factors appear to be important in the successful management of this disease. First, prompt diagnosis and early initiation of antimicrobial therapy (typically high doses of penicillin G) are very important. Second, the early use of fasciotomy and myotomy appears to improve prognosis. Both retrospective studies report a better prognosis with C. perfringens infections (19%-25% mortality) than with infection by other clostridial organisms, especially C. septicum (50%-85.7% mortality).

Diagnosis
A history of recent IM injection with physical examination findings consistent with severe acute injection site infection is sufficient for a presumptive diagnosis of clostridial myonecrosis (Fig. 5-1). Ultrasound of the affected tissues may support the diagnosis, revealing fluid accumulation, gas, and changes in the muscular/fascial echotexture. Fluid aspirate cytology or muscle sample impression smear with Gram staining can immediately confirm the presence of numerous gram-positive rods characteristic of clostridial infection (Fig. 5-2). Fluid and/or muscle samples should be submitted for anaerobic cultures.

Therapy
Prompt antimicrobial therapy is necessary for effective treatment of clostridial myonecrosis. High doses of potassium penicillin G, 44,000 IU/kg body weight intravenously (IV) every 4 to 6 hours (q4-6h), are usually recommended. However, clostridial organisms are generally susceptible to a number of antibiotics, including oxytetracycline, chloramphenicol, metronidazole, and rifampin. Evidence in a mouse model of C. perfringens myositis suggests that oxytetracycline, metronidazole, and rifampin therapy may be more effective than treatment with potassium penicillin G. This is likely related to the ability of these antimicrobials to decrease toxin production. The ideal antimicrobial regimen would have potent bactericidal effects and decrease toxin production. In vitro, C. perfringens α-toxin production and survivability are high with penicillin G treatment, suggesting that this may not be the optimal antimicrobial choice. Tetracycline and chloramphenicol suppress toxin production but have limited effect on survivability. Rifampin and metronidazole have superior efficacy for suppression of both survivability and toxin production.

Therefore, combination therapy with penicillin G and either rifampin or metronidazole may be appropriate. However, a subsequent study using the mouse model of C. perfringens myositis showed decreased survivability with penicillin G and metronidazole combination treatment compared with metronidazole alone. Currently, equine clinical data suggest that high doses of penicillin G are the first antibiotic choice for treatment of horses with clostridial myonecrosis.

Myotomy and fasciotomy are important in the treatment of clostridial myonecrosis. These procedures allow drainage and debridement of necrotic areas, oxygenation of tissues, and some degree of disinfection. In at least one large retrospective study, myotomy and fasciotomy performed early in the course of disease were thought to result in decreased overall mortality. These authors suggest that myotomy and fasciotomy should be performed as soon as possible, stressing the importance of performing a Gram stain on wound exudate at that time. Although there are no guidelines as to where and how many myotomy and fasciotomy incisions to make, starting in
surgical excision of lesions, and local or systemic administration of antifungal drugs. Therapy for specific localized or systemic fungal infections is described in detail elsewhere in this text.

Primary Parasitic Myositis

Etiology

The most common causes of parasitic myositis include *Sarcocystis* spp., *Trichinella* spp., and *Trypanosoma equine*. Aberrant parasitic migrations from various nematodes can occur. Rarely, hydatidosis has been associated with infectious myositis.

Clinical Findings

With parasitic myositis, horses usually have generalized muscle infection (unless there is a localized area of aberrant parasite migration). Trichinosis in the horse is often acute. Affected horses have variable clinical signs, ranging from mild generalized stiffness to signs of severe generalized pain with reluctance to move. Horses with chronic parasitic infections, such as sarcocystosis or trypanosomiasis, may present with weight loss or ill thrift and moderate to severe muscle wasting. Horses with hydatid disease usually have widespread systemic infection of internal organs leading to chronic wasting.

Diagnosis and Therapy

Diagnosis of parasitic myositis is usually accomplished by biopsy and histopathologic examination of the affected muscle. Treatment of specific parasitic infections is discussed elsewhere in this text. The most important health risk for humans associated with equine muscle infection is related to consumption of parasitized horse meat. Outbreaks of human trichinellosis occur fairly regularly in the countries of the European Union. Horse meat is screened for infected muscle in slaughter plants; however, it is advisable that preparation of human meals with horse meat follow appropriate guidelines for inactivation of *Trichinella* larvae in equine muscle before consumption.

Secondary Infectious Myositis

Etiology

Streptococcal infections and several viruses may contribute to development of secondary myositis in which viable infectious agents are not present in the affected muscle tissue. Lesions are usually generalized, affecting several muscle groups. The primary infectious agent triggers myositis as an inflammatory or an immune-mediated process. *Streptococcus equi* subsp. *equi* is associated with two types of myositis in horses: acute severe myositis, characterized by infarction of muscle, and chronic generalized muscle wasting. Both manifestations of streptococcal myositis are thought to be immune-mediated disorders and are discussed in more detail in Chapter 28. Myositis may occur concomitant with, or as a sequela to, acute viral infection. Viral myositis has been demonstrated or postulated to occur secondary to infection with equine herpesvirus (see Chapter 13), equine influenza virus (see Chapter 12), and African horse sickness (see Chapter 15).

Clinical Findings

Horses with myositis secondary to systemic infection present with generalized stiffness and lameness. Most affected horses demonstrate reluctance to move, and laminitis is the most common differential diagnosis. Muscles may or may not be painful on palpation. Horses with muscle infection or necrosis may have areas of localized edema and pain. When widespread, these horses can have signs of circulatory failure accompanied by poor peripheral perfusion.
Diagnosis and Therapy

Diagnosis of secondary myositis is accomplished by muscle biopsy to demonstrate histopathologic lesions of immune-mediated or inflammatory myositis. The approach to diagnosis of a specific underlying systemic infection depends on the type of infection that is suspected. Diagnosis of S. equi subsp. equi infection is discussed in Chapter 28. Diagnosis of equine influenza, equine herpesvirus, and African horse sickness is discussed in Chapters 12, 13, and 15, respectively.

SYNOVIAL INFECTIONS

Septic arthritis and tenosynovitis are common clinical problems in horses with potentially devastating consequences. Mortality estimates vary between 15% and 50%. In adult horses, these infections are most often caused by direct bacterial contamination of a synovial structure resulting from trauma or as a sequela to surgery or intrathecal injection. Hematogenous spread of infection is much rarer in adult horses but should not be overlooked as a differential diagnosis in the acutely lame horse. In foals, most synovial infections are of hematogenous origin. Failure of transfer of passive immunity, respiratory infection, and gastrointestinal infection should be considered as potential concurrent problems in foals diagnosed with septic synovial structures (see Chapter 6).

Etiology and Pathogenesis

Whether infection occurs from a wound, surgery, or injection, a similar sequence of events occurs after bacteria enter the joint. Colonization of the synovial membrane causes a severe inflammatory response. This results in the production of various inflammatory mediators, which are largely responsible for the clinical signs as well as damage to the synovial lining and joint. Therefore, treatment should include measures to control inflammation and eliminate bacterial infection.

A variety of bacteria may be isolated from synovial infections that are traumatic in origin. Enterobacteriaceae and anaerobes are most frequently isolated. Horses that develop infection as a sequela to surgery or intrathecal injection are more likely to have staphylococcal infections.

Historically, synovial infections in foals were postulated to originate from umbilical infections. It is now recognized that these infections may originate from other sources, including the respiratory and gastrointestinal tracts. Foals with poor transfer of passive immunity are predisposed to septic arthritis. The pathogens most frequently isolated from foals with neonatal sepsis are also the bacteria most often isolated from joints of foals with septic arthritis (see Chapter 6). Young foals (<3 weeks) are more likely to have infection of multiple joints, whereas older foals (>4 weeks) generally have only one affected joint. The most common bacterial organisms isolated from septic arthritis in foals are Enterobacteriaceae, most notably Escherichia coli. Other gram-negative organisms, such as Salmonella spp., are relatively common isolates. The most common gram-positive organisms isolated from foals with septic arthritis include Staphylococcus, Streptococcus, and Rhodococcus equi.

Fungal infections of synovial structures are rare but should be considered, especially if a fungal organism is cultured from more than one site or more than one sample from the same site. Fungal infection of synovial structures may originate either hematogenously or by direct inoculation.

Clinical Findings

The hallmark clinical sign of synovial infection in the appendicular skeleton of the horse is severe lameness. The onset and severity of clinical signs depend on the mode of contamination, degree of contamination, pathogenicity of the organism involved, amount of open drainage from the synovial structure, and previous treatment with intrarticular corticosteroids. Although clinical signs are evident within 24 hours of experimental inoculation of equine joints with bacteria, the onset of clinical signs from “natural” infection appears to be slower. In one study, joint infections on average became apparent on day 8 after surgery, with a range of 1 to 25 days. It is questionable whether all affected joints were inoculated at surgery.

In the authors’ opinion, postoperative joint infections can be separated into two groups: (1) those showing clinical signs within 3 to 5 days, presumably inoculated at surgery, and (2) those showing clinical signs 2 to 4 weeks after surgery, presumably resulting from extension of superficial infection. Incomplete removal of sutures and extension of infection through the suture tracts after removal appear to be major contributing factors to delayed infection.

The onset of clinical signs of synovial infection after trauma is variable. Much of this variability may be explained by the degree of open drainage (horses with sealed synovial infections tend to be more lame), inflammation, and pain associated with tissue trauma, which may be indistinguishable from that caused by synovial infection, and by delayed recognition by owners or trainers. The onset of lameness and clinical signs of synovial infection after intrathecal injections is also somewhat variable, depending on the factors just listed as well as whether or not corticosteroids were administered. Tulamo et al. showed that co-administration of corticosteroids with an injective dose of bacteria significantly delayed clinical signs and synovial fluid changes for up to 2 days. In two retrospective studies describing infection after intrathecal injection, the onset of clinical signs varied from 2.5 to 7 days.

Synovial effusion, local edema, heat, and sensitivity to palpation are usually observed in horses with synovial infection. Experimental models of infection suggest that these signs may briefly precede clinical lameness. Body temperature is usually increased in synovial sepsis, but the lack of a fever does not rule out joint sepsis, especially in adult horses. Foals typically have higher fevers than adult horses. In one study, 45% of foals with septic arthritis had a body temperature of 102°F (38.9°C) or higher.

Diagnosis

Synovial Fluid Analysis

Synovial fluid analysis is necessary for the diagnosis of infection. Grossly, synovial fluid from an infected joint is serosanguineous and turbid (increased cellularity) with decreased viscosity resulting from decreased hyaluronic acid content. Samples from affected joints may contain visible fibrin and debris. The sample should be submitted for total and differential cell count, total protein measurement, and immediate culture. Most samples from infected synovial structures have a total white blood cell (WBC) count greater than 30,000 cells/μL (normal <1000/μL, predominantly mononuclear cells), a differential with 90% or more neutrophils, and a total protein concentration greater than 4.0 g/dL (normal <2.0 g/dL). A Gram stain should be performed; positive findings confirm the diagnosis and may guide antimicrobial therapy. A sample of synovial fluid should be cultured aerobically and anaerobically. The fluid should be cultured in a broth culture system designed for culturing body fluids (see Chapter 27). Synovial biopsy and culture do not yield better results than culture of synovial fluid and are not recommended.
Diagnostic Imaging
The primary goal of diagnostic imaging of synovial infections is to determine if the infection has extended into surrounding bone or resulted in cartilage damage. This information can be used as an adjunct to determine prognosis and modify treatment strategies if necessary. Radiographs should be obtained in most horses with synovial infections.

Septic osteitis or osteomyelitis may precede or follow septic arthritis. Septic epiphysitis and physisis must be ruled out in all cases with septic arthritis. Osteomyelitis and osteitis are less common with tendon sheath infections than with joint sepsis; however, the sesamoid bones may be affected. Articular bone destruction and joint collapse are not early findings in septic arthritis and indicate that the infection has been present for at least 2 to 3 weeks. Comparative views of the contralateral extremity may be necessary to recognize subtle changes. Advanced imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) can provide additional information regarding the extent of lesions, especially in horses with septic physisis.

Therapy
Synovial infections in horses are considered a medical emergency. Three basic tenets for treating bacterial infection of synovial structures should be observed: systemic antimicrobial therapy, local antimicrobial therapy, and lavage. It is prudent, if possible, to acquire a diagnostic synovial fluid sample before administration of antibiotics. Based on the gross appearance of the fluid, treatment can be initiated immediately. At a minimum, intrarticular antibiotics and broad-spectrum systemic intravenous (IV) antibiotics are indicated until culture and sensitivity results are received. Through-and-through needle lavage (or other lavage) should be done immediately in all joints in which the synovial fluid is grossly abnormal or has an increased total nucleated cell count, increased total protein concentration, and greater than 90% neutrophils (Fig. 5-4). Infected synovial structures with abundant fibrin or cellular debris require open arthrocenteses and/or endoscopic debridement and lavage to improve removal of inflammatory debris.

Historically, chlorhexidine, iodine, and dimethyl sulfoxide (DMSO), have been recommended in addition to lavage solutions in an attempt to increase antiinflammatory or antimicrobial efficacy. However, lavage with these additives may be deleterious to synovial structures at concentrations expected to be effective for killing bacteria or decreasing inflammation. Therefore a balanced electrolyte solution without additives is recommended as the optimal lavage fluid.

The optimal frequency and duration of through-and-through lavage for treatment of septic arthritis is controversial. Some clinicians recommend that infected synovial structures be flushed daily for 3 days and the synovial fluid analyzed on the last day to determine if additional lavage is needed. Lavage and intraarticular antibiotics tend to irritate the joint, and often the WBC count and total protein count will remain increased during this time. Therefore the clinical response to treatment (lack of joint effusion, joint stability) should be strongly considered when determining the frequency and duration of joint lavage. A total WBC count less than 20,000 cells/µL is a reasonable goal and can be used as one of the indicators of when to discontinue joint lavage.

Closed suction drainage can also be used to treat infected synovial structures. Typically, a flat fenestrated silicone drain (Jackson-Pratt) is inserted within the joint and connected to a suction device that can be purchased commercially. Although clinical reports of this type of therapy are limited in horses, repeated needle evacuation during the first 3 to 7 days of infection is used with success in humans.

Initial Systemic Antimicrobial Therapy
Staphylococci are common bacterial isolates from synovial infections that occur after surgery or intrarticular injection. Amikacin and cefazolin remain the antibiotics of choice for treating these infections in horses. Amikacin is an excellent empiric choice for treatment of most synovial infections in horses. Amikacin is expensive when used systemically in the adult horse but can be economical for local antibiotic therapy, as discussed next. One common strategy for treatment of synovial infections in horses is administration of broad-spectrum antimicrobials intravenously (e.g., potassium penicillin G and gentamicin) with local delivery of amikacin. A knowledge of hospital or regional antimicrobial sensitivity patterns can assist with decisions regarding initial antimicrobial selection. For example, gentamicin was effective in 85% of isolates in one study, providing a relatively high degree of confidence in its use.

Synovial infections after trauma are often polymicrobial and caused by Enterobacteriaceae and anaerobes. Broad-spectrum antibiotics that include a reasonable anaerobic spectrum are indicated. Particular attention should be paid to wounds with gross fecal contamination or infected joints near the foot, such as the coffin or pastern joints. Bacillus fragilis is typically resistant to penicillin G. The addition of oral metronidazole to the therapeutic plan should give appropriate coverage for this organism.

After culture and sensitivity results are received, appropriate changes (if needed) in systemic antimicrobial therapy can be made (Table 5-1). The duration of treatment with systemic antibiotics varies depending on response to therapy. As a general guideline, the authors continue systemic antimicrobial treatment for a minimum of 2 weeks after amelioration of clinical signs. If osteomyelitis is present, the duration of therapy should be longer, often 4 to 8 weeks. Plasma fibrinogen concentrations can be monitored every 1 to 2 weeks and antimicrobial therapy discontinued after fibrinogen levels return to normal (usually <500 mg/dL).

Local Antimicrobial Therapy
The delivery of high concentrations of antimicrobial drugs directly into an infected synovial structure often results in rapid elimination of infection. Most local techniques result in little or no increase in serum concentrations of antibiotics and

![Fig. 5-4](image-url) Through-and-through lavage of tibiotarsal joint in foal with septic arthritis. (Courtesy Dr. Debra Sellen.)
### Table • 5-1

**Systemic Antibiotics Used to Treat Osteomyelitis and Septic Synovial Structures**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MANUFACTURER</th>
<th>SYSTEMIC DOSE*</th>
<th>OTHER USES†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Amiglyde (Fort Dodge)</td>
<td>Adult: 15 mg/kg IV q24h&lt;br&gt;Foal: 21-25 mg/kg IV q24h</td>
<td>RP, IA, AIB</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Amp-equine (Pfizer)</td>
<td>20 mg/kg IV q6h</td>
<td>RP, IA, AIB</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Rocephin (Roche Laboratories)</td>
<td>50 mg/kg IV q24h</td>
<td>RP, IA, AIB</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Ancel (Glaxo Smith-Kline)</td>
<td>10-20 mg/kg IV q6h</td>
<td>AIB</td>
</tr>
<tr>
<td>Ceftazidine</td>
<td>Fortoz (Glaxo Smith-Kline)</td>
<td>30-50 mg/kg IV q6-12h</td>
<td>RP, IA, AIB</td>
</tr>
<tr>
<td>Ceftiofur</td>
<td>Noxcel (Pharmacia &amp; Upjohn)</td>
<td>2-8 mg/kg IV q6-24h</td>
<td>IA, AIB</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Clavaron (Aventis)</td>
<td>25 mg/kg IV q6h</td>
<td>AIB</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Generic</td>
<td>50 mg/kg PO q6h</td>
<td>Human health risk</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Generic</td>
<td>10 mg/kg PO q12h</td>
<td>Variable oral absorption</td>
</tr>
<tr>
<td>Enrofloxacin</td>
<td>Baytril (Bayer Corp)</td>
<td>2.5-10 mg/kg IV q12-24h</td>
<td>Arthropathies (tends), tendon</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Generic</td>
<td>20-30 mg/kg PO q8h</td>
<td>weakening or rupture</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Diflucan (Roerig)</td>
<td>5 mg/kg PO q24h</td>
<td>May cause hyperthermia and</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Gentocin (Schering-Plough)</td>
<td>6-7 mg/kg IV q4-24h</td>
<td>diarrhea</td>
</tr>
<tr>
<td>Imipenem-cilastatin</td>
<td>Primaxin (Merck)</td>
<td>10-20 mg/kg IV q6h</td>
<td>Susceptible fungal infections; AIB</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Generic</td>
<td>15-25 mg/kg PO q6h</td>
<td>RP, IA, AIB</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>Generic</td>
<td>8-10 mg/kg IV q12h</td>
<td>AIB</td>
</tr>
<tr>
<td>Procaine penicillin G</td>
<td>Generic</td>
<td>22,00-40,000 IU/kg</td>
<td>AIB</td>
</tr>
<tr>
<td>Potassium penicillin G</td>
<td>Generic</td>
<td>IM q12h</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>Rifadin (Hoescht)</td>
<td>5-10 mg/kg PO q12h</td>
<td>Do not use alone</td>
</tr>
<tr>
<td>Ticarcillin/clavulanate</td>
<td>Timentin (Smith-Kline Beecham)</td>
<td>50 mg/kg IV q6h</td>
<td>Antipseudomonal</td>
</tr>
<tr>
<td>Trimethoprim-sulfa</td>
<td>Generic</td>
<td>20-30 mg/kg PO q12h (based on sulfa portion)</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Vancocin (Eli Lilly)</td>
<td>6 mg/kg IV q8h</td>
<td>AIB; use slow infusion</td>
</tr>
</tbody>
</table>

*IV, intravenously; PO, orally; IM, intramuscularly; q24h, every 24 hours.

†RP, Regional perfusion; IA, intraarticular; AIB, antibiotic-impregnated beads.

...can be used safely in combination with appropriate systemic dosing. Several methods of local administration of antimicrobials are possible. The simplest technique is repeated intramuscular administration of antibiotics using a needle. Intravenous regional perfusion (Box 5-1 and Fig. 5-5), intravenous regional perfusion (Box 5-2), constant-rate infusion pumps, and antimicrobial-impregnated beads (Box 5-3) may also be used to deliver antimicrobial drugs to tissues at a minimum inhibitory concentration (MIC) several orders of magnitude higher than that achievable by systemic administration.

**Aminoglycosides** are the most common class of antimicrobial agent used for direct intrasynovial injection. The ideal dose and frequency are dependent on the synovial fluid volume, pathogenic organism involved, and antimicrobial used. As a general guideline, 1 g of gentamicin will maintain a MIC effective against most microorganisms in the joint for 24 hours and in the surrounding bone for 8 hours. Similarly, cefotaxime at a dose of 150 mg in the antibrachialcarpal joint will maintain sufficient bactericidal concentrations for 24 hours.

**Intravenous regional limb perfusion** is performed by catheterizing a vessel (typically a vein) in the area of infection and applying a tourniquet above and below the region (see Box 5-1 and Fig. 5-5). Antimicrobials are perfused into the local area through the catheter. Typically, antimicrobial doses of one third and up to the systemic dose are diluted to a final volume of 30 to 60 mL and injected slowly. The tourniquet is maintained for 30 minutes. In infected areas, inflammation and vascular impairment may decrease the exposure of diseased tissue to systemic antimicrobials. Conceptually, with regional limb perfusion, the vascular system in the region is dilated, and increased vascular hydrostatic pressure and concentration gradient drive the antimicrobial into the soft tissue, resulting in high local concentrations that would be unachievable by nontoxic systemic doses. The most frequently used (reported) antimicrobials are the aminoglycosides; however, the authors have successfully used third-generation cephalosporins for regional limb perfusion. With aminoglycoside regional IV perfusion, antimicrobial concentrations within the joint fluid are expected to be 5 to 50 times greater than that achievable with systemic IV administration and remain above the MIC of most organisms for 24 hours. Based on these data, the authors generally perform regional limb perfusions daily for the first 3 to 5 days or until a clinical response is evident.

**Intravenous regional limb perfusion** is performed by inserting a cannulated screw into the medullary cavity of a long bone in proximity to the infected area (see Box 5-2). Importantly, the cannulated screw must be customized or purchased with an
Box • 5-1

**Intravenous Regional Limb Perfusion**

- Aseptically prepare area over the blood vessels to be used for perfusion.
- Prepare appropriate dose of antimicrobial drugs, diluted in saline, to a final volume of 30 mL for lower limb perfusion or 60 mL for upper limb perfusion.
- Appropriate anesthesia or sedation should be administered, depending on whether the procedure is performed in the anesthetized or standing horse. If the procedure is to be performed standing, consider adding 10 mL of local anesthetic agent (e.g., lidocaine 2%) to the perfusate. Alternatively, appropriate regional nerve blocks may be performed.
- Apply tourniquets proximal and distal to the region to be perfused. Perfusion of regions including the fetlock and below does not require a distal tourniquet.
- Insert small-gauge, over-the-needle catheter or butterfly catheter into the appropriate blood vessel.
- Begin injection of the perfusate. The volume should be injected slowly over 5 to 10 minutes to avoid damage to small blood vessels. If the perfusion is performed standing, it is recommended to tape the extension set to the tourniquet to prevent movement of the horse and inadvertent removal of the catheter.
- During the injection, periodically aspirate with the syringe to confirm that the needle remains appropriately situated in the blood vessel.
- After completion of the regional perfusion, the catheter may be removed and a small pressure bandage placed over the vessel puncture site. Alternatively, the catheter may be left in place for the duration of the soaking time and the extension set secured to avoid backflow of blood.
- The tourniquet should be left in place for 20 to 25 minutes after completion of the injection.
- Treatment of a wound, lavage of a joint, and other therapies may be performed while the regional perfusion is “soaking.”

*Recommended antibiotics for regional limb perfusion in an adult horse: cefaduril, 1g; amikacin, 500 mg; and gentamicin, 1g.*

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Box • 5-2

**Intraosseous Regional Limb Perfusion**

- Procure a 5.5 × 20-mm cannulated screw with a Luer-Lok attachment affixed to the screw.
- Alternatively, a standard extension set will fit snugly into a 4.0-mm drill hole, obviating the need for a cannulated screw.
- The procedure may be performed under general anesthesia or in the standing, sedated adult patient. The tourniquets and intraosseous perfusion tend to be painful. A regional perineural block is recommended in patients that will undergo cortical drilling while standing.
- Aseptically prepare the skin overlying the area in which the bone will be drilled. Ideally, select a metaphyseal region close to the region to be perfused.
- Prepare antibiotics and saline to a total volume of 25 to 30 mL for perfusion of the metacarpus or tarsus or 40 to 50 mL for perfusion of the radius or a larger long bone.
- Infuse local anesthetic into the soft tissues overlying the site in the bone to be cannulated (e.g., dorsolateral cortex of center of metacarpus).
- Make a 1-cm stab incision into the skin, subcutaneous tissue, and periosteum. Retract the tissues gently, and drill a unicortical hole 4 mm in diameter. The hole should be tapped to 5.5 mm in diameter.
- Place the cannulated screw with the Luer-Lok attachment into the predrilled and tapped hole.
- Apply tourniquets proximal and distal to the region to be perfused. Perfusion of regions including the fetlock and distal areas does not require a distal tourniquet.
- Attach the male end of the extension set to the Luer-Lok adapter, and infuse the antibiotics and saline over 5 minutes. Anesthetic solution such as 2% mepivacaine (5 mL) may also be injected to decrease discomfort associated with the procedure.
- Thirty minutes after completion of the antibiotic infusion, the tourniquet may be removed.
- The screw is removed under aseptic technique. The skin should be closed over the incision. Alternatively, a sterile bandage may be placed without closing the incision. The skin incision may be opened for successive treatments.
- At the completion of treatment regimen, the skin and subcutaneous tissues should be debrided and the incision closed.

*Courtesy Dr. Julie Cary.*

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**Fig. 5-5** Regional limb perfusion performed in foal with septic tibiotarsal joint. (Courtesy Dr. Debra Sellon.)
Antimicrobial-Impregnated Polymethylmethacrylate (PMMA) Beads

**Items needed:**
- Half-dose PMMA bone cement (Surgical Simplex P Radiopaque Bone Cement, Howmedica Osteonics, Mahwah, NJ). This package contains 20 g of sterile PMMA powder and 10 mL of sterile liquid that is 97.4% w/v methylmethacrylate.
- Mixing bowl (sterile) with spatula or mixing device
- Sterile gloves
- Sterile field (table cover or drapes)
- Scissors (sterile)
- Antibiotics

**Recommended antibiotic doses:**
- Cefazolin, 1 g
- Amikacin, 1 g
- Imipenem, 500 mg

**Procedure:**
1. Using sterile technique, open pocket with 20 g of sterile PMMA powder and empty into sterile bowl.
2. Add antimicrobials to dry powder. If antibiotics are in dry powder form, add them to the PMMA powder dry, without reconstitution.
3. Mix sterile PMMA powder and antimicrobials well.
4. Add 10 mL of liquid methylmethacrylate and mix until tacky and starting to set.
5. Immediately begin rolling portions of resultant mixture into small, cigar-shaped rods or small, round beads. After the mixture starts to set, only a brief time is available to change the shape of the beads. Therefore, several people with sterile gloves may be required to prepare all beads within the available time.
6. Beads are ready to use within 10 to 15 minutes.
7. Remaining beads may be sealed in sterilization pouches and gas-sterilized for later use.

![Figure 5-6](image)

**Fig. 5-6** Example of constant-rate infusion system (On-Q Painbuster) that can deliver antimicrobials and anesthetics to synovial structure. (Courtesy I-Flow Corp., Lake Forest, Calif)

adapter that will fit an extension set for perfusion. As with IV regional limb perfusion, tourniquets are placed above and below the infected area. Antimicrobial solution (30- to 60-mL volume) is infused slowly through the cannulated screw at a dose similar to that previously described for IV regional limb perfusion. The tourniquets are maintained for a total time of 30 minutes. Experimentally, studies have shown that intraosseous perfusion results in lower synovial concentrations of antibiotic than does IV regional limb perfusion. Increased technical difficulty (placing a bone screw) and a small risk of fracture are additional disadvantages to this technique.

**Constant-rate infusion pumps** and intrasynovial catheters may also be used to deliver high concentrations of antimicrobials and obviate the need for multiple needle punctures. Latex balloon infusion systems with calibrated delivery systems can deliver a constant volume of antimicrobial solution to the joint (Fig 5-6). This results in very high antimicrobial concentrations within the joint. Lesun et al.22,23 showed that by delivering 1 g of gentamicin every 8 hours to the tarsocrural joint, concentrations exceeding 100 times the MIC of most equine pathogens could be maintained for several days. They showed no significant effects on histologic scores of cartilage or synovium using this protocol for 5 days. In the authors' practice, these systems are routinely used to treat infected synovial structures. One advantage is the ability to add local analgesics in severely painful infections, although compatibility with the antimicrobial used should be investigated. Catheter placement also requires some planning. For example, catheters placed dorsally in the antebrachial-carpal, midcarpal, and pastern joints can become crushed as the animal ambulates. This can result in loss of catheter function or even foreign debris within the joint. The catheter should be placed in an area where it will not be subjected to crushing, such as the back of the joint or palm or plantar poudches.

**Intrasynovial use of antimicrobial-impregnated beads** provides another method to deliver high concentrations of antimicrobials to synovial structures (see Box 5-3). Farnsworth et al.24 showed that gentamicin-impregnated polymethylmethacrylate (PMMA) could be used intrasynovially. However, when PMMA beads were inserted into the tarsocrural joint of horses with diffuse synovitis, acute increases in synovial WBC count, prolonged increases in total protein concentration, superficial cartilage erosions, and in some cases marked capsular thickening resulted. Therefore, because of the associated inflammatory reaction, potential for mechanical abrasion of cartilage surfaces, necessity for removal (if nonabsorbable), and availability of superior methods, antimicrobial-impregnated beads may not be the best option.

The prognosis for septic arthritis is guarded to good with appropriate and timely therapy. Foals typically have a poorer prognosis than adult horses. Multisystemic disease often accompanies septic arthritis in foals and significantly decreases their chance of survival. A guarded to grave prognosis should be given for foals with multiple infected joints and concurrent osteomyelitis or multisystemic disease. Extension of infection into the surrounding bone, joint collapse, and protracted infection are strong indicators of a poor prognosis.
BONE INFECTION (SEPTIC OSTEOMYELITIS AND OSTEITIS)

Etiology and Pathogenesis
Infection of bone can be caused by direct trauma, hematogenous spread, extension of a contiguous focus of infection, or inoculation at surgery. One key conceptual difference is that hematogenous infections spread from the "inside out," whereas most other causes of osteomyelitis spread from the "outside in." The pathogenesis after trauma to bone involves acute inflammation of bone, with vascular engorgement, edema, cellular infiltration, and abscess formation. The associated increase in intramedullary pressure spreads pathogens throughout the bone cortex, with intracortical extension facilitated by the Haversian systems and Volkmann's canals. With continued extension, the periosteal space may become involved.

In foals, hematogenous spread of infection into the bone is a common cause of osteomyelitis. Typically, the metaphyses of long bones are affected. In young animals, blood flow is slow and turbulent in the venous sinuses of the metaphyses near the site of endochondral ossification. Bacteria can become lodged at these sites and readily establish infection. In the neonatal foal the metaphyseal blood supply communicates with the epiphyseal blood supply via the transphyseal vessels. The epiphyseal blood supply communicates with the blood supply of the joint synovium. This provides a direct route for infection from the joint to spread to the bone, or vice versa. As the animal ages, the epiphyseal and metaphyseal blood supplies become independent. In foals the transphyseal vessels start to regress at 14 days of age and disappear almost completely by 45 days of age. Generally, this protects the epiphysis from infection, and septic arthritis and septic physis/epiphysis is less likely to coexist in older foals.

In adult horses there is a paucity of information regarding the most likely etiologic agents of osteomyelitis. Retrospective studies suggest that most horses with traumatic osteomyelitis have mixed antimicrobial infections, with Enterobacteriaceae, beta-hemolytic streptococci, and staphylococci being the most frequently isolated organisms. Osteomyelitis after surgery is often caused by staphylococci, but mixed infections may also occur. In foals, Enterobacteriaceae are the most common organisms isolated from osteomyelitis. In older foals, Rhodococcus equi osteomyelitis should be considered as a differential diagnosis (see Chapter 32). Mycotic or pyogenic infections can be found in the bone in horses but are less common than bacterial infections (see Chapter 55).

Clinical Findings
The clinical signs of osteomyelitis are variable. Most horses with osteomyelitis of the limbs will present with moderate to marked lameness. Soft tissue swelling, heat, and pain on palpation are almost always present and may be the only clinical signs of osteomyelitis involving the head. Exceptions are osteomyelitis involving bones heavily covered by muscle or subcutaneous fat. In these horses, lameness may be the only clinical sign. Laboratory findings are variable. Leukocytosis or hyperfibrinogenemia may be present but are certainly not diagnostic.

The most common sites of osteomyelitis in the foal are the distal tibial physis and the distal third metacarpal/tarsal physis. Affected foals will generally present with marked lameness and palpable heat, pain, and swelling, which often can be distinguished from joint effusion if the joint is not involved. The swelling in affected foals may be soft and fluctuant, in contrast to swelling in affected adults, which usually is firm. This difference is caused by the relatively loosely attached periosteum and thin cortex in young animals, which allows suppuration and expansion. In more proximal limb locations (e.g., proximal humerus, femur), swelling may not be obvious because of surrounding muscle mass.

The most common sites of osteomyelitis in the adult horse are the metacarpal and metatarsal bones and the phalanges. In these areas, lameness is a common clinical finding, whereas in the head and axial skeleton, painful soft tissue swelling with or without draining tracts may be the only clinical sign.

Diagnosis
Diagnosis of osteomyelitis and osteitis is usually confirmed by radiography. Lesions typically appear lytic, with varying degrees of sclerosis and periosteal new bone production (Fig. 5.7). Ossous sequestra are a relatively common feature of osteomyelitis in horses, especially in areas with minimal soft tissue covering. With periosteal damage or wound infection, the outer cortex of the bone is susceptible to ischemia and infection. If the bone becomes necrotic, it will separate from the parent bone, forming a sequestrum.

Radiographic changes require 30% to 50% bone density (mineralization) with at least 1 cm of affected area. This may result in delayed recognition of lesions, especially early in the disease process. Radiographs of the contralateral limb can assist in detecting subtle changes, but it may take 10 to 14 days after injury or onset of clinical signs to see radiographic evidence of infection. Unfortunately, this can delay the diagnosis and therefore timely treatment of osteomyelitis.

In human patients, advanced imaging techniques such as nuclear scintigraphy, MRI, and CT are often used to improve the accuracy of diagnosis of osteomyelitis. These modalities are becoming more widely accessible to veterinarians and are being increasingly used for diagnosis of osteomyelitis in horses.

A three-phase scintigraphic scan with methylene diphosphonate (MDP) can aid in the diagnosis of equine osteomyelitis. Increased uptake of the radiopharmaceutical in all three phases (flow, pool, bone) is supportive of osteomyelitis. However, the diagnosis may be complicated by recent trauma, surgery, or orthopedic implants. These coexisting conditions significantly decrease the specificity (as low as 38% in human patients) of results. WBC scans can be performed in horses using...
hexamethylpropyleneamine oxime (HMPAO)-labeled WBCs. The main advantage to this technique is an increase in specificity for detection of osteomyelitis. False-negative scans are possible with chronic or partially treated osteomyelitis. In the future, newer techniques [e.g., ciprofloxacin labeling] may provide more accurate and less technically demanding methods to detect osteomyelitis.

CT provides high spatial as well as contrast resolution of bone and its surrounding tissue. It is best used for determining cortical changes associated with osteomyelitis and providing a three-dimensional image that can be used to guide surgical treatment or biopsy. In horses, complex joints such as the hock can be difficult to evaluate with plain radiography. CT is especially useful for localizing and characterizing these lesions. The presence of metallic implants often precludes the use of CT because of beam-hardening artifact. Other limitations in the horse include the necessity for general anesthesia and a limited field of view. In adult horses, CT is often limited to the distal extremities and head. Large horses may be difficult to image, except for lesions distal to the tarsus or carpus. MRI is one of the most sensitive tools for diagnosis of osteomyelitis in human patients. MRI can detect the differences between normal and abnormal bone from the differences in their density of water protons. Several clinically available imaging sequences and contrast agents can be used to increase the accuracy of detection. In the area of lesions, T1-weighted images will show low signal intensity (fluid is dark, fat is bright), and T2-weighted images will show increased signal intensity (fluid is bright, fat is dark). MRI will clearly define the extent of osteomyelitis lesions and provide information related to the chronicity of the infection. Images cannot be obtained from horses with ferrous implants. Nonferrous implants are routinely used in human patients and allow subsequent MRI. MRI shows some of the limitations of CT regarding aperture size and ability to image much of the adult canine skeleton. The increasing availability of equine MRI facilities will change the way veterinarians diagnose and treat osteomyelitis.

Ultrasound may be used to evaluate soft tissue swelling and is especially useful for detection of increased quantities of synovial fluid or abscesses. In severely swollen or heavily muscled areas, subperiosteal fluid or pus may be visible, which can support the clinical diagnosis of osteomyelitis. These fluid pockets can be aspirated for culture. Sequestra and foreign bodies may be detectable and aid in treatment planning or the decision for further diagnostic efforts. With experience, ultrasound can be used to detect early changes (not radiographically apparent) of osteomyelitis. A thin fluid layer immediately adjacent to the bone is usually detectable, and occasionally, periosteal irritation or synovitis may be observed.

Biopsy, culture, and sensitivity are necessary to confirm septic osteomyelitis and to determine the best course of antimicrobial treatment. However, because many horses with osteomyelitis require surgical debridement, these diagnostic procedures are often done at treatment.

Therapy

The treatment of osteomyelitis can be involved and often requires intensive care best provided in a hospital environment. Many of these horses should be referred to veterinary hospitals where the appropriate diagnostic testing and necessary treatments are routinely performed. Systemic antimicrobial treatment for osteomyelitis should be selected after consideration of the most likely pathogens. Whenever possible, the causative organism(s) should be identified and antimicrobial sensitivity patterns determined. Long-term antimicrobial therapy is often necessary, and adverse effects and economics should be considered. Initial empiric therapy in horses generally consists of broad-spectrum IV antimicrobials (e.g., combination of β-lactam and aminoglycoside antibiotic).

Oral antimicrobial options are limited but can be used effectively. Trimethoprim-sulfamethoxazole (TMS) antimicrobials are often effective against β-hemolytic streptococcal infection; however, resistance is common, and use of TMS alone is questionable for treatment of most horses with osteomyelitis. Chloramphenicol is effective against many organisms typically isolated from equine osteomyelitis lesions; however, human health concerns and controversy over its oral absorption in horses tend to limit its use by many clinicians. In the authors' opinion, chloramphenicol remains one of the few clinically effective oral antibiotics for osteomyelitis that can be safely used long term. Rifampin in combination with a macrolide or azalide antimicrobial drug is often used to treat Rhodococcus equi infections (see Chapter 32). Additionally, the authors have used rifampin in combination with TMS or enrofloxacin to treat osteomyelitis. In human patients, rifampin is considered one of the most effective antibiotics for osteomyelitis, although it has been useful in combating intraleukocytic bacteria and penetrating the bacterial glyco-lyx. Rifampin should not be used alone because resistance will quickly develop. As a general rule, antimicrobial administration should be continued for several weeks after the resolution of clinical signs.

Unfortunately, by the time most cases of osteomyelitis in the horse are diagnosed, they have advanced beyond the point when systemic antimicrobial therapy alone is effective. Surgical debridement is indicated when nonviable tissue is present. Nonviable tissue can provide a continuous nidus of infection, leading to persistence or recrudescence of infection. Debridement removes debris, eliminates dead space, restores soft tissue integrity, encourages vascular supply, and thus encourages complete healing and resolution of infection. Necrotic bone can be distinguished from healthy bone during curettage; healthy bone is much harder and bleeds. Bone should be debrided until healthy bleeding margins are obtained. Large defects in the bone may require cancellous bone grafts to restore structural integrity and promote healing. Local antimicrobial delivery techniques described earlier, such as IV regional limb perfusion, interosseous perfusion, and antimicrobial-impregnated beads, are indicated for treatment of horses with osteomyelitis. Antimicrobial-impregnated beads made with PMMA may be especially useful for treatment of osteomyelitis because they can be implanted and left to deliver antimicrobials for an extended time. They can be prepared at surgery or stored for future use. Antimicrobial release from PMMA occurs in a bimodal manner. First, in a rapid phase, approximately 5% of the antimicrobial is released within the first 24 to 48 hours. A slow-release phase then provides bactericidal concentrations for the next few weeks to months. Single agents or combinations of antimicrobials may be used. Several factors affect release of antimicrobials from PMMA beads, including heat stability and water solubility. Table 5-1 lists some common antimicrobials that effectively elute from PMMA. PMMA beads are nonabsorbable, and removal at a later date may be required. Tissue irritation often leads to some degree of fibrous tissue formation. In difficult osteomyelitis cases, the benefits of therapy with PMMA beads generally outweigh these disadvantages.

Plaster of Paris (POP) beads can also be used to deliver antimicrobials. POP beads have the advantage of being absorbable and have reported osteoinductive and osteoconductive properties. Disadvantages are that most of the antimicrobial is released in the first 48 hours (80% with gentamicin), they are unlikely to maintain concentrations above MIC for
Fig. 5-8  A, Foal with infected distal tibial physis and metaphysis. B and C, Foal with infected epiphysis (lateral styloid process). The bone abscess was debrided and drained percutaneously and a PMMA bead left to deliver local antimicrobials.

longer than 2 weeks, and they require fabrication and gas sterilization in advance to implantation.

In the future, better carriers for antimicrobials will likely be available, providing better biocompatibility, longer release times, and enhancement of new bone production.

Foals with septic osteomyelitis involving the metaphysis, physis, and epiphysis are difficult to manage. The diagnosis is generally not evident until radiographic changes are apparent (Fig. 5-8). Typically, an area of soft tissue swelling with pus formation can be found at the affected site. This is usually adjacent to the affected side of the physis. The prognosis generally worsens after radiographic changes are evident. If elected, treatment should be aggressive. If osteomyelitis involves the physis and metaphysis, drainage should be established through the skin. Often, a curette can be used to open and debride the affected area of bone. Care should be taken to avoid excessive damage to the physis and surrounding bone when debriding. Implant antibiotics activated combined with regional perfusion techniques can be used for local antimicrobial therapy. Less frequently, osteomyelitis will involve the epiphysis. Infection of the adjacent joint is almost always present concurrently. Lesions may be debrided arthroscopically. However, every effort should be made to preserve the weight-bearing surface and structural integrity of the epiphysis. If peripheral, the lesion can be opened and debrided through the skin and joint capsule.

Infected orthopedic implants generally must be removed before infection can be resolved. Unfortunately, there is often a trade-off with necessary stability provided by the implants. In situations where it is not practical to remove the implant(s), efforts must be made to minimize extension of the infection and further destruction of the implant bone interface. Removal of implants not providing stability, all possible glycocalyx (bacterial slime), dead bone, and any other foreign material is necessary for host defenses to fight infection effectively.

Many factors affect the prognosis for horses with osteomyelitis. Unfortunately, the body of knowledge regarding osteomyelitis largely consists of retrospective studies with relatively small case numbers, and information often must be extrapolated from other species. Duration of osteomyelitis is one of the most important factors affecting prognosis. Delays in diagnosis and referral are major factors contributing to treatment failure.

Horses with significant radiographic evidence of osteomyelitis have a guarded to poor prognosis and require aggressive surgical intervention. Extensive joint or other synovial structure involvement also has a significant negative impact on prognosis. Osteomyelitis in these locations complicates surgical treatment, and necessary debridement may result in loss of cartilage and joint congruity. Only in select joints such as the proximal interphalangeal joint, fetlock, carpus, or distal tarsal joints can arthrodesis or facilitated ankylosis be considered an option. In these cases, immobilization combined with debridement, bone graft, and potentially limited implants can result in salvage of the animal. Conversely, osteomyelitis in areas of the head, metacarpals and tarsals, and coffin bone can often be treated effectively with debridement and antimicrobial therapy. In general, if osteomyelitis is focal and surgically accessible, debridement may be curative, and often the joint infection will resolve after bone removal. The horse with diffuse, multifocal or surgically inaccessible osteomyelitis, particularly with concurrent joint infection, has a poor or guarded prognosis.

Supportive Care for Horses with Severe Lameness from Infection

The management of pain in acute and chronic equine musculoskeletal infections can be difficult. The physiologic consequences of severe pain are beyond the scope of this chapter. However, in the adult horse, support-limb laminitis is a major concern in all horses in which the unaffected limb bears the majority of the weight. Nonsteroidal antiinflammatory drugs (NSAIDs), primarily phenylbutazone, are indicated in almost all cases. Unfortunately, NSAIDs may be insufficient in controlling pain and promoting weight bearing on the injured limb. A simple method of providing additional analgesia is to
use morphine (0.06-0.12 mg/kg IM q6h) with acepromazine (5-10 mg). Other options include regional nerve blocks, epidural anesthesia [hindlimb pain], fentanyl patches, lidocaine patches, and continuous-rate infusion of butorphanol. If an infusion pump or catheter is being used to deliver antimicrobials constantly and locally into the joint, meperidine or other local analgesic can be added if it is compatible. Systemic IV infusion of lidocaine (50 μg/kg/min) can be an effective analgesic agent.

Horses developing support-limb laminitis may exhibit a sudden increase in weight bearing on the injured limb or greater time spent in recumbency. Differentiating clinical improvement in the affected limb from the development of laminitis in the support limb is critical. It is not unusual for pain from laminitis to supersede pain from severe infection. Careful monitoring of digital pulses and willingness to bear weight on the support limb is important. Providing adequate sole support, primarily in the heel region, appears to be beneficial for prevention and treatment of laminitis in some horses. This can be accomplished with soft bedding (ideally sand), foam pads taped to the bottom of the foot, or dental impression material molded to the sole. Systemic IV infusion of lidocaine (50 μg/kg/min) has some antiinflammatory properties that may be beneficial in management of pain associated with early support-limb laminitis.

Pain management to encourage weight bearing on the injured limb is important in foals. Increased loading of the support limb can create varus angular limb deformities and pain from physis, whereas decreased weight bearing on the injured limb can result in limb contracture. These complications can occur within 1 to 2 weeks in foals and can become the limiting factor in recovery if the infection resolves. Support of the infected limb with bandages or splints may be necessary to encourage loading.

REFERENCES

See the CD-ROM for a list of references linked to the abstract in PubMed.

CHAPTER • 6

Neonatal Septicemia*

L. Chris Sanchez

Localized and systemic bacterial infections remain a leading cause of morbidity and mortality in the equine neonate despite recent advances in prevention and treatment. Many factors can influence a foal’s risk for the development of sepsis in the peripartum period. This chapter discusses those factors as well as causative organisms and therapeutic options. In addition, factors influencing prognosis and potential preventive strategies are addressed.

ETIOLOGY

Predisposing Factors and Routes of Infection
Many maternal and postnatal events can predispose an equine neonate to infection, including maternal illness, alterations in gestational length, partial or complete failure of passive transfer of immunity, poor sanitary conditions, and improper umbilical care. Maternal factors predisposing to neonatal sepsis include dystocia, premature placental separation, placentalitis, and various other forms of maternal illness (e.g., colic). These problems were contributing factors in 24% of bacteremic foals in a recent study. Many of these factors can be interrelated, with placentalitis as a primary event and other problems such as premature placental separation occurring secondarily (see Chapter 8). In utero infection of the fetus caused by placentalitis occurs typically by ascending infection and often results in premature delivery. Because chronic placentalitis in the mare often results in precocious fetal maturation, a premature foal born to such a mare likely has a greater chance of being septic but a higher probability of survival than a foal born at a similar gestational age to a mare without placentalitis or other chronic stimulation.

Failure of passive transfer of immunoglobulin (IgG) is a major risk factor for equine neonatal sepsis. Because the foal is relatively immunosuppressed at the time of birth, postnatal transfer of immunoglobulin through ingestion and absorption of colostral antibodies is critical for prevention of foal infection. A number of studies have documented a close relationship between the concentration of foal serum immunoglobulin G (IgG) and incidence of disease. Clearly, factors other than the magnitude of passive transfer also are involved in determining disease risk. The route and timing of transfer are likely relevant, along with the potential for bacterial challenge. Farm management is particularly important, including general cleanliness, stocking density, exposure to disease, maternal nutrition, and prepartum vaccination and deworming programs. One study has demonstrated that foals with partial IgG were at no greater risk of disease than those with adequate transfer on a well-managed Standardbred farm.

Postnatal routes of infection include the umbilicus, gastrointestinal (GI) tract, and respiratory tract. Although the umbilicus has been traditionally regarded as an important site for bacterial pathogen entry into the foal, the role of the intestinal tract has been recently reevaluated. It is suggested that too much emphasis is placed on the magnitude of colostral antibody transfer, rather than the timing of ingestion of colostrum. This concept was raised 30 years ago, when it was demonstrated that noninvasive Escherichia coli could
Summary of Reported Frequency of Bacterial Isolates

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<th>WILSON AND MADIGAN&lt;sup&gt;36&lt;/sup&gt;</th>
<th>KOTERBA et al&lt;sup&gt;8&lt;/sup&gt;</th>
<th>RAISIS et al&lt;sup&gt;18&lt;/sup&gt;</th>
<th>MARSH AND PALMER&lt;sup&gt;6&lt;/sup&gt;</th>
<th>STEWART et al&lt;sup&gt;22&lt;/sup&gt;</th>
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*Blood cultures only: whether samples analyzed were restricted to culture of blood only or if they included culture of blood or infected tissue collected at necropsy.
†Admission only: whether samples analyzed were restricted to those obtained on the date of a particular foal’s admission to the hospital.
*Data are expressed as a percentage of the total isolates from each study.

be absorbed by the intestine of neonatal piglets before gut closure.<sup>20</sup> In the pig and the lamb, the ability to absorb macromolecules is regulated by luminal content, and closure can be delayed for up to 5 days by deprivation of milk or colostrum. Conversely, the period before gut closure can be shortened by feeding a large volume of colostrum or milk shortly after birth.<sup>21,22</sup>

Less work has been performed in the foal, but several key details have been established. The foal does not fully discriminate between maternal IgG and other macromolecules, and absorption of macromolecules occurs through specialized cells by pinocytosis. The absorption of macromolecules peaks shortly after birth and declines to less than 1% by 20 hours.<sup>23</sup> Unlike other species, absorption of IgG does not appear to be Fc receptor mediated in the foal. The foal will selectively absorb IgG and immunoglobulin M (IgM) over IgA.<sup>24</sup> Unlike the piglet or the lamb, intestinal permeability to IgG cannot be delayed through withholding of macromolecules in the foal.<sup>25</sup> It is not known whether premature closure can be induced by the feeding of macromolecules immediately after birth.

Significant postnatal factors other than FPT that affect risk for neonatal sepsis include gestational age and environmental conditions. Foals with exceptionally short or long gestation are at increased risk for the development of sepsis.<sup>26</sup> Unsanitary environmental conditions can result in an increased bacterial load to the neonatal GI tract, especially during the initial period of after weaning.

**Causative Organisms**

Retrospective studies have examined the most common organisms isolated from blood culture and necropsy specimens of septic foals (Table 6-1). Although gram-positive organisms predominated in the 1940s to 1950, *E. coli* has been the predominant organism isolated from septic foals in recent studies regardless of clinic location or methodology.<sup>4</sup> Era and geographic location appear to play a major role in the significance of other pathogens. In Pennsylvania in the late 1990s, gram-positive bacteria (*Enterococcus, Streptococcus, and Staphylococcus spp.*) cumulatedly played a major role in disease pathogenesis<sup>8</sup> whereas *Actinobacillus spp.* accounted for approximately 30% of all isolates at Ohio State University in the late 1990s.<sup>12</sup> A Georgia study has reported a dramatic decrease in the percentage of *E. coli* isolates between 1986

*References 8, 12, 28, 30, 33, 35.*
and 1990 and later 5-year sampling periods (1991–1995 and 1996–2000).\textsuperscript{33} The organisms with increased prevalence over the same period were \textit{Enterococcus} spp. and \textit{Staphylococcus} spp. A study evaluating trends by decade (1980s and 1990s) in a Florida population found that \textit{E. coli} remained the predominant isolate, percentages of gram-negative nonenteric and gram-positive organisms remained steady, the percentage of anaerobes increased, and the gram-negative, nonenteric organisms decreased.\textsuperscript{36}

Systemic fungal infections also can occur in neonatal foals. The most frequently isolated organism is \textit{Candida albicans}, a dimorphic fungus, although other organisms may play a similar role\textsuperscript{37,38} (see Chapter 53). These infections are typically associated with prolonged hospitalization and invasive monitoring techniques\textsuperscript{39} or immunodeficiency.\textsuperscript{40} Prolonged antimicrobial therapy and the administration of parenteral nutrition have been suggested as risk factors for the development of candidiasis. A common clinical sign is fever unresponsive to antimicrobial therapy. Most foals with systemic candidiasis will develop thrush (white plaques on the lingual surface of the tongue) either concurrently or before showing clinical signs of systemic infection; thus a daily oral examination is recommended for all hospitalized foals. Antifungal therapy should be strongly considered in any presumed septic foal that develops thrush and is clearly indicated in any animal with a confirmed isolate.

**PATHOGENESIS**

Much of the clinical syndrome classically associated with equine neonatal sepsis is caused by a nonspecific inflammatory response to the infectious organism. Many terms have been used to describe this response and its associated syndromes and processes. A set of definitions was described in 1991 by the American College of Chest Physicians and the Society of Critical Care Medicine,\textsuperscript{3} and a summary of this consensus report follows.

The systemic inflammatory response syndrome (SIRS) refers to a systemic inflammatory response, regardless of the inciting cause, which results in at least two of the following four clinical manifestations: (1) fever; (2) tachycardia; (3) tachypnea or hyperventilation; and (4) leukocytosis, leukopenia, or a relative increase of circulating immature neutrophils. When SIRS occurs in response to a confirmed infectious process, the process is termed sepsis. Sepsis refers to the invasion of normally sterile host tissue by microorganisms or to the inflammatory response generated in response to those organisms. The presence of viable bacteria in the blood is termed bacteremia, and the presence of other viable pathogens in the blood is described similarly (e.g., viremia, fungemia). When sepsis is associated with organ dysfunction, hypoperfusion, or hypotension, the event is termed severe sepsis. Septic shock is defined as sepsis-induced hypotension that persists despite adequate fluid therapy and is accompanied by hypoperfusion abnormalities or organ dysfunction.

Manifestations of organ dysfunction in the horse can include laminitis and coagulopathy in addition to renal, GI, hepatic cardiovascular, or pulmonary dysfunction.\textsuperscript{4} The multiple organ dysfunction syndrome (MODS) describes the alteration of organ function in an acutely ill patient such that homeostasis cannot be maintained. MODS can occur either as a primary event (i.e., direct result of trauma) or secondary to a host response. Recently, a syndrome of immunosuppression caused by an exuberant systemic antiinflammatory response resulting in increased circulating levels of antiinflammatory mediators, leukocyte energy, or increased susceptibility to infection has been termed the compensatory antiinflammatory response syndrome (CARS). If an individual fluctuates between episodes of SIRS and CARS, the term mixed antiinflammatory response syndrome (MARS) applies.\textsuperscript{5}

Endotoxin plays a critical role in the pathogenesis of septic shock in gram-negative sepsis,\textsuperscript{6,7} and is particularly important in the foal, because the most frequently isolated organisms are gram-negative bacteria.\textsuperscript{8} The pathogenesis of sepsis, endotoxemia, and the systemic inflammatory response has been reviewed extensively in both humans and horses and is covered in detail in Chapter 37.\textsuperscript{9-11}

**CLINICAL FINDINGS**

**Physical Examination Findings**

The initial clinical signs of sepsis in foals can be vague and vary widely but frequently include depression, decreased or absent suckling from the mare, and lethargy, which may progress to recumbency. For those foals considered normal at any time before onset of illness, depression and anorexia are often the first clinical signs recognized. The examination of the foal should include an examination of the mare's udder to assess fill. Depressed foals will often stand with their head underneath the mare and can have dried milk on their foreheads. As a result of lack of suckling, dehydration and hypoglycemia become more significant problems as time progresses. Tachycardia and tachypnea are common but not always present. The mucous membranes often develop a bright or injected appearance, and the capillary refill time may be rapid. Rectal temperature may be normal or mildly increased, and sepsis should not be ruled out on the basis of a normal rectal temperature. Hypothermia can be associated with advanced sepsis or moderate to severe prematurity. Left untreated, these early signs will progress to septic shock, in which there is deterioration of the cardiovascular system (cyanosis, muddied mucous membranes, tachycardia, weak pulse, and peripheral shutdown) and often death.

In addition to the systemic parameters mentioned previously, septic foals may have additional localizing signs associated with specific foci of infection. Diarrhea is one of the most common early localizing signs in foals with sepsis and no other evidence of enteric pathogens. Occasionally, diarrhea may be the first clinical sign observed. Other localizing signs of sepsis include uveitis, seizures, joint effusion with or without lameness, lameness alone or in association with edema and pain over a physes, respiratory disease or distress, subcutaneous abscesses, patent urachus, and omphalitis. Importantly, many foals with umbilical remnant infection or abscessation often have normal external umbilical structures. Thus, ultrasonographic examination of the umbilical structures is recommended in any presumed septic foal.

**Clinicopathologic Findings**

Clinical signs and historical information alone often are sufficient for the clinician to develop a reasonable suspicion of neonatal sepsis. In addition to the physical examination findings, however, laboratory data may be helpful for diagnosis of early sepsis. Leukopenia, characterized by neutropenia, is the most common hematologic finding associated with acute sepsis. In one study, septic foals less than 1 week of age had a lower total white blood cell (WBC) count, both neutrophils and lymphocytes, and higher bands and monocytes than healthy, age-matched controls.\textsuperscript{27} Premature or dysmature foals also will often have neutropenia in the absence of sepsis; however, septic foals typically have a degenerative left shift and evidence of toxicity (e.g., Döhle bodies, toxic granulation,
vaccination), whereas these findings are not typical of uncomplicated prematurity. In older septic foals (8-14 days) the total WBC count, neutrophils, and bands are higher than in age-matched controls. A high fibrinogen concentration at or shortly after birth should raise the suspicion of in utero infection.

Abnormal serum glucose concentrations are common in septic foals. Hypoglycemia is common initially, especially in foals less than 24 hours of age. Although hypoglycemia is related predominantly to decreased intake, endotoxemia can contribute to hypoglycemia by decreasing hepatic gluconeogenesis and increasing peripheral glucose uptake. In the initial phase of treatment, the rate of glucose supplementation should be monitored carefully because many foals develop hypoglycemia in response to dextrose infusion. Other biochemical abnormalities common in septic foals include azotemia and hyperbilirubinemia.

Common abnormalities found on arterial blood gas (ABG) analysis include acidemia and increased lactate concentrations. One early report demonstrated a high incidence of metabolic, respiratory, or mixed acidosis. A recent report has indicated significant differences in arterial lactate concentration between foals with a positive versus negative blood culture, those that met the criteria for SIRS versus those that did not, and those that met the criteria for septic shock versus those that did not. These differences were noted at admission and at 18 to 26 hours after admission for the blood culture and SIRS variables, but numbers precluded an analysis for the septic shock variable. Stewart et al. have noted that foals with gram-negative enteric bacteremia were more likely to have an elevated arterial carbon dioxide tension (Paco₂) than other foals with bacteremia.

The coagulation and fibrinolytic systems of the septic newborn are often abnormal, with clinically relevant decreases in antithrombin III and increases in prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen and fibrin degradation products (FDPs). A detectable plasma endotoxin concentration but not a positive blood culture result was significantly correlated with abnormal PT and APTT in this study, thus endotoxemia, not bacteremia, is likely associated with the development of coagulopathy in septic foals. Some patients may develop active hemorrhage or thrombosis, which can include thrombosis of major arteries, such as the aorta or iliac, femoral, or brachial artery (Fig. 6-1).

Focal or Localized Infection

Signs consistent with a secondary focus of infection, such as pneumonia, septic arthritis, osteomyelitis, omphalitis, and meningitis, also may occur in septic foals.

Respiratory Involvement

The lungs are a very common site of focal infection in the septic foal, with a reported incidence of pneumonia ranging from 28% to 50%. Respiratory rate and effort, thoracic auscultation, and rectal temperature often can alert the clinician to the possibility of pneumonia in a patient. Respiratory function is best assessed in septic foals with ABG analysis. Thoracic radiographs provide an estimation of disease severity and distribution (Fig. 6-2). In addition to hematocegously acquired pneumonia, septic foals are at risk for aspiration of other meconium or milk, depending on their presentation. Directed antimicrobial therapy and the maintenance of an acceptable arterial oxygen tension (Paco₂) with intranasal oxygen insufflation are the most frequently administered forms of therapy. In those foals with severe hypercapnia in addition to hypoxemia, mechanical ventilation may be necessary.

Gastrointestinal Involvement

Diarrhea or enteritis also is common in septic foals, with a reported incidence of 16% to 38%. In a study from Ohio State University, foals with Actinobacillus spp.-induced bacteremia were six times more likely to have diarrhea than those with other isolates. With or without enteritis, septic foals also may display signs of ileus or colic. Most of these problems resolve with symptomatic treatment and systemic improvement. The clinician must carefully monitor fluid, electrolyte, and acid-base status in foals with diarrhea and replace ongoing losses. Options for analgesic therapy in colicky foals are somewhat limited; flunixin meglumine should be used cautiously because of the potential for gastric ulceration. Opiates such as butorphanol provide a reasonable short-term option for analgesia in such foals.

Umbilical Involvement

Omphalitis refers to infection of umbilical structures (Fig. 6-3). Umbilical remnant infections are considered to be a common source of continued bacterial shedding and have been
Fig. 6-2 A, Lateral radiographic view of 1-day-old foal with severe interstitial pneumonia, consistent with hematogenous infiltration of lung secondary to sepsis. B, Lateral radiographic view of thorax of neonatal foal with severe aspiration pneumonia. Note the more severe radiographic abnormalities within the cranioventral thorax compared with A.

Fig. 6-3 Enlarged external umbilicus consistent with infection of urachus and vascular structures external to body wall. Ultrasonographic examination of the abdomen of this foal revealed enlargement of the internal urachus and umbilical arteries. The entire umbilicus was surgically resected.

Fig. 6-4 Ultrasonogram of umbilical structures of foal. This image was obtained just cranial to the bladder and caudal to the umbilical stump and demonstrates dilation of the left umbilical artery with thickening of the arterial wall.

Reported to occur in 13% of septic foals. Ultrasonographic evaluation of these structures is critical because external signs (pain, heat, and swelling) are frequently absent (Fig. 6-4). Treatment options include long-term antibiotic therapy or surgical resection. Many septic foals will develop a patent urachus without involvement of other structures; the reported incidence in septic foals is 21%. This problem will often resolve with continued antibiotic therapy, with or without topical therapy.

In one study, uroperitoneum was diagnosed in 2.5% of hospitalized neonates, and foals with uroperitoneum were less likely to survive if they had a positive versus negative sepsis score. An interesting note from that study was that, presumably, septic foals receiving fluid therapy were typically older and less likely to have the classic electrolyte abnormalities associated with uroperitoneum. This suggests that the septic foals were diagnosed earlier, but the condition occurred later in life. Thus, ischemia and subsequent necrosis of the bladder or urachus may be the cause of uroperitoneum in the septic population. Because of these risks, routine ultrasonographic assessment of the umbilical structures is recommended for all hospitalized neonates in whom sepsis is either confirmed or suspected. The frequency of repeat ultrasound examinations depends on the individual foal’s clinical progression.

**Septic Arthritis and Osteomyelitis**

Orthopedic infections are common in septic foals and represent one of the most important life-threatening and performance-limiting complications (Fig. 6-5). The reported incidence of septic arthritis ranges from 26% to 33%, and that of osteomyelitis is 1.1% to 12%. Clinical signs include lameness and joint effusion, thus daily palpation of every joint in all hospitalized neonates is imperative. Any sign of lameness...
Neonatal septicemia

Meningitis

Meningitis is a rare but extremely serious complication of neonatal sepsis (see Chapter 4). Severe depression is common in foals with bacterial meningitis; however, this can be difficult to assess in a severely compromised, obtunded, or comatose foal. Other clinical signs may include seizures, head tilt, strabismus, nystagmus, and extensor rigidity depending on the areas of the central nervous system (CNS) that are involved. Identification of neutrophilic pleocytosis in cerebrospinal fluid (CSF) usually provides a definitive diagnosis. Prognosis is poor to grave, but if therapy is attempted, third-generation cephalosporins (e.g., cefotaxime) have been recommended.40

Ocular involvement

The most common ocular complication in the septic foal is corneal ulceration (Fig. 6-6) (see Chapter 10). Ulceration can occur because of entropion in a dehydrated foal or, more often, because of trauma. Because foals do not always show clinical signs of corneal ulceration, a daily ophthalmic examination, including fluorescein staining, should be performed in all hospitalized foals. Another possible ophthalmic complication in septic neonatal foals is uveitis. When uveitis occurs, it is typically an ocular extension of the systemic disease process.

Coagulopathy

Disorders of coagulation can occur in septic neonatal foals, manifested clinically by either hemorrhage or thrombosis. The most common abnormality probably is jugular venous thrombosis at the site of an indwelling venous catheter. Other areas of thrombosis include the brachial artery, digital artery, metatarsal and metacarpal arteries, diffuse vascular thromboses throughout the distal limb, the aortic termination, the lungs, and the colon27,60 (see Fig. 6-1).

DIAGNOSIS

A blood culture is the “gold standard” for the diagnosis of systemic bacterial infection (see Chapter 27). The identification of a causative organism allows for directed antimicrobial therapy. Samples for culture should be collected from a large vein (usually the jugular or cephalic, but other sites, e.g., saphenous vein, can be used as well) after surgical clip and aseptic preparation. The sample should be collected in a sterile syringe without anticoagulant and placed immediately into an appropriate medium, such as thioglycolate and tryptic soy broth (BBL Septi-Chek, Becton Dickinson, Sparks, MD). A fresh needle should be used for the instillation of blood into the culture medium. Sample collection from a venous catheter is acceptable, provided the procedure is performed directly from the catheter at the time of placement without compromising sterile technique. For foals that are receiving antimicrobial therapy before sample collection, an appropriate medium, such as tryptic soy broth with resins (BBL Septi-Chek), is also available and may improve microbial recovery. Regardless of the medium used, care should be taken to infuse the recommended volume of blood to promote optimum recovery.

Two considerations limit the usefulness of blood cultures for diagnosis of sepsis. First, positive results are not usually available for at least 48 hours. Second, false-negative results are common. Many foals with histologic evidence of sepsis...
at necropsy have historical evidence of a negative blood culture. This finding can result from a number of factors, including previous antimicrobial therapy and low circulating bacterial numbers. In one study, only 40% of *E. coli* infections were successfully identified by blood culture compared with necropsy culture. Thus, additional means for identifying at-risk foals would be a valuable tool for the attending clinician.

The first scoring systems were adopted and modified in the 1980s, with a stated aim of predicting whether a foal would be septic before the return of blood culture results. The modified “sepsis score” currently used in many hospitals is calculated based on a number of historical and physical findings and laboratory data and has a reported sensitivity and specificity of 92.8% and 85.9%, respectively. The sepsis score has not been as accurate at other institutions. Recent data have shown a false-negative rate of 48% in blood culture-positive foals in Ohio. In a study at the University of Georgia that examined foals with a sepsis score greater than 11, a positive blood culture, or greater than three foci infection, 13 of 247 foals had a sepsis score less than 11 but at least one of the other criteria, and 46 of 250 had a sepsis score greater than 11 without either of the other criteria. In a Virginia study, the modified and original sepsis scores each produced a positive predictive value of 84%, with negative predictive values of 55% and 53%, respectively. Results from these studies stress the importance of regional and institutional variability in the accuracy of scoring systems.

The modified sepsis score was reevaluated recently at the University of Florida, the same geographic population from which it was originally generated, and obtained a similar sensitivity (89%) but lower specificity (57.5%) using positive blood culture alone as a gold standard, rather than including evidence of specific foci of infection at necropsy as well (Sanchez and Lester, unpublished observations, 2003). Because of the heavy weighting of historical information and related problems, moderately to severely premature foals often have a positive sepsis score without a positive blood culture. However, because many of the maternal problems resulting in prematurity also can lead to septicemic sepsis, this crossover is readily predictable. The problems with the clinical application of these scoring systems are their relatively low specificity and negative predictive value. Thus, although a “positive” score is supportive of sepsis in a suspected animal, a “negative” score alone should not be used to withhold antibiotic therapy from an at-risk foal. Similarly, the use of a positive score alone, without complementary culture results or necropsy findings, should be used cautiously to confirm a diagnosis of sepsis for retrospective studies.

### THERAPY

**Antimicrobial Therapy**

Antibiotics provide the basis of therapy for septic foals. Initially, a broad-spectrum bactericidal approach must be used based on previous experience and costs. Antimicrobial therapy should begin immediately in any foal in which sepsis is suspected. Treatment should not be delayed pending blood culture results because sensitivity data typically require 3 to 4 days. Therapy can be altered if necessary when these data become available. A minimum therapeutic course of 2 weeks is recommended for bacteremic foals without localizing clinical signs. If localizing signs such as pneumonia or septic arthritis are present, a minimum course of therapy of 4 weeks is preferred. Table 6-2 presents the recommended dosages for frequently used antimicrobials. Chapter 71 provides a detailed general discussion of antimicrobial therapy in horses.

Few published veterinary reports discuss antimicrobial sensitivity of organisms isolated from bacteremic neonatal foals. A common theme is that a lower percentage of gram-negative isolates are sensitive to gentamicin than to amikacin. Paradies has reported that 95% and 91% of gram-negative isolates were sensitive to amikacin and ceftiofur, respectively, whereas sensitivity to gentamicin and trimethoprim-sulfa was much lower. The same study found that the three antimicrobials to which staphylococcal organisms were most sensitive were cephalothin, tetracycline, and chloramphenicol, whereas streptococcal organisms were most sensitive to chloramphenicol, ampicillin, and penicillin. Wilson et al. reported a cumulative sensitivity of all isolates from 33 foals as greater than 90% for imipenem, ciprofloxacin, ceftaxime, and ceftazidime; 80% to 89% for amikacin and ceftiofur, and only 70% to 79% for gentamicin and ceftriaxone. Organisms such as *Enterococcus* spp., *Actinobacillus* spp., *Enterococcus* spp., and coagulase-positive *Staphylococcus* spp. have demonstrated substantial resistance. *Enterococcus* spp. also demonstrated increasing resistance to amikacin, gentamicin, and trimethoprim-sulfa in another study. Interestingly, a study from the University of Georgia revealed considerable gram-positive and gram-negative resistance to ceftiofur but no amikacin resistance for *Enterococcus* isolates. The same study revealed an efficacy of at least 70% against all organisms for chloramphenicol or ceftiofur.

#### Table 6-2

<table>
<thead>
<tr>
<th>Agent</th>
<th>Preparation</th>
<th>Route</th>
<th>Frequency (hr)</th>
<th>Dosage (mg)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Sulfate</td>
<td>IV, IM</td>
<td>24</td>
<td>21-25 mg</td>
<td>75, 76</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Sulfate</td>
<td>IV, IM</td>
<td>24</td>
<td>6.6 mg</td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Sodium</td>
<td>IV, IM</td>
<td>6</td>
<td>25 mg</td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Trihydrate</td>
<td>IM</td>
<td>12</td>
<td>25 mg</td>
<td></td>
</tr>
<tr>
<td>Penicillin G</td>
<td>Potassium</td>
<td>IM</td>
<td>6</td>
<td>20,000-40,000 IU</td>
<td>22,000 IU</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>Procaine</td>
<td>IM</td>
<td>12-24</td>
<td>22,000 IU</td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Sodium</td>
<td>IV</td>
<td>6</td>
<td>40 mg</td>
<td>40, 77</td>
</tr>
<tr>
<td>Ceftiofur</td>
<td>Sodium</td>
<td>IV, IM</td>
<td>12</td>
<td>2.2-4.4 mg</td>
<td>78</td>
</tr>
</tbody>
</table>

IM, Intramuscular; IV, intravenous.
Thus, based on available data, a recommended initial therapeutic approach involves combining amikacin or a third-generation cephalosporin with penicillin or ampicillin. The use of amikacin should be tempered in light of the foal's cardiovascular and renal status. If a foal is severely hypovolemic and azotemic, cephalosporin would be a safer initial choice. If amikacin is used, therapeutic drug monitoring is recommended to ensure appropriate dosing for each individual.

An additional recommendation is to monitor creatinine levels serially every 2 to 3 days to perform serial urinalyses that include sediment examination to monitor for potential adverse renal effects. Cefotaxime is a good choice for foals with gram-negative meningitis or those with unresponsive pneumonia.

Unfortunately, the range of oral antibiotics for use in horses is limited. Because of significant resistance, trimethoprim-sulfonamide combinations should not be used in septic foals without documented sensitivity, and then only as a long-term option after initial parenteral therapy. Aminobenzyl penicillins (amoxicillin and ampicillin) and first-generation cephalosporins (cefadroxil and cephadrine) have good bioavailability in young foals (in contrast to older foals and adult horses) but have a limited gram-positive spectrum of activity. Cefpodoxime proxetil, a third-generation cephalosporin available for oral administration, was recently shown to be effective against 90% of Klebsiella spp., Pasteurella spp., and Bacteroides fragilis. An increase in the frequency of administration would likely increase the effectiveness of this drug against E. coli. Fluoroquinolones, such as enrofloxacin, have an excellent spectrum of activity against gram-negative and some gram-positive organisms but have been associated with arthropathy in foals. Thus, these agents should be reserved for those cases with documented resistance to other antimicrobial agents and informed owner consent.

**Antitoxin Antibody Therapy**

Not surprisingly, many septic foals have detectable plasma endotoxin concentrations. Recent in vitro work suggests that β-lactam antimicrobials may be more likely than aminoglycosides (alone or in combination with ampicillin) to induce endotoxemia and tumor necrosis factor-α activity during the treatment of E. coli sepsis. Agents often used for the treatment of endotoxemia include flunixin meglumine, pentoxifylline, and polymyxin B sulfate. None of these agents has been scientifically evaluated for the treatment of endotoxemia in foals; thus, recommendations are extrapolated from work in vitro and in adult horses (see Chapter 37). Flunixin and polymyxin B are potentially nephrotoxic and should be used with caution. Flunixin meglumine also has the potential for causing gastric ulceration. Pentoxifylline may reduce mortality without adverse effects in septic neonates but not adults.

**Antifungal Therapy**

Antimicrobial agents for treatment of systemic candidiasis include fluconazole, itraconazole, miconazole, and amphotericin B. Fungal sensitivity profiles, if available, may help direct therapy (see Chapters 49 and 56). The pharmacokinetic and pharmacodynamic activities of these drugs have not been well established in foals. Amphotericin B has been administered intravenously (IV) at a range of 0.1 to 0.5 mg/kg once a day, starting therapy at the lower dose and increasing by 0.1-mg/kg increments per day. Because this drug can cause potentially life-threatening nephrotoxicity, serum creatinine concentrations, urine production, and urinalysis should be monitored closely. Fluconazole has previously been administered orally at 4 to 10 mg/kg once daily. This agent is less expensive, easier to administer, and has fewer adverse effects. Miconazole has been administered at a dosage of 1 mg/kg IV every 8 hours.

**Cardiovascular Support**

Fluid therapy is critical in foals with hypovolemia, acid-base disorders, septic shock, or hypotension. In-depth discussions of fluid therapy and the use of inotropes and vasopressors in the neonatal foal have been recently presented. These are two of the most important concepts in the initial treatment of sepsis, and the reader is directed to the cited references for additional information.

When a foal presents in septic shock, fluid resuscitation is critical. Initial choices typically include a combination of crystalloid (e.g., lactated Ringer's solution) and colloid (e.g., hydroxyethyl starch) preparations. Arterial or venous lactate concentration, systemic blood pressure, cardiac output, and central venous pressure can provide additional information regarding volume status and estimation of tissue perfusion. Once normovolemia has been restored, neonates typically require approximately 100 mL/kg/day (5 L/day for 50-kg foal) to maintain adequate hydration.

Clinicopathologic variables to monitor continuously in septic foals include arterial or venous blood gases (depending on pulmonary status), electrolytes (especially sodium and potassium), and glucose. Physical parameters of importance include careful examination for the development of edema (conjunctiva, distal limbs, and other signs), urine output, vital signs, and temperature of the distal limbs. Derangements in any of the monitored parameters should be addressed as they arise to maintain optimal tissue perfusion.

**Gastric Protectants**

Although uncommon, sick foals may develop gastric ulcers, especially in the glandular region of the stomach. The use of prophylactic antacid therapy is controversial and depends on the preference of the clinician. The gastric pH in critically ill foals can differ greatly from that seen in healthy foals. Severely ill, predominantly recumbent patients frequently have alkaline gastric pH patterns. In addition, sick foals capable of acid production respond more variably to IV ranitidine administration than their normal cohorts. Thus, glandular ulcer disease in sick neonates is likely not strictly an acid-related problem, and factors such as alterations in mesenteric blood flow may contribute. In addition, gastric alkalization can contribute to bacterial translocation. Therapeutic options for acid suppression in the neonatal foal include omeprazole and ranitidine. Sucralfate remains a possible alternative for ulcer prophylaxis, especially in foals receiving nonsteroidal antiinflammatory drugs. For a more complete discussion of this topic, the reader is directed to more recent reviews.

**Experimental Therapy**

Although a variety of experimental therapies have shown promise for treatment of sepsis, few have resulted in reduced mortality in large-scale human clinical trials. Administration of recombinant activated protein C has consistently been associated with decreased mortality, especially in the most severely affected patients. This agent, however, has been associated with significant adverse effects and is currently not a viable therapeutic option in foals. Although high-dose corticosteroid administration has been associated with increased mortality in septic patients, hydrocortisone administered at physiologic doses decreases mortality attributable to septic shock in human patients.
PROGNOSIS

Survival rates for foals with neonatal sepsis have increased from the rate of 25% reported in the early 1980s. More recent retrospective studies have reported short-term survival rates ranging from 45% to 55%. Other investigators have reported survival rates ranging from 32% to 72%. Approximately 50% to 60% of all bacteremic foals admitted to the University of Florida neonatal unit survive to discharge (Sanchez and Lester, unpublished observations, 2003).

Several factors have been associated with survival in retrospective studies. Barton et al. found that foals infected with gram-negative organisms are more likely to die than those with gram-positive infections. In a Texas study the duration of illness before admission was inversely related to survival, whereas the ability of a foal to stand on admission was positively correlated with survival. A study of septic foals at the University of Georgia found that foals were more likely to survive if they had a sepsis score less than 11, a negative blood culture at admission, a serum glucose level of greater than 60 mg/dL, a body temperature greater than 100°F, a total CO2 greater than 15 mmol/L, or a low or normal plasma fibrinogen concentration. In the Florida study the prognosis worsened if multiple organisms were isolated from the blood or if multiple foci of infection were involved (Sanchez and Lester, unpublished observations, 2003). In the Ohio State study, foals with multiple blood isolates had longer periods of hospitalization, but not decreased survival. Corley et al. reported that a normal arterial lactate concentration at admission or 18 to 36 hours after admission was a good predictor of survival, whereas increased blood lactate concentrations were not a good predictor of non-survival.

Few studies have addressed the long-term survival and performance of neonatal intensive care unit (NICU) survivors, much less those specifically of septic foals. In a summary of septic Thoroughbred foals admitted to the University of Florida, approximately 75% of short-term survivors are registered, and approximately 50% start at least one race (Sanchez and Lester, unpublished observations, 2003). This observation is similar to that reported for overall NICU survivors, in which the percentage of starters was lower than the control population, but performance over a 2-year period was not different in those animals able to make at least two starts. Similar findings have been reported for foals with neurologic disease and those with pneumonia caused by *Rhodococcus equi*.

PREVENTION

Clearly, given the wide range of potentially devastating problems associated with sepsis, attempts to prevent disease are extremely important. Not surprisingly, methods of disease prevention add the documented risk factors and routes of infection discussed previously. The following suggestions constitute a basic guide for veterinarians and horse owners. Although many of the options presented make sense, none has been proved to reduce the incidence of sepsis. Thus the decision to implement some or all of these practices will depend on the individual farm situation.

Maintain Clean Environment

Although this is one of the most basic concepts in all of medicine, its importance cannot be overemphasized. Foaling stalls should be thoroughly cleaned and disinfected between mares. For each inhabitant, the stall should be cleaned at least daily, if not twice daily, and plentiful clean, dry, fresh bedding should be provided for the mare and foal.

Reduce Potential Bacterial Load Introduced during Udder Seeking

The mare's hindquarters, perineum, and udder should be thoroughly cleaned with soap and water after foaling but before the foal's introduction. The key feature to this step, which is often overlooked, is that the mare also must be dried. Drying should be performed just outside the stall, rather than in the stall, to prevent contamination of the foal's new environment, which is the point of the exercise. This step requires great commitment on the part of the farm because it is labor intensive.

Ensure Rapid Gastrointestinal Intake

The volume, quality, and timing of colostrum administration are all likely important factors for optimizing passive transfer of immunity. Ideally, foals should receive 6 to 8 ounces of good-quality colostrum as soon as they develop a strong suckle reflex. The risk of milk aspiration when untrained individuals attempt to bottle-feed a newborn, potentially weak foal must be considered. Colostrum administration through nasogastric tube is recommended for foals with a suboptimal or absent suckle reflex.

Ensure Adequate Passive Transfer of Immunoglobulin G

Traditionally, passive transfer of maternal IgG to the foal has been considered to be the most important factor in disease prevention. Although other factors clearly play a role, adequate IgG transfer should still be assessed and treated, if necessary. Assessment of blood immunoglobulin concentrations should be performed for all foals at 24 to 48 hours of age. Optimally, IgG concentration should exceed 800 mg/dL at this time (see recent reviews of diagnosis and treatment of FPT in foals for further information).

Ensure Appropriate Umbilical Care

No published studies in foals have critically evaluated the different preparations used for routine postpartum umbilical care. In human neonates, surprisingly few randomized, double-blind clinical trials have broached this issue. In a recent review of published studies, 4% chlorhexidine consistently reduced the risk of umbilical and periumbilical infections. This concentration of chlorhexidine also is typically used for treatment of foals and thus appears to be a preferred alternative to the povidone-iodine solutions used previously.

REFERENCES

See the CD-ROM for a list of references linked to the abstract in PubMed.
Skin infections, especially contagious dermatologic diseases, include some of the most common causes of equine skin disease. In one report, 25% of all dermatologic diagnoses made over a 21-year period were infectious in origin. For the clinician, it is important to diagnose these conditions quickly to prevent spread to other horses and potentially their human companions. Many of these infectious agents are discussed in detail elsewhere in this book. The purpose of this chapter is to provide an overview that assists the clinician in differentiating, diagnosing, and treating conditions given the appropriate historical information, clinical presentation, and laboratory data.

GENERAL COMMENTS

A detailed history is an extremely important component of any dermatologic workup (Box 7-1). The age at time of onset, time of the year, presence of itching, and any other notable detail not generally observed during a short examination can assist physical diagnosis. Additional questioning should include whether any topical medications, home remedies, or systemic medications have been used. Response to medications (independent of season) and time to relapse (if a response occurred) are valuable pieces of information to assist diagnosis.

The environment is a causal or predisposing factor for many diseases of the skin. A detailed description or personal inspection of the environment is needed. Chronic exposure to moisture, such as wet bedding, constant rain, or muddy pastures, can contribute to the original condition and prevent response to therapy.

A basic physical examination should be performed on every patient that exhibits skin disease. Many infectious diseases of the skin reflect the underlying health, nutrition, and immune status of the horse. This can help differentiate primary from secondary conditions. In addition, it is important to determine if the skin lesions reflect the primary condition of the skin. Often the clinician's first examination is performed after many other therapies have been attempted. Primary lesions consist of pustules, papules, and macules. Most secondary lesions consist of crusts, scales, and alopecia. Noting the presence or absence of pruritus will rule out (or rule in) many diseases. It is important to note if the lesions occur singly or multiply. Determining what structures are involved should also be part of the physical diagnosis (in addition to confirmation by biopsy).

Dermatologists have a basic and straightforward diagnostic armamentarium that differentiates most diseases. Skin scrapings are essential for diagnosis of parasitic infections (see Chapter 64). Punch biopsies of skin are quick and inexpensive and can yield much needed information. Collection of a sterile biopsy for culture is necessary for bacterial and some fungal infections. When disease is global and long-standing, a wedge biopsy may yield more information regarding the primary etiology. Accurate histopathologic assessment with appropriate knowledge of equine-specific diseases is essential. For example, horses develop sarcoids frequently and fibrosarcomas rarely, and the two conditions are treated very differently (see Chapter 25). Special stains for bacteria and fungi should be pursued when appropriate.

Although many therapies for skin disease in the horse are palliative, etiology-specific treatment should be pursued rather than overuse of broad-spectrum antibiotics. Many primary conditions (e.g., autoimmune disease) have a suppressive component from secondary infection or a leukoclastic feature (e.g., purpura hemorrhagica). Understanding which conditions require antibiotics will save time and money and will be safer for equine patients and owners.

CRUSTING/SCALING DERMATOSES

Bacterial Etiologies

Crusting/scaling dermatoses affect primarily the epidermis and upper levels of the dermis and have many causes. Often these dermatoses start as small papules that quickly progress to crust and scale. In addition, clinical signs may include small papules, erosions, excoriations, alopecia, and varying degrees of pruritus (Boxes 7-2 and 7-3).

**Bacterial folliculitis** is most often caused by staphylococcal bacteria (*Staphylococcus aureus, S. intermedius, S. hyicus*). Other bacteria infrequently associated with folliculitis include *Streptococcus equi subsp. equi, Streptococcus equi similis*, and *Corynebacterium pseudotuberculosis*. **Dermatophilosis** is another bacterial crusting/scaling dermatosis in the horse (see Chapter 31).
Pruritic Crusting/Scaling Dermatoses

Noninfectious
- Choriotic mange
- Sarcoptic mange
- Psoroptic mange
- Pediculosis
- Cutaneous onchocerciasis
- Culicoides hypersensitivity
- Atopy
- Food allergy

Infec tious
- Dermatophytosis
- Dermatophilosis
- Staphylococcal folliculitis
- Corynebacterial folliculitis
- Malassezia dermatitis
- Besnoitosis

Nonpruritic Crusting/Scaling Dermatoses

Noninfectious
- Trombiculiasis
- Idiopathic seborrhea
- Pemphigus foliaceus

Infectious
- Dermatophytosis
- Dermatophilosis
- Staphylococcal folliculitis
- Corynebacterial folliculitis
- Malassezia dermatitis
- Poxvirus

Clinical Findings
Most cases of folliculitis start in the spring or summer. The lesions start as small follicular papules that can develop into transient pustules that rupture to form crusted pustules (Fig. 7-1). Small foci of alopecia with scaling develop in areas of infected follicles, leading to a moth-eaten appearance of the hair coat. In severe cases, lesions may enlarge, ulcerate, and have a purulent or serosanguineous discharge. If complicated by furunculosis, nodules and fistulous tracts may be present. Pustular lesions can be more painful than pruritic. Most of these lesions start in the tack areas and are associated with friction, high temperature and humidity, excessive sweating, poor grooming practices, and possibly biting insects. Horses also develop staphylococcal folliculitis of the caudal aspect of the pastern and fetlock, which is considered to be one of the causes of "grease heel." If left untreated, lesions of folliculitis may become widespread.

Diagnosis
Diagnosis is made by cytology of lesions (pustules, crusts), culture of lesions, and histopathology. Samples for culture are best obtained from fresh papules or pustules. If these are not available, the exudate from underneath a crust is acceptable. The histopathologic findings of bacterial folliculitis are characterized by epidermal acanthosis with variable degrees of folliculocentric neutrophilic pustules and serocellular crusting. Neutrophils fill the follicular lumens. Follicular distention with rupture and resultant pyogranulomatous dermatitis may be present. Bacteria may or may not be detected within the lesions.

Therapy
Treatment consists of systemic antibiotics, topical therapy, and improved grooming practices and attempts to eliminate other predisposing factors. Antibiotic selection should be based on results of culture and sensitivity testing. This is especially true now that methicillin-resistant Staphylococcus aureus (MRSA) infections that potentially can be transferred to horse personnel are being diagnosed more frequently in horses5-9 (see Chapter 29). Antibiotic therapy should last at least 3 to 4 weeks, or 7 to 10 days beyond clinical cure. Topical therapy may consist of chlorhexidine or benzoyl peroxide shampoos. Benzoyl peroxide has the most antibacterial activity but may dry and bleach the coat. Therefore the frequency of topical application depends on the severity of disease and the topical agent used. For most cases, once-weekly to every-other-week application is adequate.

Prevention
Improved hygiene is required both for prompt resolution of infection and for prevention of recurrences. All blankets should be thoroughly cleaned with hot water and bleach. Tack should be kept as clean as possible. Cleaning of equipment should be continued on a routine basis. The horse should
not be ridden while lesions are active. After the lesions have improved, the horse should be cooled properly and rinsed well after each ride. The horse should be bathed once or twice weekly in hot weather and should always have a clean saddle blanket each time it is ridden.

**Fungal Etiologies**

Dermatophytosis is a common cause of crusty and scaling (see Chapter 54). Malassezia has recently been associated with crusty/scaling dermatitis in the horse.10 Malassezia pachydermatis is a lipophilic, nonmycelial, saprophytic yeast often found on normal and abnormal skin of various mammals, including the horse. A novel Malassezia species also inhabits normal horse skin. This organism has not been completely characterized but is closely related to Malassezia sympodialis. As in the dog and cat, Malassezia in the horse tends to be associated with other dermatologic diseases, including atopy, insect bite allergy, food allergy, and dermatophytosis.

**Clinical Findings**

Lesions consist of greasy to waxy crusts and scales with a foul odor. Pruritus ranges from negligible to severe. The lesions usually start in the intertriginous areas (axilla and groin) but can become generalized.

**Diagnosis**

Diagnosis is confirmed by finding numerous Malassezia organisms on skin surface cytology. Histopathologic changes of Malassezia dermatitis in the horse have not been specifically described. In other species, Malassezia-associated dermatitis is characterized by epidermal acanthosis and hyperkeratosis with parakeratotic crusts. Yeasts are detectable in high numbers within the keratin. Inflammation is mild and consists of mixed leukocytes within the dermis.

**Therapy**

Successful treatment includes management of predisposing conditions and specific antifungal therapy. Ketoconazole, miconazole, clotrimazole, and selenium sulfide all have good activity against Malassezia. These antifungal agents are available in a variety of mainly small animal shampoo, rinse, and cream preparations. Many are available in gallon containers and can be used on horses. The affected areas should be kept dry as possible, as should the horse’s environment.

**Parasitic Etiologies**

Borrelia spp. is a rare coccidian protozoal infection caused by *Borrelia bennetti* (see Chapter 61). It has been reported throughout the world in both wild and domestic animals. The definitive host for some species of *Borrelia* is the domestic cat. Sporulated oocysts shed in the feces of the definitive host release sporozoites when ingested by susceptible intermediate hosts, such as the horse. Parasitic replication and migration through the connective tissues of the intermediate host leads to parasitic cyst formation in many tissues. Numerous cysts can be found in the dermis and subcutaneous tissues. Lesions start as small papules in glabrous areas. These papules spread to cover the entire ventrum, perineum, and face and may become generalized. The nasal, oral, and pharyngeal mucosa may also be affected. As the lesions mature, they become thick and crusty. Alopecia and pruritus are common and affected horses may be febrile, depressed, and weak.

**Diagnosis**

Diagnosis of borrelia is made by biopsy. Histopathologically, the dermis and subcutis contain many large (300-650 μ), round, thick-walled cysts filled with protozoal bradyzoites. There is a perivascular mononuclear infiltrate and marked epidermal hyperplasia with hyperkeratosis. Cysts are actually hyperplastied fibroblasts.

**Therapy**

Successful treatment of borrelia is not yet reported in the horse, although trimethoprim-sulfamethoxazole was effective in a miniature donkey.

**Viral Etiologies**

**Poxvirus**

Poxvirus infections in horses are rare and have several forms. Poxviruses have been associated with some cases of exudative dermatitis of the flexor aspects of the hind pasterns (another possible cause of “grease heel”). A mucocutaneous form of poxviral infection affects the muzzle and buccal cavity and can spread to the face and other parts of the body. A third type of poxvirus infection is equine papular dermatitis, seen in the United States and Australia.

**Clinical Findings**

Horses develop firm papules up to 0.5 cm in diameter. Lesions begin on the lateral neck, shoulders, and thorax, and eventually become generalized. Equine papular dermatitis is highly contagious and spread by direct contact and fomites. In Kenya, a generalized poxviral disease called Uasin Gishu disease is characterized by generalized papules that become large papillomatous proliferations over time.

**Diagnosis**

Histopathologically, the lesions of Uasin Gishu disease are identical to those of molluscum contagiosum. Lesions of poxvirus infection begin as erythematous macules that quickly become papular, leading to a transient vesicular stage that gives rise to a pustule and then a crust. Healing with scar formation is typical. In haired areas a fine, powdery scale may form. Histopathologic changes vary with the stage of the lesion. The cells of the epidermal stratum spinosum often show cytoplasmic swelling, leading to keratinocyte rupture and vesicle formation. The dermis is edematous with variable degrees of perivascular mononuclear cell and neutrophil infiltration. Neutrophils migrate into the epidermis to form pustules which rupture to form crusts. The epidermis becomes extremely hyperplastic. Intracytoplasmic inclusions typical of poxvirus infection may be evident. Affected horses may show various systemic signs, including pyrexia, lameness, ptismus, and depression. The symptoms are self-limiting and last 20 to 30 days.

**Molluscum Contagiosum**

**Etiology.** Molluscum contagiosum is a rare proliferative poxviral disease in horses caused by a molluscipoxivirus.11 The disease is mildly contagious between horses, and transmission occurs by direct skin-to-skin contact and indirect contact with fomites.

**Clinical Findings**

The clinical and histopathologic changes of molluscum contagiosum are identical to those seen in horses with Uasin Gishu disease. However, the causative agent of equine molluscum contagiosum cannot be grown in culture, whereas the agent of Uasin Gishu can be cultured. Lesions usually begin in one area, such as the chest or neck, then become widespread, with affected animals having hundreds of lesions. Lesions start as papules that become hyperplastic with thick crusts and horny projections.
Diagnosis. Diagnosis of molluscum contagiosum is made by biopsy and is characteristic of the disease. Discrete foci of endophytic epidermal hyperplasia form pear-shaped lobules in the superficial dermis. Keratinocytes are greatly swollen and contain large intracytoplasmic inclusions known as "molluscum bodies." Affected keratinocytes slough through a pore that forms in the stratum corneum and enlarges to become a central crater. The dermis is not inflamed.

Therapy
Treatment of poxvirus infections consist of supportive care and prevention of secondary bacterial infections. Topical therapy with antibacterial shampoo, clean blankets, and dry stalls all help to prevent secondary infection. No reported treatment, including an autogenous bacterin, has been successful for treatment of molluscum contagiosum. Horses may remain covered with hundreds of lesions for several months to years. In some cases, many of the lesions will regress over time, although the regression of all lesions has not been reported. Occasionally, horses will have small numbers of incidental and self-limiting lesions.

PAPULONODULAR DERMATOSES

Papulonodular dermatoses have deeper lesions that extend into the lower layers of the dermis (Box 7-4). These lesions consist of multiple or large papules to nodules that may ulcerate, drain, and crust over.

Bacterial Etiology, Diagnosis, and Treatment
Bacterial furunculosis is merely a progression of folliculitis. The most prominent lesions are often seen in the saddle region and include furuncles, draining tracts, and ulcerations. Diagnosis, histopathologic findings, and treatment are the same as discussed for folliculitis. Antibiotic choice should always be based on culture and sensitivity results, and systemic antibiotic therapy should continue for at least 6 to 8 weeks instead of 3 to 4 weeks. If only a few lesions are present, 2% mupirocin ointment can be tried instead of systemic antibiotic therapy.

Papillomavirus
Papillomatosis in the horse is caused by several different DNA papovaviruses (see Chapter 25). Lesions begin as small, smooth, white to gray papules that grow into pedunculated lesions with multiple frondlike keratin projections. Diagnosis is made by histopathology; viral papillomas are characterized by an epidermal, extremely hyperkeratotic and hyperplastic epidermis supported by thin dermal cores. The keratinocytes of the spinous and granular layers have ballooning degeneration and may have intranuclear, pale, basophilic viral inclusion bodies. The stratum granulosum has large and irregularly shaped keratohyaline granules.

Leishmaniasis
Etiology
Leishmania, an intracellular protozoal parasite of the mononuclear phagocyte system, can cause papulonodular skin disease in horses. Cutaneous leishmaniasis in horses is seen primarily in South America but has been reported in horses residing in the United States. Endemic foci of leishmaniasis exist in Texas, Oklahoma, and Ohio. The majority of cases reported in the United States have been in the dog. Leishmaniasis is caused by Leishmania braziliensis braziliensis, a protozoal parasite transmitted by the sandfly. Lesions consist of papules and nodules that become ulcerated and crusted. Common locations for lesions include the muzzle, pinnae, scrotum, neck, and legs.

Diagnosis
Histopathology is usually diagnostic for leishmaniasis, and lesions consist of a superficial and deep granulomatous dermatitis. Inflammation can be diffuse or organized as distinct granulomas (Fig. 7-2). Leishmania amastigotes can be identified within macrophages, giant cells, or occasionally within endothelial cells or fibroblasts or free in the interstitium.

Therapy
Few reports of treatment of leishmaniasis in horses have been published. One horse was successfully treated with sodium stibogluconate. This drug is specific for the treatment of leishmaniasis and is a systemic therapy. Many potential adverse effects are associated with this medication, including pain with intravenous injection. Arrhythmias occur in people, and

![Fig. 7-2 Leishmania infection in horse. Changes consist of granuloma containing giant cells.](https://via.placeholder.com/150)
the drug is contraindicated in pregnant women and patients with renal disease.

LARGE NODULAR/MASS DERMATOSES

Etiology

Nodular/mass dermatoses form a single mass lesion or several large nodular lesions grouped together and have many different etiologies (Box 7-5). These lesions affect primarily the deep dermis and subcutaneous tissue. Eventually, the underlying muscle tissue may also be involved. The overlying epidermis may be completely normal or may contain multiple draining tracts and ulcers.

Subcutaneous bacterial abscesses in the horse can be caused by any bacterium that is inadvertently inoculated into the skin or subcutaneous tissue. *Staphylococcus aureus* is the most frequent cause, but other staphylococcal species are also frequently cultured from these lesions (see Chapter 29). *Streptococcus* spp. (see Chapter 28), *Actinomyces* spp., *Nocardia* spp. (see Chapter 30), *Pseudomonas aeruginosa*, and *Mycobacterium* spp. (see Chapter 33) have been reported less frequently. *Corynebacterium pseudotuberculosis* causes particularly deep-seated abscesses (see Chapter 30). The typical presentation is a solitary, large abscess on the ventral chest, although multiple lesions anywhere on the body can be seen. Insect bites have been reported as the means by which *C. pseudotuberculosis* is inoculated into the subcutaneous tissue.

Subcutaneous mycoses in the horse can be caused by a myriad of ubiquitous soil saprophytes that are inadvertently inoculated into viable tissue. Fungal fungi such as *Bacillus cereus*, *Bacillus subtilis*, and *Bacillus megaterium* have been reported as the means by which *C. pseudotuberculosis* is inoculated into the subcutaneous tissue.

These are normally solitary lesions that may or may not have draining tracts. The grains in the exudate may be dark or white depending on the particular fungus involved. *Phaeohyphomycosis* fungi form pigmented hyphae in tissue but not granules. These fungi normally form multiple, nonulcerative nodules. *Zygomycosis* fungal infections are characterized by nonpigmented, poorly staining hyphae in the tissue. These fungi usually cause solitary, ulcerative, granulomatous masses (see Chapter 55). *Sporotrichosis schenckii*, a dimorphic fungus (see Chapter 52), and *Pythium insidiosum*, an oomycete (see Chapter 55), cause lesions similar to those just described.

Diagnosis

Diagnosis is made by cytologic examination with culture and sensitivity testing of the exudate. If the abscess does not mature, open, and drain, histopathology and tissue culture may be needed to make the diagnosis. Diagnosis and differentiation of subcutaneous fungal infections is best accomplished by histopathology with tissue culture and sensitivity. Most subcutaneous mycoses are characterized by a nodular to diffuse, granulomatous to pyogranulomatous, deep dermatitis and panmyelitis (Fig 7-3). Lymphocytes and plasma cells may be numerous, and microabscesses may be present. The fungal organism can usually be identified within the areas of inflammation. The overlying epidermis may be acanthotic or ulcerated.

Therapy

Treatment of bacterial subcutaneous infections is best accomplished by using heat or poultices to promote drainage. Once mature, the abscess should be surgically incised, drained, and lavaged. This therapeutic approach is much more effective than systemic antibiotic therapy. Systemic antibiotics should be reserved for cases in which the abscess does not mature or cannot be drained. Antibiotic selection should be based on culture and sensitivity results. Treatment of fungal infections consists mainly of complete surgical excision. These fungi are notoriously resistant to antifungal drugs. However, specific antifungal therapy may be beneficial in treatment of sporotrichosis (see Chapter 52).

### PASTERN DERMATITIS

*Equine pastern dermatitis* (EPD) is an infectious disease of horses variously known as "scratches," "mud fever," "grease heel," and "cracked heels." This disease is highly variable in terms of etiology, duration, and response to therapy (even during sequential outbreaks in the same horse). Etiologic agents
responsible for EPD include *Staphylococcus aureus*, *Dermatophilus congolensis*, and *Chorioptes mites*. A recent case reported in the literature described concurrent infection with intradermal spirochetes and *Pelodera strongyloides*. This etiology may be similar to that of papillomatous digital dermatitis of cattle.

A severe form of pododermatitis, *verrucous pustern dermatitis*, has been described in draft horses. This disease may be staged based on severity and degree of histopathologic change. An increased risk of disease is associated with poor hygiene in the stable and poor quality of the pasture on which horses are managed. However, others have hypothesized an autoimmune etiology for this condition.

**Clinical Features**

EPD can affect any breed of horse, although it is most often described in draft breeds. Feathering over the pasterns is a likely predisposing factor. This disease has no age or gender predilection but is reported more frequently in adult horses. Dermatitis affects the caudal aspect of the pasterns, especially in the hindlimbs. The lesions occasionally spread dorsally and anteriorly, involving the front of the pastern and fetlock area. The condition is frequently bilateral and symmetric, although a single limb may be affected in some horses. Lesions are most common on the nonpigmented areas of the pasterns. If left untreated, lesions coalesce and may produce large areas of ulceration and suppuratation.

EPD is not usually associated with systemic clinical signs, and the general health of the animal is unaffected. If there is severe disease, secondary distal limb edema and fever may occur. Ultimately, the disease can progress to severe ascending cellulitis. Lameness is variable and can be quite severe.

**Diagnosis**

Diagnosis of EPD is frequently made solely on the basis of clinical signs. If pustules are present, contents may be obtained for Gram stain of smears, bacterial culture, and antibiotic sensitivity testing. Punch biopsy, obtained with sterile technique, is the appropriate sample for culture. Pastern folliculitis should be differentiated from other causes of pastern dermatitis, especially allergic contact dermatitis, photosensitization, dermatophytosis, dermatophilosis, and idiopathic pastern dermatitis ("grease heel"). The lesions of grease heel are generally those of a diffuse inflammation rather than papules and pustules. The lesions of photosensitization are not limited to the posterior aspect of the pastern or fetlock regions and only involve areas that lack pigmentation.

**Therapy**

It may be necessary to heavily sedate or anesthetize an affected horse for initial therapy because lesions can be quite painful. The affected area(s) should be clipped and washed well with an antiseptic solution (e.g., povidone-iodine, benzoyl peroxide). Application of an antiseptic such as aluminum acetate solution (Dormeuro, Bayer) may be helpful. An appropriate antimicrobial ointment is then applied every 2 to 3 days. Systemic antibiotic therapy is rarely, if ever, indicated. In severely affected horses, therapy with injectable procaine penicillin may be considered. Broad-spectrum antibiotics or those with a predominantly gram-negative spectrum may be indicated based on culture results.

**References**

See the CD-ROM for a list of references linked to the abstract in PubMed.

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**CHAPTER 8**

**Reproductive Tract Infections**

Ahmed Tibary and Cheryl L. Fite

Infections of the reproductive tract cause a myriad of clinical disorders manifesting primarily as infertility, abortion, and birth of septic foals. This chapter discusses the etiology, pathogenesis, clinical manifestations, treatment, and prevention of these diseases in the mare and stallion. Infectious processes of the reproductive tracts may be divided into *venereal* and *opportunistic*. The venereal diseases present important economic and regulatory issues and are reviewed separately in this chapter.

**REPRODUCTIVE TRACT INFECTION IN NONPREGNANT MARES**

Infection of the reproductive tract in the mare, especially endometritis, is the leading cause of infertility in horses and results in substantial annual losses. The female reproductive tract possesses a variety of mechanisms to protect itself against infection. These include physical barriers (vulva, vestibulovaginal sphincter, cervix), local immune mechanisms, and the physical ability to eliminate products of inflammation. Uterine infections, reported in 25% to 40% of barren mares, become established when one or several of these natural defense mechanisms fail or become overwhelmed. Bacterial infections result in infertility, early embryonic loss, placentitis, birth of septic foals, and postpartum metritis. Salpingitis, cervicitis, and vaginitis may be part of the clinical presentation of acute or chronic reproductive tract infections in the mare.

**Uterine Infections**

**Etiology**

Infectious *endometritis* is a major cause of infertility and early pregnancy loss* and is estimated to affect 25% to 40% of

*References 23, 24, 107, 110, 111, 148, 149, 323, 326, 335.
broodmares. These infections become established when normal defense mechanisms fail to clear potentially pathogenic organisms after they are introduced into the uterus. The most common sources of uterine contamination include colitis, perturbation, artificial insemination, and aseptic genital examination and manipulation. **Age, parity, number of barren years, and uterine biopsy grade influence likelihood of persistence of infection.**

The organisms most frequently isolated from mares with endometritis are Streptococcus equi subsp. zooepidemicus, Escherichia coli, Pseudomonas aeruginosa, and Klebsiella pneumoniae. Infections caused by *P. aeruginosa* or *K. pneumoniae* are often considered venereal diseases because the organism is often introduced during colitis, insemination with infected semen, or genital manipulations. *K. pneumoniae* capsule types 1, 2, and 5 are highly pathogenic.

Commensal bacteria such as *Actinomyces pyogenes*, *Proteus* spp., and *Staphylococcus* spp. are occasionally isolated from mares with endometritis. They are considered likely to be the causative organisms of endometritis if the diagnosis is supported by cytologic or histopathologic evidence of concurrent inflammation. Alpha-hemolytic *Streptococcus*, Enterobacter spp., and *Staphylococcus epidermidis* are rarely causes of equine endometritis and are considered the simple contaminants. *Corynebacterium* spp. and anaerobic bacteria such as *Bacteroides fragilis* may occasionally cause endometritis in horses. *Anaerobes* are most often isolated from postpartum and foal death samples. *Taylorella equigenitalis* is a causative agent of a highly contagious venereal metritis, contagious equine metritis (CEM) (see Chapter 41). The pathogenicity of bacteria depends on their ability to adhere to the endometrium, preventing their removal by normal uterine clearance mechanisms. Adhesive properties of *S. equi* subsp. *zooepidemicus* are probably mediated by fibronectin-binding proteins and hyaluronic acid capsule. Attachment of *K. pneumoniae* to endometrial cells is facilitated by pili and capsule. Persistent colonization by *P. aeruginosa* is assisted by the secretion of an adhesive matrix that forms a biofilm. These biochemical properties also are important in resistance to bacteria to osmotic, phagocytosis, and the action of antimicrobials. Resistance to phagocytosis is often observed with *S. equi* subsp. *zooepidemicus* and *K. pneumoniae* and is probably mediated by antigenic variation, antigenic M-like proteins, hyaluronic acid capsule, or polysaccharide and Fc receptors. Bacterial toxins promote deterioration of complement and exacerbate uterine inflammation.

*Candida* spp. and *Aspergillus* are the most common fungal isolates from the uterus of mares with endometritis. The incidence of fungal infection in mares with endometritis is estimated to vary between 0.1% and 1%, **and** in mares with endometritis include *Aspergillus* spp., several *Candida* spp., *Cryptococcus neoformans*, *Fusarium* spp., *Hansenula anomala*, *Hansenula polymorpha*, several *Rhodotorula* spp., *Scedosporium apiospermum*, *Sakcharomyces cerevisiae*, *Trichosporon beigelii*, and *Torulopsis candida.*

Prolonged antibiotic therapy may be a predisposing factor for yeast overgrowth. The use of antibiotic-containing semen extenders for artificial insemination may be partially responsible for the apparent increase in the number of mares with fungal endometritis (J. Aurich, personal communication). Transmission of fungal organisms from stallions has not been demonstrated, although fungi have been cultured from the urethra (Mucor spp.), fresh semen (Abubia spp.), and extended semen (Candida spp.) of stallions.

*Mycoplasma* spp. have been isolated from the external genitalia and semen of clinically normal and fertile stallions, but their exact role in uterine infection is not well established. *M. equinogenitalis* produces a consistent cytotoxic effect on the ciliated epithelium of the oviduct, with variable severity depending on strain. *M. equinogenitalis*, *M. simulans*, and *Acholeplasma* spp. are associated with infertility, endometritis, vulvitis, and abortion in mares and with reduced fertility and balanoposthitis in stallions. *M. equinogenitalis* and *M. simulans* were isolated from the genital tract of mares (5%-34%) and aborted equine fetuses (7%); however, the presence of mycoplasmas is not always correlated with reduced fertility.

**Pathogenesis**

**Physical Barriers.** The uterine cavity is protected from ascending infection by several anatomic structures. The first line of defense is provided by the seal of the normal vulvar labia. Evaluation of vulvar and perineal conformation should be included in all prebreeding examinations or evaluations for infertility. The vulva should be in a vertical position aligned with the anal opening (Fig. 8-1, A). The labia should be tight, with most of its length below the tuber ischi. The vulvar lips may become apart as a consequence of malformation caused by previous traumatic injuries or lesions (Fig. 8-1, B). In older multiparous mares, there is a tendency for extreme relaxation of the vulvar lips particularly during estrus, as well as tilting of the dorsal aspect of the vulva caused by relaxation of the perineal body. In this situation the vulva becomes horizontal as it is pulled cranially over the tuber ischi (Fig. 8-1, C). These anatomic changes predispose the mare to *Pневмомиогния* (windsucking) and *pneumoperitoneum*, ultimately causing urine to pool in the cranial vagina and contaminate the uterus when the cervix is open. Contamination with fecal material adds to the increased risk of infection.

The second physical barrier in the prevention of contamination of the vagina and eventually the uterus is the *vestibulovaginal sphincter*. In a normal mare the vestibulovaginal area remains sealed even when the vulvar labia are parted. Compromised vestibulovaginal sphincter function is suspected when air is sucked into the vagina or if the examiner is able to visualize the vaginal cavity directly after parting the vulvar lips. The vestibulovaginal sphincter may become compromised secondary to rectovaginal tears and other foaling injuries.

The third important anatomic barrier to infection is the cervix. The cervix is open during estrus, late gestation, and in the immediate postpartum period. However, compromised cervical function is observed in some mares, and this entity may remain open during anestrus and even diestrus. The most common cause of cervical incompetence is a cervical lesion consequent to dystocia.

A plan for treatment and prevention of uterine infection should include a plan to reestablish normal barrier function. Surgical procedures such as episiotomy, vestibulovaginoplasty, and rectovaginal tear repair should be considered if indicated.

**Immunity and Uterine Defense.** The concept that mares may be innately "resistant" or "susceptible" to uterine infection was introduced in the 1960s based on the ability of mares to clear experimentally induced or naturally acquired bacterial endometritis. Young mares experimentally inoculated with *S. equi* subsp. *zooepidemicus* clear infection within a few
Fig. 8-1  A, Normal conformation of vulva in the mare. B. Abnormal conformation with parting of vulvar lips at dorsal commissure. C. Abnormal conformation with tilting of vulvar lips.

hours, whereas barren mares inoculated with S. equi subsp. zooepidemicus and P. aeruginosa have a delayed elimination of bacteria. These observations led to further investigation into uterine defense mechanisms to clarify the role of local immunity, neutrophil function, opsonization, and phagocytosis in the prevention and clearance of uterine infection.

**Immunoglobulins.** The predominant immunoglobulins in uterine secretions are IgG and IgA produced within the endometrium. Uterine immunoglobulin concentration does not differ between mares susceptible and resistant to endometritis, suggesting that this is not a major factor in susceptibility to infection. In fact, susceptible mares tend to have slightly higher concentrations of intraterine immunoglobulins than do resistant mares, but susceptible mares are less efficient at opsonizing streptococci during acute infection. 

**Neutrophils.** Neutrophil chemotaxis is induced by bacteria, endotoxin, spermatozoa, semen extenders, and even sterile water and saline. A massive influx of neutrophils into the uterine lumen occurs in both susceptible and resistant mares after local exposure to foreign proteins. In some mares, this stimulation elicits a persistent inflammatory response after breeding that has been termed *persistent mating-induced endometritis* (PMIE). Neutrophils play an important role in this phenomenon, and their effects are exacerbated if bacteria are present.

The events leading to PMIE are initiated by a local reaction to the primary antigen, with local production of inflammatory mediators, especially prostaglandin E₂ (PGE₂), and neutrophil influx. Increased vascular permeability resulting from proinflammatory mediators exacerbates the neutrophil influx and leakage of serum proteins into the uterus, peaking as early as 4 hours after inoculation.

This response is primarily mediated by inflammatory mediators such as leukotriene B₄ (LTB₄) and PGE₂. Mares susceptible to PMIE have a higher expression of proinflammatory cytokines (interleukin-1 beta [IL-1β], IL-6, and tumor necrosis factor alpha [TNF-α]) during estrus and IL-1β and TNF-α during diestrus. It is unclear whether chemotactic responsiveness differs between PMIE-susceptible mares and nonsusceptible mares. A second influx of inflammatory fluid is seen 12 hours later. Susceptible mares are able to eliminate most fluid by 12 hours in response to the effects of oxytocin and prostaglandin on the myometrium. Susceptible mares fail to eliminate fluid, often because of inherent endometrial or myometrial pathology that renders uterine contractions less efficient in uterine clearance.

The phagocytic activity of neutrophils is thought to be enhanced on entry into the uterine cavity. Phagocytic activity is higher in ovarioctomized mares treated with estrogens, suggesting that neutrophil phagocytic activity may be highest during estrus. Phagocytic activity of circulating neutrophils is no different between susceptible and resistant mares; however, phagocytic activity and life span of uterine neutrophils are significantly reduced in susceptible mares. Susceptible mares are more likely to have uterine clearance problems and accumulate more fluid, which may contribute to a reduction in the viability of neutrophils. Differences in neutrophil function between mares susceptible and resistant to endometritis have been demonstrated.

Opsonizing activity in the uterus peaks 8 hours after inoculation with streptococci. Studies using heat-treated uterine fluid suggest that complement is not a primary opsonizing factor in the uterus. Complement is cleaved in uterine fluid, reducing its opsonizing ability within the uterine environment. The uterine environment of endometritis susceptible mares seems to be hostile to complement. In contrast, the opsonizing capacity of serum and degree of serum complement activity does not differ between susceptible

*References 15, 234, 272, 420, 434, 438.*
Fig. 8-2 Persistent mating-induced endometritis (PMIE). A, C, and D, Ultrasenograms of uterus at 6, 12, and 18 hours after insemination, respectively. B, Corpus hemorrhagicum. E and F, Uterus after initiation of oxytocin therapy.

and resistant mares. These observations provide a rationale for the use of serum infusion for the treatment of endometritis.

Physical Clearance of Infection. Physical clearance of pathogens and inflammatory debris from the uterus plays a major role in the prevention of persistent infection and is most effective during estrus. Younger mares are able to eliminate both antigenic (S. equi subsp. zooepidemicus) and nonantigenic (microsphere) particles more quickly than older mares. Mares susceptible to infectious endometritis are unable to eliminate bacteria from the uterus in the immediate postovulatory period.

The effect of uterine pathology on susceptibility to endometritis has been demonstrated. Gross anatomic changes, such as large pendulous uteri, defective myometrial activity, pendulant broad ligaments, and degenerative changes to the vascular and lymphatic drainage of the uterus, are also involved in delayed uterine clearance and the pathogenesis of endometritis. Microscopic alteration of the endometrium (ulceration, degeneration, or lack of cilia) may be involved in failure of mucociliary clearance.

Myometrial contractions are less frequent and of shorter duration and intensity in susceptible mares perhaps because of increased fibrosis or biochemical factors affecting uterine contractility. Uterine contractions are reduced in the presence of nitrous oxide (NO), which is found in high concentration in susceptible mares. The role of prostaglandin secretion in PMIE remains unclear despite numerous investigations, possibly reflecting variation in factors inherent to the endometrium that cannot be easily controlled in experimental studies.

Diagnosis
Uterine infection may be suspected on the basis of a history of infertility, recurrent endometritis, mucopurulent vaginal discharge, predisposing anatomic features, early embryonic loss, or observation of fluid accumulation on examination of the uterus by ultrasonography. Clinical signs may include vaginal discharge. Confirmation of the diagnosis of uterine infection requires endometrial cytology and uterine culture. Uterine biopsy may be helpful in some cases.

Accumulation of large quantities of fluid during estrus or postbreeding is a good indication of mare susceptibility to endometritis (Fig. 8-2). Resistant mares eliminate mating-induced endometritis within 6 to 12 hours after breeding, whereas susceptible mares may retain variable amounts of
fluid for several days. Accumulation of fluid in the uterus is associated with decreased pregnancy rates. All mares should be evaluated 24 hours after breeding and treated if a pocket of fluid remains within the uterine cavity. Mares with a history of infertility or that are known to be susceptible to endometritis should be evaluated or treated as early as 6 hours after breeding.

Several methods for collection of uterine cytology samples have been described. These include the use of double-guarded swabs, uterine cytology brushes, and low-volume uterine flushes. In the authors' opinion, uterine cytology brushes and small-volume uterine flushes provide the best specimens for endometrial cytology (Fig. 8-3). Swabs are often reliable if there is fluid in the uterus or if the swab is wetted with a sterile saline solution before sampling.

Interpretation of uterine cytology samples may be confusing because of the lack of standardized methodology for evaluation. The most common staining technique for uterine cytologic specimens is a rapid Wright-Giemsa stain (Diff-Quik). Interpretation is based on evaluation of the type of cells and organisms observed (Fig. 8-4). Quantitative methods for the interpretation of equine endometrial cytology have been reviewed recently. Diagnosis of endometritis may be based on the number of neutrophils per number of

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**Fig. 8-3** Top, Single-guarded uterine swab with "pop-out" cap that can be used to collect material of endometrial cytology. Middle, Double-guarded swab for endometrial culture and cytology. Bottom, Double-guarded endometrial brush for cytology.

**Fig. 8-4** Endometrial cytology stained with Diff-Quik. A, Normal endometrial cells. B, Slight inflammatory reaction. C, Mating-induced inflammation (note sperm cells). D, Severe infectious inflammation.
high-power microscopic fields, as a ratio of neutrophils to epithelial cells, or as a percentage of all cells. Endometrial cytology may provide an important clue to fungal infection. Cytology may be negative if infection is recent.109

Endometrial swabs should always be submitted for anaerobic and aerobic bacterial as well as fungal culture. Blood agar plating may be used in the initial fungal culture, but specific culture techniques are required for more precise diagnosis.109

Endometrial biopsy is an important and highly accurate method for the diagnosis of uterine inflammation. Special staining techniques, such as Gomori’s methamine silver, are particularly helpful for the diagnosis of fungoidal endometritis.110 Interpretation of diagnostic results may be challenging at times. Bacteriologic culture and cytology from endometrial biopsy are most accurate (high sensitivity and positive predictive value) for diagnosis of endometritis. The sensitivity of bacteriologic culture from endometrial biopsy is 82%; diagnosis based on cytologic and bacteriologic examination of endometrial swabs has a sensitivity of 77% and 34%, respectively.270

Therapy

Treatment of equine endometritis may include local or systemic antimicrobial therapy, uterine lavage, plasma infusions, and colostroven. Most treatment recommendations are made on the basis of clinical experience, with limited evidence for comparative efficacy within the veterinary literature. The authors most frequently recommend treatment of uterine infections with uterine lavage to remove debris and other products of inflammation that may reduce antimicrobial activity, followed by antimicrobial therapy for 5 to 7 days.

Uterine Lavage. The goal of uterine lavage is to “clean” the uterine cavity of organisms, dead neutrophils, cell debris, and products of inflammation before local antimicrobial therapy.401,402 Uterine lavage may enhance uterine contractions and clearance as a result of transient irritation of the endometrium.488 Uterine lavage is performed using warmed, balanced electrolyte solution (e.g., lactated Ringer’s, physiologic saline) with or without added antiseptics. A new solution specifically formulated for flushing of the equine uterine (Aquavite Uterine Flush, AB Technology, Pullman, Wash) is adjusted to appropriate pH and osmotic pressure and contains surfactants to aid in the removal of organisms and debris. Uterine lavage is preferably performed using a large Foley catheter in the same manner as for embryo collection (Table 8-1).

The addition of antiseptics such as povidone-iodine or chlorhexidine to uterine lavage fluid is occasionally recommended for the treatment of equine endometritis. However, there is some concern about the effect of these antiseptics on neutrophil function. At high concentrations, antiseptics may cause severe inflammation (necrosis) and irreversible damage to the endometrium, with evidence of discomfort at the time of infusion.401 Povidone-iodine solution may be used at a concentration of 0.05% (5 mL of 10% povidone iodine solution in 1 L of balanced salt solution) to facilitate elimination of bacterial infection. Adverse reactions are observed in mares after infusion with solution at a concentration of 1% or more.57 Uterine lavage with 0.05% solution of povidone-iodine solution 4 hours after breeding did not adversely affect pregnancy rates.59 Use of chlorhexidine diacetate is contraindicated in mares.17 Chlorhexidine gluconate may cause vulvar inflammation and vaginal straining at concentrations as low as 0.5% and endometrial inflammation at concentrations of 0.25%.186

Lavage with EDTA-TRIS (1.2 g NaEDTA and 6.05 g TRIS/L of H2O, titrated to pH 8.0 with glacial acetic acid) 3 hours before infusion of antibiotic has been recommended for treatment of persistent uterine infection with Pseudomonas spp. Ethylenediaminetetraacetic acid (EDTA) is thought to bind Ca++ in bacterial cell walls, making cell walls permeable to antibiotics and bacteria more susceptible to bactericidal activity of antibiotics.442

Antimicrobials. The aim of local uterine infusion of antimicrobials is specifically to eliminate the causative organism(s).223,228 (Table 8-2). The choice of antibiotic is dictated by results of endometrial culture and sensitivity, predicted antimicrobial efficacy in the uterine environment, and consideration of possible adverse uterine effects. Nonbuffered or precipitating solutions should be avoided. Streptococcus equi subsp. zooepidemicus and E. coli, two of the most common bacterial causes of endometritis, are sensitive in vitro to amikacin and gentamicin.390 The selection of antimicrobial for intrauterine infusion should take into account the pH and solubility of the drugs as well as the solution used for infusion. Some antibiotics, such as cefoxitin, will lose most of their activity if diluted in a saline solution.32 The volume of solution should be sufficient to treat the entire uterine cavity, usually between 50 and 120 mL. Aqueous solutions of sodium benzylpenicillin, neomycin, polymyxin, and furadonin are generally safe and useful for treatment of horses with acute endometritis.320,322 Aqueous solutions of penicillin, ampicillin, carbenicillin, ticarcillin, ticarcillin, and clavulanic acid, lanamycin, and neomycin have also been recommended. Low-pH antimicrobials such as gentamicin and amikacin should be buffered with an equal volume of 7.5% sodium bicarbonate before infusion.17,38,365

Uterine infusion of enrofloxacin was an effective treatment for endometritis in 80% of 17 mares.141 Antimicrobial concentrations in endometrial tissues were greater than the minimum inhibitory concentration (MIC) for most bacterial pathogens for up to 24 hours after intrauterine infusion of enrofloxacin at a dosage of 2.5 mg/kg.143 Moderate endometrial inflammation was observed 24 hours after infusion but resolved progressively within 2 weeks.

Treatment of fungal endometritis requires large-volume uterine flushes followed by intrauterine therapy with antifungal drugs for 7 to 10 days. Treatment for a longer duration may be required for some mares. The drugs most often used are polyene antifungal agents (e.g., amphotericin B, nystatin, natamycin), which alter membrane permeability, and imidazole derivatives (e.g., clotrimazole, econazole, ketoconazole, fluconazole, itraconazole), which interfere with nutrient exchange across the fungal cell wall and cell membrane.400 The prognosis for fertility after treatment of fungal endometritis remains generally poor because of the histologic changes resulting from the chronic inflammation.444

Lufenuron, a benzoylphenyl urea derivative and inhibitor of chitin synthesis, used for flea control in dogs and cats, has been recommended for treatment of mares with Candida parapsilosis, Candida tropicalis, and Aspergillus fumigatus uterine infections. The inhibition of fungal growth is thought to be caused by disruption of the chitin-rich cell wall that surrounds these organisms. Intrauterine lavage is performed with lufenuron (540 mg) suspended in 60 mL of sterile saline solution.174

Systemic antimicrobials (e.g., amikacin,36 gentamicin,207 ticarcillin,360 procaine penicillin G, ampicillin, potentiated sulphonamides, cefoxitin sodium121) have been used for the treatment of endometritis, but little is known about drug concentrations obtained within the endometrium or treatment efficacy for systemic administration. Systemic treatment
### Guidelines for Uterine Flushing and High-Volume Uterine Lavage

<table>
<thead>
<tr>
<th>UTERINE FLUSHING</th>
<th>HIGH-VOLUME LAVAGE (POSTPARTUM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Partial or total placental retention</td>
</tr>
<tr>
<td>Chronic endometritis, pyometra</td>
<td>Metritis</td>
</tr>
<tr>
<td>Endometritis</td>
<td>After obstetric manipulation/fetotomy</td>
</tr>
<tr>
<td>Persistent mating-induced endometritis</td>
<td>After uterine prolapse</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Equipment</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Silicone Foley long catheter (28 or 34 French, 100-mL cuff)</td>
<td>Stomach tube; make sure that tube has several side openings (1-1.5 cm in diameter).</td>
</tr>
<tr>
<td>Flushing bag (2.5 L)</td>
<td>Bucket</td>
</tr>
<tr>
<td>Stomach pump</td>
<td></td>
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<table>
<thead>
<tr>
<th><strong>Mare Preparation</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation if needed.</td>
<td>Often needed.</td>
</tr>
<tr>
<td>Wrap tail in plastic sleeve.</td>
<td>Wrap tail in plastic sleeve.</td>
</tr>
<tr>
<td>Palpation per rectum to evacuate feces.</td>
<td>Palpation per rectum to evacuate feces.</td>
</tr>
<tr>
<td>Clean perineal area and vulva.</td>
<td>Clean perineal area and vulva.</td>
</tr>
<tr>
<td>Place catheter using sterile sleeve and lubricate.</td>
<td>Place nasogastric tube deep into uterine cavity (within chorionicallantoic cavity if placenta is retained).</td>
</tr>
<tr>
<td>Insert catheter into cervix and inflate balloon, making sure it is snug against anterior cervical os.</td>
<td>Protect orifices of tube by cuffing hand around it.</td>
</tr>
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<table>
<thead>
<tr>
<th><strong>Fluid Choice</strong></th>
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</thead>
<tbody>
<tr>
<td>Warm saline (least preferred)</td>
<td>Warm saline</td>
</tr>
<tr>
<td>Warm lactated Ringer's solution (LRS)</td>
<td>Warm distilled water + 34 g of table salt per liter</td>
</tr>
<tr>
<td>Proprietary fluid (e.g., Equine Uterine Flush lavage solution)</td>
<td>Warm LRS (may be too expensive)</td>
</tr>
<tr>
<td></td>
<td>Warm tap water with 5 mL of 10% povidone-iodine solution and 8.5 g of table salt per liter</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th><strong>Fluid Delivery and Monitoring</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravity using flushing bags</td>
<td>Pumped directly into uterine cavity</td>
</tr>
<tr>
<td>Volume varies from 500 mL to 2 L</td>
<td>Up to 15 L (depends on size of uterus)</td>
</tr>
<tr>
<td>Palpate transrectally to make sure that both uterine horns are sufficiently distended before emptying.</td>
<td>Flush twice a day if mare retained placenta or mare is sick.</td>
</tr>
<tr>
<td>Repeat flushing until return is clear.</td>
<td>Repeat flushing daily as needed (until placenta is passed if retained).</td>
</tr>
<tr>
<td>Monitor fluid retained by ultrasonography or measuring fluid collected.</td>
<td>Monitor by transabdominal ultrasound.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Evacuation Help</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Before and after flushing: oxytocin (10-20 IU intramuscularly)</td>
<td>Retained placenta (20 IU oxytocin every 4 hours in first 12 hours)</td>
</tr>
<tr>
<td>Postbreeding flushing should be started no earlier than 4 hours after breeding.</td>
<td>Exercise mare.</td>
</tr>
</tbody>
</table>

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has the advantage of preventing inadvertent recontamination of the uterus and repeated trauma to the vagina and cervix in mares. Ciprofloxacin (2.5 g/day) and probenecid (1 g/day) were recommended for systemic treatment of *Pseudomonas* infection. Although an oral dose of ciprofloxacin of 0.5 mg/kg has been used by some practitioners, pharmacokinetic studies have shown that bioavailability of the drug is not very high. Fluoroquinolone antibiotics such as enrofloxacin and ciprofloxacin reach therapeutic concentrations in endometrial tissue after intravenous (IV) administration. Endometrial concentrations of metronidazole were very low after systemic treatment for 4 days.

**Mannose Infusion.** Development of resistance to multiple antibiotics has become an important issue in practice. The efficacy of specific sugar solutions in preventing bacterial adhesion to the endometrium has been investigated in vitro. Mannose solution significantly reduced adhesion of *E. coli, P. aeruginosa,*
Table 8-2

**Antimicrobials for Treatment of Endometritis in Mares**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE*</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-Positive Bacterial Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin sodium of potassium salt</td>
<td>5 million units (U)</td>
<td>Very effective for streptococci; economical.</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>1-3 g</td>
<td>Can be very irritating; use at high dilutions; sodium salt precipitates on endometrium that remains in uterus for prolonged period.</td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>2-5 g</td>
<td>Reserved for persistent <em>Pseudomonas</em> (synergistic efficacy with aminoglycosides); usually given on alternate days with aminoglycosides; slightly irritating.</td>
</tr>
<tr>
<td><strong>Gram-Negative Bacterial Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin sulfate</td>
<td>500-1000 mg</td>
<td>Highly effective; generally nonirritating when mixed with an equal volume of NaHCO₃ and diluted in saline.</td>
</tr>
<tr>
<td>Amikacin sulfate</td>
<td>2 g</td>
<td>Use for <em>Pseudomonas</em>, <em>Klebsiella</em>, and persistent gram-negative infections.</td>
</tr>
<tr>
<td>Kanamycin sulfate</td>
<td>1 g</td>
<td>Toxic to spermatozoa; do not use close to breeding.</td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>1 million U</td>
<td>Particularly effective against <em>Pseudomonas</em>.</td>
</tr>
<tr>
<td>Neomycin sulfate</td>
<td>3-4 g</td>
<td>Use for sensitive <em>E. coli</em>; can be irritating; do not use near time of breeding.</td>
</tr>
<tr>
<td><strong>Gram-Positive and Gram-Negative Bacterial Infections (broad spectrum)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephazolin sodium</td>
<td>1 g</td>
<td>Use for <em>Pseudomonas</em>; do not use for <em>Klebsiella</em>.</td>
</tr>
<tr>
<td>Ticarcillin</td>
<td>1-3 g</td>
<td>Once daily either intramuscularly or by intrauterine infusion.</td>
</tr>
<tr>
<td>Ceftriaxone sodium</td>
<td>1 g</td>
<td></td>
</tr>
<tr>
<td><strong>Fungal (Yeast) Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nystatin</td>
<td>0.5-2.5 million U</td>
<td>Primarily for yeast (e.g., <em>Candida albicans</em>) in the growing phase; insoluble, suspend in 100-250 mL sterile water and vigorously mix immediately before infusion.</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>100-200 mg</td>
<td>For infections with <em>Aspergillus</em>, <em>Candida</em>, <em>Mucor</em>, or <em>Histoplasma</em>; dilute in 100-250 mL sterile water, a relatively insoluble suspension.</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>500-700 mg</td>
<td>For yeast infections (<em>Candida</em> spp.); crushed tablets mixed with 40 mL sterile water. For <em>Candida</em> spp. infections.</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>100 mg</td>
<td>Most efficacious for yeast infections (<em>Candida</em> spp.) and some resistant fungal infections; infuse once daily for up to 10 days; dilute in 40-60 mL sterile saline before infusion.</td>
</tr>
<tr>
<td>Micronazole</td>
<td>200 mg</td>
<td></td>
</tr>
</tbody>
</table>

*All doses are for intrauterine infusion unless otherwise indicated.

and *S. equi* subsp. *zooepidemicus* to the endometrium. Inhibition of adhesion of *E. coli* was possible with a concentration as low as 0.4 mg/mL, whereas inhibition of *P. aeruginosa* adhesion required a concentration of 75 mg/mL; a concentration of 3.13 to 25 mg/mL caused significant inhibition of *S. equi* subsp. *zooepidemicus* adhesion. N-acetyl-D-galactosamine inhibited adhesion of *E. coli* and *P. aeruginosa* only. If these results are confirmed in vivo, lavage with mannose solution might be a good adjunct or alternative to antibiotic therapy of endometritis.¹⁹⁹

Plasma Infusion. Intrauterine infusion of autogenous plasma (100 mL) anticoagulated with heparin or sodium citrate is suggested to enhance neutrophil function in endometritis-susceptible mares.¹⁴¹,¹₈ Some clinical trials showed significant benefit with this approach,¹¹,¹₄,¹₂,²² whereas others were unable to show enhanced bactericidal activity after plasma infusion.¹³,¹₁,¹₁¹ Infusion of plasma with leukocytes may improve pregnancy rate compared with infusion of plasma alone.²⁴ The discrepancies between results may be caused by several factors, including the strain of bacteria and the amount and type of antibodies present in plasma. Infusion of serum from horses hyperimmunized against specific strains of *S. equi* subsp. *zooepidemicus* is reportedly more effective in increasing phagocytosis than the infusion of nonimmune serum.⁴²¹

**Colostrum Infusion.** The goal of colostrum infusion is to enhance the local uterine defense mechanisms by increasing the concentration of immunoglobulins in the uterine cavity. This treatment is reported to be successful in uncontrolled studies.¹⁰⁹,¹⁶³

**Prevention.** Prevention of uterine infection is accomplished by decreasing the likelihood of contamination and by early recognition and treatment of PMIE. Contamination of the uterus can be prevented by correcting vulvar conformation and observing strict hygiene during breeding and genital manipulation. Susceptible mares should be monitored before breeding and bred using minimum-contamination breeding technique.¹⁰⁹ The purpose of this monitoring is to reduce the chance of contamination of the uterus by bacteria and to eliminate the products of the inflammatory reaction caused by semen.

The primary mechanism for prevention of fluid accumulation in the uterus is contraction of the uterine musculature in
response to oxytocin. Oxytocin release is observed in mares after mating, teasing, genital manipulation, and infusion of fluid into the uterine cavity.11,129,130,131 Oxytocin injection improves uterine defense by promoting uterine fluid evacuation,11,129,127,130 Administration of 20 IU of oxytocin intramuscularly (IM) induces uterine contraction for up to 90 minutes.129 Oxytocin administration to mares susceptible to PMIE at 4 hours after breeding aids in the elimination of excess fluid and improves fertility.133,134 The standard dose for an average mare is 10 IU intravenously (IV) or 20 to 25 IU IM.135 Oxytocin therapy may be repeated every 6 hours for 24 to 48 hours after breeding.129,136,137 A 7% increase in pregnancy rate is reported with a single injection of oxytocin (25 IU IM) within 72 hours of breeding.130 Oxytocin does not interfere with ovulation or gamete transport if administered no earlier than 4 hours after breeding.135,137

Prebreeding and postbreeding uterine lavage may be indicated in mares that tend to accumulate a substantial amount of fluid during estrus.57,59,60,67

Prostaglandin F2α (PGF2α, 5-10 mg IM) or its analog, cloprostenol (250 µg IM) is recommended for the treatment of mares with PMIE because of their eclampsic properties.55,220,278,296 Cloprostenol induces weaker but more sustained uterine contractions than oxytocin and is helpful when excessive uterine edema is present.93 Repeated administration of cloprostenol should be avoided because it has been associated with transient reduction of circulating progesterone levels during diestrus.55,278

Prophylactic in utero administration of antibiotics to PMIE-susceptible mare after breeding has been suggested. A combination of oxytocin treatment and intratubular infusion of broad-spectrum antibiotics increases pregnancy rates in susceptible mares.129 However, such an approach may pose some risk of development of antimicrobial resistance.

**Postpartum Metritis**

Postpartum uterine infections are of particular importance because of their severity and effect on the general health of the mare. Septic postpartum metritis is often a result of non-lymphatic manipulation during foaling, obstetric manipulations, and retained placenta. Mares with postpartum metritis may present with severe systemic complications of endotoxemia and leukocytosis. Treatment consisting of daily large-volumne uterine flushes, systemic antimicrobial therapy, and appropriate therapy for endotoxemia and dehydration should be immediately initiated in affected mares.12,138,290

**Other Infections of Nonpregnant Mares**

Infectious *eovaginitis* and *cervicitis* may occur as part of the uterine infection process or as a result of local irritation or laceration. Vaginal injuries secondary to breeding or parturition may lead to abscess formation and adhesions.33,101,261,322,343

Infectious inflammation of the ovaries (*oophoritis*) with abscession and peritoneal adhesions may occur after abdominal surgery or peritonitis (Fig. 8-5). Oophoritis may also occur as a consequence of repeated transvaginal ultrasound-guided follicular aspiration.57 Affected mares may present with abdominal pain, anorexia, fever of unknown origin, and weight loss. Transrectal ultrasonography may help in the diagnosis of these infections. Confirmation of the diagnosis and evaluation of the extent of the lesions may be achieved by laparoscopy. Ovariotomy is usually required for treatment of this condition.103,311

Salpingitis is rare in the mare but may result from ascending infection from the uterus after parturition.104 Salpingitis has been described in mares with contagious equine metritis (CEM)1 (see Chapter 41). Bilateral salpingitis results in sterility.

**INFECTIONOUS CAUSES OF ABORTION**

Causes of equine abortion in several countries have been extensively reviewed (United Kingdom,44,45,46 United States,193,197,198,213,214,215,216,240,277 New Zealand and Australia,22 France,219,220,221 Egypt,221,222 India221). One third to half of all equine abortions are estimated to be the result of infection.221 Numerous organisms have been associated with infectious abortion, including viruses, bacteria, and fungi. The prevalence of each organism differs geographically. In England, equine herpes virus abortion predominates.221 In France, 79% of infectious abortions are caused by bacteria and 21% by viruses.44

**Bacterial Abortions and Placentitis**

Placentitis is a significant cause of equine late-term abortion, premature delivery, and neonatal death. It is implicated as a cause of abortion in as many as 50% of all mares that abort.1 Peritonitis is diagnosed in approximately 150 cases of fetal loss each year in Kentucky (approximately 30% of all submitted fetuses).445 It may be caused by a variety of bacterial, fungal, viral, and protozoal organisms.304,305,306 Bacterial placentitis is most common; fungal placentalitis is reported in fewer than 10% of horses with placentitis.177,178,359

Placentitis is generally classified as three types: ascending, diffuse, and focal miosis.445 With the exception of *Lactobacillus* spp., most bacterial or mycotic placentalitis of mares is the result of an ascending infection.246,374

**Ascendam Placentitis**

Ascending placentalitis is the most common type of placentalitis in horses.404,316,445 Bacteria isolated from the placenta are comparable to those isolated from the uterus of mares with endometritis.173,311,445 *Streptococcus equis* subsp. *zooepidemicus*, *E. coli*, *Pseudomonas aeruginosa*, Enterobacter spp. and *Klebsiella pneumoniae* are the most frequent isolates.39,412,413,414

In a retrospective study of 954 cases of equine abortion, placentalitis was recognized in 24.7% of all submissions.178 A bacterial or fungal organism was isolated in 68.8% of all cases and 57.4% of cases yielded bacteria both from the placenta and the fetal organs. The most common

CHAPTER 8 • Reproductive Tract Infections

Fig. 8-6 Placenta showing severe ascendant placentitis. A: Allantoic surface. B: Chorionic surface.

microorganisms isolated include S. equi subsp. zooepidemicus, E. coli, Leptospira spp., nocardioform Actinomyces, P. aeruginosa, Streptococcus equisimilis, Enterobacter agglomerans, K. pneumoniae,α-hemolytic streptococci, Staphylococcus aureus, and Actinobacillus spp. Other bacteria included Proteus mirabilis, Citrobacter diversus, and fecal and environmental contaminants. Abortions resulting from hematogenous infection with Actinobacillus equuli and Corynebacterium pseudotuberculosis have been reported. There is a wide geographic variation in the frequency of specific bacterial and fungal isolates associated with equine placentitis and abortion. A high incidence of fungal placentalitis is reported in England. The incidence of mycotic placentitis varies from region to region because of climate and other environmental factors. Emphysematous placentalitis caused by clostridial infection was one of the top four causes of bacterial abortion in an early study. There are numerous reports of Enterobacter agglomerans placentalitis in horses.*

The importance of anaerobic bacteria, Mycoplasma spp., Chlamydia, and rickettsial organisms in equine placentitis is uncertain.

Except for placentalis caused by Leptospira spp., the nocardioform actinomycetes, most equine placentitis occurs in two forms: (1) acute diffuse placentalitis with infiltration of neutrophils in the intervillosus spaces or (2) focal necrosis of the chorionic villi. Placentitis from abortions before midgestation are chronic, focal, or focally extensive at the cervical area and characterized by necrosis of chorionic villi, presence of eosinophilic material on the chorion, and infiltration of mononuclear inflammatory cells in the intervillous spaces, stroma of villi, chorion, allantois, and vascular layer. Lesions may be either acute or chronic.

Bacterial placentitis most often induces abortion between 6 and 9 months of gestation. Placentitis resulting from E. coli tends to cause later abortion and more stillbirths. Placentitis from S. equi subsp. zooepidemicus tends to be acute and focal or diffuse. In acute bacterial placentitis the fetus is generally expelled before 8 months of pregnancy. Acute or diffuse placentitis may not be easy to recognize on gross examination of the placenta. Histologic evaluation of the allantochorion may reveal bacterial emboli with necrosis of chorionic villi or infiltration of neutrophils in the intervillous space. Chronic or focal placentitis typically results in birth of premature or weak foals or late-term abortions. Lesions tend to be located at the cervical star, where discoloration and thickening are observed (Fig. 8-6).

Escherichia coli placentalis is usually acute in mares that abort before 7 months of gestation but is more likely to be chronic and focally extensive, involving the cervical star in mares that abort after 9 months of gestation. Placentomal edema and the presence of a white mucoid exudate on the chorion and fetal surface are common findings after abortion caused by E. coli placentalitis (Fig. 8-7).

Pseudomonas aeruginosa placentalis causes abortion between 6 and 9 months of gestation. It is usually acute and may be either focal or diffuse with a thickened and discolored cervical star. Histologically, the primary abnormality is ulceration of the chorion with infiltration of neutrophils in the villi, chorionic stroma, and vascular layer.

Lesions caused by infection with Streptococcus equisimilis are similar to those of S. equi subsp. zooepidemicus. Abortion occurs between 6 and 8 months of pregnancy.

Gross and histologic features of mycotic placentitis were described in detail by Hong et al. Mycotic placentitis and abortion are most likely to occur in the late gestational period. Fungal organisms associated with equine abortion include Aspergillus spp., Candida spp., mucoraceous fungi, Histoplasma capsulatum, and Cryptococcus neoformans. Focally extensive placentitis is usually observed at the cervical star and adjacent area as a thick, leathery area. Histologically, except for histoplasmosis and candidiasis, the fungi induce a chronic, extensive placentitis characterized by extensive necrosis of the chorionic villi, neovascularization in the chorionic stroma, infiltration of neutrophils, mononuclear cells, or

References 101, 133, 134, 152, 210, 229, 261, 307, 322, 386.
mixed inflammatory cells in the villi and chorionic stroma, and presence of fungal hyphae in the necrotic debris. Adenomatous hyperplasia with or without squamous metaplasia of the chorionic epithelium are frequently observed.\textsuperscript{178} 

*Histoplasma capsulatum* caused a multifocal granulomatous placentalitis and abortion in one mare in the seventh month of gestation and three mares in the tenth month. Four newborn foals died from severe granulomatous pneumonia within a few days of birth, and a weanling Thoroughbred developed granulomatous pneumonia and lymphadenitis at 5 months of age.\textsuperscript{130}

With *Candida* spp. infection, placentalitis is generally diffuse, necrotizing, and proliferative with extracellular, yeastlike spores in the chorionic epithelium. Chronic, focally extensive placentalitis is most common, with expulsion of foals late in gestation.\textsuperscript{178}

**Hematogenous Multifocal or Diffuse Placentalitis**

Multifocal or diffuse placentalitis is less common than acute, focal placentalitis and is usually a result of hematogenous spread of microorganisms to the uterus. This occurs with leptospirosis, salmonellosis, histoplasmosis, and candidiasis. A special focal mucoid form of placentalitis, *nocardioid form placentalitis*, is emerging as common in several U.S. regions.\textsuperscript{178}

**Leptospira spp. Placentalitis**

*Leptospira* spp. placentalitis is characterized by diffuse lesions secondary to hematogenous spread (see Chapter 34). Leptospirosis as a cause of placentalitis seems to be more frequently diagnosed in Kentucky\textsuperscript{135,118,178,448} than in other regions of the world,\textsuperscript{131,132,133} probably because of specific regional characteristics and the difficulty in isolating or detecting the pathogen. An outbreak of leptospiral abortions has been described on a Thoroughbred farm in California after a flood.\textsuperscript{138}

Most leptospiral abortions occur between 6 and 9 months of gestation. The affected placenta is thick, heavy, edematous, hemorrhagic, and occasionally covered with a brown mucoid material on the chorionic surface. Occasionally the affected placenta lacks detectable gross lesions. Green discoloration or cystic adenomatous hyperplasia of the allantois is observed in some cases. Fetal antibody against *Leptospira* spp. may be detected in foals by microagglutination test.\textsuperscript{178} Spirochetes are present in large number in the placental sections. Several species of leptospire have been isolated from aborted equine fetuses (e.g., *L. pomona*, *L. grippotyphosa*, *L. interrogans* serovars bratislava and pomona type kennevicki, serovar harbo type hardjoprajitno).\textsuperscript{130} High-titer agglutinating antibody (>1:6400) may be observed in mares, but interpretation of serologic tests remain difficult without confirmation of infection by culture and isolation. Antibiotic treatment for 5 days (penicillin G) has been reported to help prevent abortion during an outbreak.\textsuperscript{138}

**Nocardiform Placentalitis**

Nocardiform placentalitis is a distinct type of equine placentalitis first described in the United States in the late 1980s. Over the past 15 years an increasing number of cases of equine nocardiform placentalitis have been diagnosed in Kentucky.\textsuperscript{137,153,177,449}

Nocardiform actinomycetes induce a chronic placentalitis that results in late-term abortion, stillbirth, or premature birth. The lesion is an extensive and severe exudative, mucopurulent, and necrotizing placentalitis centered on the junction of the placental body and horns rather than the cervical pole.\textsuperscript{178} Infection of the placenta is generally thought to be a sequela of the hematogenous spread of the microorganisms from a primary port of entry.\textsuperscript{179,443} The fetus is often severely underdeveloped, with no remarkable gross or histologic lesions. The placental lesion is focally extensive (15-30 cm) and frequently located at the base of the uterine horns or at the junction between the body and horns of the placenta. The affected area is thickened, and its chorionic surface is covered with brown, necrotic, mucopurulent exudate and dotted with white or yellow granular structures. Underneath this mucoid material, the chorionic surface is reddish white, mottled, and roughened. Villous necrosis and adenomatous hyperplasia of the allantoic epithelium and hyperplasia with or without squamous metaplasia of the chorionic epithelium are frequently observed.\textsuperscript{175,178}

Various groups of gram-positive, filamentous, branching bacteria have been implicated as etiologic agents in mares with nocardiform placentalitis, including *Nocardia* spp., *Rhodococcus rubodigerotus*, and *Amycolatopsis* spp.\textsuperscript{40,124,177,443} However, most severe infections of this type are caused by the actinomycete *Crostella equi*.\textsuperscript{118}

A nocardiform isolate from equine placental lesions in the United States was determined by phylogenetic analysis to be closely related to *Crostella cryophilophila*, a member of the genus *Crostella* described in 2001.\textsuperscript{417} Subsequent polyphasic identification found that the isolates represent a new species of *Crostella*, for which the name *C. equi* was proposed.\textsuperscript{118} Polyphasic taxonomic studies on actinomycete strains isolated from equine placentas from horses in Kentucky and southern United States indicate that the isolates are members of the genus *Amycolatopsis*. It is proposed that these strains be classified as three novel species of the genus *Amycolatopsis* and named *Amycolatopsis kentuckiensis*, *Amycolatopsis lexingtonensis*, and *Amycolatopsis prairiensis*.\textsuperscript{413}

During the 2002 and 2003 foaling seasons, *Cellulosimicrobium (Cellulomicrobium) cellulans* (formerly *Oryckobacterium xanthophytophobium*) was isolated from fetal tissues or placentas from cases of equine abortion, premature birth, and term pregnancies in Kentucky. Significant pathologic findings included chronic placentalitis and pyogranulomatous pneumonia. In addition, microscopic and macroscopic alterations in the allantochorion from four of seven cases of placentalitis were similar to those caused by *Crostella equi* and other nocardiform bacteria.\textsuperscript{449}

**Pathogenesis and Diagnosis of Placentalitis**

Because of the importance of placentalitis in the pathogenesis of bacterial abortion, researchers at the University of Florida developed models for study of ascendant placentalitis to gain insight into the pathogenesis of disease and provide a method to optimize diagnostic and treatment recommendations.\textsuperscript{225,226,255,262,268} Bacterial infection of the chorioallantois induces an increase in expression of proinflammatory cytokines (IL-6 and IL-8) in placental tissue. Subsequent release of PGE\textsubscript{2} and PGF\textsubscript{2α} into the allantoic fluid leads to premature delivery.\textsuperscript{223,228,245,249} The premature delivery of the fetus is most likely caused by acceleration of the fetal maturation process induced by changes in placental function. The resulting endocrine changes lead to increased uterine contractures and intrauterine pressure, causing dilation and induction of labor. A premature increase in maternal plasma progesterones may be an indication of accelerated fetal maturation or fetal stress. Foals may survive if they are near term (>305 days).\textsuperscript{225,288,287}

Clinically, placentalitis is suspected in mares with premature udder development or lactation and vaginal discharge. However, most mares with placentalitis do not show any outward signs of infection.\textsuperscript{225,445}
Placentitis may be diagnosed by transrectal and transabdominal ultrasound examination. Measurement of the combined thickness of the uterus and placenta (CTUP) by transrectal ultrasonography is particularly helpful in the diagnosis and monitoring of ascendant placentitis. The measurements are obtained 2.5 to 5 cm cranial to the cervical-placental junction using a 5- or 7.5-MHz linear transducer. The area measured should be on the ventral aspect of the uterine body just above the middle branch of the uterine artery (Fig. 8-8). Normal CTUP for light horses is less than 8 mm between 271 and 300 days of gestation, less than 10 mm between 301 and 330 days of gestation, and less than 12 mm from 330 days of gestation to term. These measurements are slightly higher in Warmblood and Draft horses and lower in ponies. Placental dysfunction has been associated with CTUP of greater than 15 mm in horses and greater than 12 mm in ponies after 310 days of gestation.

During ultrasonographic evaluation, other features of infectious placentitis may be identified. These include placental separation and accumulation of purulent hyperechoic heterogeneous fluid between the endometrium and the placenta and increased echogenicity of fetal fluid. Increased echogenicity of fetal fluid is caused by meconium, inflammatory debris, and hemorrhage.

Endocrinologic evaluation may also help in determining placental pathology and risk for abortion. The most important hormones evaluated are progestins, which are relatively stable during a normal pregnancy. A change in serum progestin concentration (increase or decrease) by more than 50% or a value that is constantly out of reference laboratory range signals placental pathology or fetal stress.

After abortion or premature birth, most cases of chronic placentitis are easily recognized on gross examination, but microscopic histologic examination is important to determine the presence of acute placentitis (Fig. 8-9). In acute placentitis the infection may be contained within the placenta, and the fetus is usually sterile. Some foals may be born alive with neonatal septicemia.

Treatment of Placentitis
The ultimate goal in treatment of equine placentitis is to maintain gestation for as long as possible to enhance foal viability. Treatment recommendations include tocolytic drugs to reduce uterine contraction, antiinflammatory drugs to block the production of cytokines and prostaglandins, and antimicrobial therapy to control growth of bacteria.

Antimicrobial therapy should be based on culture and sensitivity patterns of bacteria isolated from vaginal discharge or cervical swabs. Pharmacologic studies have shown that potentiated sulfonamides, gentamicin, potassium penicillin, and ceftiofur can cross the placenta and reach MICs sufficient to control S. equi subsp. zooepidemicus for penicillin G (22,000 IU/kg every 6 hours [q6h] IV) and E. coli or K. pneumoniae for gentamicin (6 mg/kg q24h IV).

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Fig. 8-8 Ultrasoundogram showing area of measurement of combined uteroplacental thickness. A, Normal. B, Slightly thickened.
Trimethoprim-sulfamethoxazole (30 mg/kg q12h orally [PO]) presents an excellent choice for the treatment of placentitis caused by susceptible organisms because of its good uterine penetration. 

Antiinflammatory therapy is recommended for mares with placentitis to diminish the effects of proinflammatory cytokines and prostaglandins. The most frequently used medications are nonsteroidal antiinflammatory drugs (NSAIDs) such as flunixin meglumine (0.5-1.1 mg/kg twice daily PO or IV). Pentoxifylline has also been used to block the effects of endotoxin (8.5 mg/kg q12h), as discussed in Chapter 37. 

Induction of uterine quiescence is obtained by administration of progestins to interfere with upregulation of prostaglandin and oxytocin and reduce myometrial activity. The oral synthetic progestin, altrenogest, is used at the label (0.044 mg/kg PO q12-24h) or two times the label (0.088 mg/kg PO q24h) dose. Alternatively, progesterone in oil can be administered at 300 mg IM q24h. 

**Diagnostic Approach for Equine Abortion**

A precise diagnosis should be pursued in any case of abortion, premature birth, or birth of a compromised or septicemic foal. Diagnosis of the cause of abortion or in utero infection can be made in most cases with proper history, clinical observations, and collection and submission of all required samples. In one study, only 7.7% of equine abortions, stillbirths, or neonatal foal loss remained undiagnosed when the fetus, placenta, and serum from the dam were submitted. The undiagnosed cases were associated with extensive damage to tissues by scavengers, as well as absence of placenta or early abortion. Samples from the dam should include serum and vaginal or uterine swab.

The importance of placental examination in the diagnosis of abortion, stillbirths, or premature births cannot be overemphasized. Normal and abnormal characteristics of the placenta and descriptions of proper examination of the equine placenta and its pathology have been described elsewhere. Clients should be instructed to obtain the placenta for proper examination as soon as possible after each foaling. Weight of the placenta should be determined; normal placental weight is approximately 11% of the foal weight. The placenta is usually expelled inside out with the allantoic surface exposed (see Fig. 8-9). It should be gently cleaned of any bedding material, grass, or dirt with cold water, then laid out flat and all surfaces examined. The umbilical cord should be of normal length. The amniotic sac and chorionic surface (red velvety surface) is examined from the cervical star to the tips.
of the horns on all sides. Samples should be obtained from areas of grossly normal and abnormal placenta and submitted for histopathology, immunohistochemistry, and culture. Some morphologic characteristics of the placenta may allow immediate exclusion of infectious causes of abortion (e.g., umbilical cord torsion, body pregnancy, twin pregnancies). Chronic infectious inflammation is generally easy to detect because of the thick, leathy nature of the placenta. Lesions of placenta appear tan or brown and thick and may have overlying tenacious, fibrinonecrotic exudate. Cytologic evaluation of a contact smear may reveal inflammatory cells and responsible organisms. Lesions of ascending placenta are usually located on the cerebral surface, whereas diffuse homogeneous placenta, as in leptospirosis, may cause diffuse lesions. Nocardioform plaenca has characteristic lesions on the cranial ventral uterine body.392

Although it is possible to perform feral or neonatal necropsy in the field when necessary, it is preferred that the entire carcass be sent to a diagnostic laboratory if possible. If fetal necropsy is performed in the field, proper precautions should be taken to document lesions, prevent contamination, and obtain appropriate samples. Fetal blood samples are obtained as well as pleural and peritoneal fluids should be obtained. Tissue samples from any abnormal-appearing tissues and from all major organs (e.g., liver, lung, kidney, adrenal gland, placenta, heart, thymus, brain, spleen, small intestine) should be submitted for histopathologic evaluation.482

**Viral Causes of Abortion**

**Equine Herpesvirus**

Despite the widespread use of inactivated and live herpesvirus vaccines, equine herpesvirus (EHV) remains a common cause of equine abortion.52,123,208 (see Chapter 13). EHV-1 abortion storms continue to be reported in various areas of the world.69 The principal mode of transmission from horse to horse is by direct contact with the virus through nasal secretions, reproductive tract discharge, placenta, or aborted fetuses. However, short-distance airborne spread of infection is possible.55,124,125 Farm personnel, equipment, feed, and water may act as fomites to facilitate transmission.126,208

Some abortions are likely caused by reactivation of latent infection rather than primary exposure.69,80 The most common cause of equine herpesvirus abortion is EHV-1, although EHV-4 has also been isolated from some equine abortion cases. Both viruses cause similar lesions in the liver and lung; evaluation of the spleen is particularly useful for identification of red pulp necrosis caused by EHV-4.432 Regardless of which herpesvirus is involved, the pathogenesis of abortion is attributed to vascular necrosis.9,146,50,501,503 Viral nucleic acid can be demonstrated in endothelial cells of endometrial arteries, within endometrial glands, and within placental microcotyledonic infarctions.290,290a Transplacental transfer of the virus may result in a virus-positive fetus, or severe endometrial vascular pathology (vasculitis and multifocal thrombosis) may result in abortion of a virus-negative fetus.290,362 Abortion occurs most often during the last third of pregnancy. In utero infection near term may result in the birth of a live infected foal that usually dies a few days later.290

For confirmation of herpesvirus abortion, antigen detection in combination with virus isolation, immunohistochemistry, or polymerase chain reaction (PCR) on fetal lung, liver, spleen, and thymus is recommended. Virologic and serologic investigation of the mare is also recommended.62,216,307

It is important to realize that EHV-1 abortion may occur despite regular vaccination. Causative factors include the mare’s individual immunity, level of contamination, virulence of the viral strain, and the performance of available vaccine.59,212 Therefore, for maximum protection, vaccination strategies should be combined with appropriate biosecurity measures to minimize the likelihood of exposure of pregnant mares to EHV.9,505

Vaccines for the control of respiratory diseases caused by EHV-1 have been available for several decades, and currently more than a dozen commercial vaccines are available throughout the world.290,295 There are also several vaccines that claim protection against abortion caused by EHV-1. These vaccines should be administered according to the manufacturer’s label instructions, usually at 3, 7, and 9 months of gestation.

Management practices that should be part of an EHV abortion prevention program include maintenance of small groups of horses segregated by age and by immune and physiologic status (pregnancy status and stage). Failing mares should be segregated from the rest of the herd. Particular attention should be given to the risk of mixing equids from different species that may carry different susceptibility or strains of EHV.9 The most important epidemiologic risk is posed by introduction of new horses onto the farm. If introduction of new animals cannot be avoided, a 21-day quarantine is recommended.

An outbreak of EHV mandates early diagnosis of infected animals and interruption of viral transmission using strict sanitary measures for movement of personnel and animals between stables and paddocks, as well as use of disinfectants. Particular attention should be given to disposal of or shipping of fetuses and placentas to appropriate diagnostic laboratories. Mating activities should preferably be halted during an active outbreak.9

**Equine Viral Arteritis**

Equine viral arteritis (EVA) is a venereal disease of horses that can result in abortion (see Chapter 14). Abortion storms have been reported as part of the clinical presentation of the disease.6,7 Abortion rates can approach 60% in a naive population, as the result of direct impairment of placental function and severe fetal infection.190,456,456 Diagnosis can be made by virus isolation, immunohistochemistry, PCR, or serology.136,180,370 Aborted fetuses may show subcutaneous edema, petechial hemorrhages in the pleura and epicardium, and increases in pleural fluid. However, these changes are not necessarily present in all EVA abortion. Gross pathologic changes have also been reported in a few aborted placentas, including placentitis and full-thickness necrosis. Other nonpathognomonic histopathologic lesions in the fetus may include vasculitis and perivascularitis in the heart, lung, and spleen; pneumonia and hemorrhage in alveoli; and inflammatory changes in the liver, spleen, and placenta. Control of the disease is based on vaccination.

**Parasitic Causes of Abortion**

Abortion in mares has been associated with a variety of protozoa, including Trypanosoma evansi,57 Trypanosoma equiperdii,86 Babesia spp.,50,208,302 and Neospora spp.502 However, there are no studies on the pathogenesis of abortion caused by these parasites.

Neospora caninum, an apicomplexan protozoan parasite, has been isolated from an aborted equine fetus in North Carolina and in one fetus from Normandy in France.131 However, great discrepancies exist between the prevalence of

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1References 27, 165, 267, 298, 382, 408.

2References 90, 92, 105, 125, 188, 283, 380, 387.
Neospora-positive horses, estimated at between 2% and 23% depending on location, and infected fetuses. Serologic surveys show 11.5% (n = 536) Neospora-positive horses in Alabama, 81 23% (n = 296) in slaughtered North American horses, 123 23% (n = 434) in France, 202 and 2% (n = 208) in horses from several locations in the United States. 69 Although not statistically significant, a higher prevalence of antibodies against *N. caninum* has been reported in mares with a history of reproductive failure than in mares with normal fertility. 258 Seroreivalence of antibodies to *Neospora* spp. is significantly higher in recently aborting mares in France compared with mares with no history of recent abortion. *N. caninum* deoxyribonucleic acid (DNA) was detected in three fetal brains, two fetal hearts, and one placenta. 302 The identification of *N. caninum* sequences in fetal tissues is interesting, but the role of *N. caninum* in equine reproductive failure and abortion can only be speculative at present and must be further evaluated. 301,302

**Other Infections Causing Abortion**

**Chlamydia**

Genital chlamydial infection is a well-documented cause of abortion in horses, with decreased reproductive rates reported. 173,241 Detection of chlamydial organisms in aborted equine fetuses ranges from 20% to 55%. 13,108,229 However, other infectious organisms were isolated from many of the same cases, and it was not possible to determine the primary cause of abortion. Chlamydial organisms that have been isolated from horses include *Chlamyphila pneumoniae*, equine bovine, associated with respiratory diseases, and *C. abortus* and *C. psittaci*, identified in equine abortion cases. 371

In Hungary, chlamydial were detected by immunohistochemistry and PCR in 83% of equine abortions, but they were not determined to be the primary cause of abortion. 408 The significance of chlamydial infection to equine abortion is contested by others. No chlamydial inclusions were found in a retrospective study of tissues from 142 aborted foals in Switzerland examined by immunohistochemistry. The same authors were unable to detect any *Chlamydia* organism (culture and PCR) from 49 aborted foals in northern Germany. 171

**Mycoplasma**

The significance of agnoleplasmas and mycoplasmas in equine abortion is undetermined. Mycoplasma has been isolated from the lungs or liver of aborted equine fetuses. 304 Of 404 mares, mycoplasmas were cultured from the cervix of 5%, 398,402 Mycoplasma hominis was isolated from an aborted equine fetus. 314 Mycoplasmas were isolated from the placenta and placental membranes of an equine fetus aborted 35 days prematurely. The only gross pathological lesions observed were darkening of the dorsal apical lobes of the lungs and a few necrotic patches 15 to 25 cm in diameter in the placenta. 273

**Other Infectious Organisms**

Abortions have been associated with *Salmonella abortus equi* in horses and donkeys, 176,192 *Shigella* spp., 194 *Brucella abortus*, 47,313,338 and *Brucella suis*. 339 *Neoricketssia risticii* has also been identified as a cause of abortion in horses. 32,103,169,356 (see Chapter 43). Abortion from *Aeromonas hydrophila*, a bacterium found in stagnant water, has been reported in a few horses. 306

An unusual case of abortion in a 6-year-old mare has been associated with a spirochete (*Borreliia parkeri*—B. turicatae) transmitted by ticks in California. 615 The 9-month-pregnant mare presented with a history of yellow vaginal discharge and did not respond to antimicrobial or antiinfectious treatment. The spirochete was isolated from the fetus, suggesting transplacental transmission.

During the *mare reproductive loss syndrome (MRLS) outbreak in Kentucky in 2000 and 2001, significant bacterial growth (*Actinobacillus spp., beta-streptococci*) was a common feature in tissues of aborted fetuses. 396 This led some authors to hypothesize that the pathogenesis of MRLS implicated hematogenous spread to the fetomaternal unit of bacteria carried from the oral cavity and intestinal tract by the sire, or still bristlykered hair of the exoskeleton of the Eastern tent caterpillar. 398

**REPRODUCTIVE TRACT INFECTION IN STELLIONS**

**Infectious Disease of Prepuce and Penis**

Acute inflammation of the prepuce (fothitis) and inflammation of the penis (balanitis) may occur secondary to other infectious diseases. Balanoposthitis is most often caused by coital exanthema (EHV-3 infection), dourine, or parasitic infestation (e.g., *Onchocerca spp., Sarcoptes spp., habronemiasis*). 385 Preputial abscesses may occur subsequent to bacteremia (*Streptococcus equi* subsp. equi or *Corynebacterium pseudotuberculosis*). In some areas of the world, *C. pseudotuberculosis* abscesses may have a seasonal incidence that parallels the increase in arthropod (vector) population. 148,302 (see Chapter 30). Factors such as a high concentration of horses and *Habronema spp. infestation are predisposing factors for these abscesses. 268 Treatment is generally limited to medical or surgical management of the abscess because systemic antimicrobial therapy is often unsuccessful. 395

Several infectious diseases may cause lesions on the penis, including dourine, coital exanthema, EVA, and equine infectious anemia. Non-specific balanitis is generally caused by superinfections with bacteria or fungi. 383 Predisposing factors include increased accumulation of smegma or overzealous cleaning of the penis with disinfection. Excessive use of antiseptic solution may promote the destruction of the normal flora of the penile mucosa and the selection of some bacteria (e.g., *P. aeruginosa, K. pneumoniae*). 32 Treatment of nonspecific balanitis requires sexual rest and local application of antimicrobial ointment.

Coital exanthema (EHV-3) and dourine (see Chapter 61) are specific infectious processes that involve the penis and are discussed in the section on venereal diseases.

Cutaneous habronemiasis (summer sores) is characterized by granulomatous lesions caused by larvae of *Draschia megastoma, Habronema muscae*, and *Habronema microstoma* (see Chapter 62). Habronemiasis is generally seasonal and parallels the fly population. These infections are often found in areas with high heat and humidity and in areas with high density of animals and poor sanitation. Occurrence of this disease has declined with regular use of avermectin anthelmintics. 152,355 The larvae of gastroplasms are carried by infected flies to the genital area and cause an inflammatory process with rapid development of a granulomatous lesion. 268,458 (Fig. 8-10).

Diagnosis of habronemiasis is based on the location and characteristics of the lesions as well as the presence of predisposing factors (e.g., season, lack of sanitation). Lesions are generally observed at the level of the glans penis or urethral process. Yellow caseous masses composed primarily of eosinophils and larvae are present within the lesions. These lesions should be differentiated from sarcoids or squamous cell carcinoma. 270,271,276,383
Confirmation of the diagnosis is easily made with histopathologic evaluation of a biopsy of the lesion or by contact smears. Wright-stained smears may allow visualization of the larvae. \(^{270,271,278}\) Slices of larvae may be seen surrounded by masses of eosinophils on histopathologic evaluation. Squamous cell carcinoma lesions may be complicated by larval infestation because these lesions tend to attract flies. \(^{270,272,276,278}\)

Treatment of habronemiasis consists of killing parasites, reducing the degree of inflammation, and treating the secondary bacterial infection. The drugs most often used for elimination of larvae are diethylcarbamazine, organophosphates, and ivermectin. Local and systemic treatment with an organophosphate compound has been advocated in the past but is controversial because of its toxicity. \(^{288,389,447}\) Ivermectin (ivermectin, 0.2 mg/kg) remain the best choice for local and systemic treatment. The majority of larvae are killed within 1 week, and improvement of the lesions is generally observed within 1 to 5 weeks after treatment. \(^{108,171,172}\) Treatment with a single oral dose of ivermectin (120 mg for a 570-kg horse) has been reported; about 15% to 20% of horses require a second treatment. \(^{99}\) Old extensive lesions may require up to three treatments at 10-day intervals. \(^{12}\) Chronic severe lesions may require surgical ablation. \(^{192,270,370,385}\)

The inflammatory process may be reduced by treatment with diethylcarbamazine or corticosteroids. Ointment containing 30 mg of dexamethasone and 120 mg of nitrofurzone has been used to diminish the inflammatory reaction caused by dead larvae after ivermectin treatment. Prevention of habronemiasis should include protection of genital lesions with insect repellent, \(^{51}\) regular cleaning of the external genitalia, and regular use of ivermectin, especially during the peak of fly season \(^{395}\).

**Infections of Testes and Epididymis**

Ovaritis may be caused by bacteria, viruses, or parasites. Bacterial ovaritis and periovitis are relatively rare in stallions. \(^{29}\) Infection may be ascendant, secondary to trauma, or hematogenous. \(^{29,54,385}\) Hematogenous infection with S. equi subsp. zooepidemicus, S. equi subsp. equi, Actinobacillus equuli, Pseudomonas mallei, Salmonella abortus equi, Brucella abortus, and C. pseudotuberculosis may occur. \(^{29,54,385}\) Hematogenous infection with Actinobacillus equuli has been described in a 2-month-old colt presenting with acute abdominal pain, leukocytosis, and mature neutrophilia. \(^{29}\) Infections caused by Streptococcus spp., Staphylococcus spp., and E. coli occur secondary to peritonitis.

Systemic clinical signs may include fever, abdominal pain, and poor libido. Local signs may include increased scrotal size, scrotal edema, and increased sensitivity of the scrotal area. Scrotal/testicular ultrasonogram may identify areas of liquefaction of the testicular parenchyma or development of granulomatous lesions \(^{314,385}\) (Fig. 8-11). Horses with chronic...
Ophritis may have adhesions between the tunica vaginalis and subcutaneous tissue, azospermia, high numbers of neutrophils in the ejaculate, a high percentage of sperm abnormalities, and poor motility.\textsuperscript{36,54,385}

Differential diagnosis should include all other causes of increased scrotal size, including inguinal hernia,\textsuperscript{20} hematocoele,\textsuperscript{32,161} hydrocoele,\textsuperscript{383,384} testicular cord torsion,\textsuperscript{31} spermatic artery thrombosis,\textsuperscript{30,181} and testicular neoplasia.\textsuperscript{77,383} Neutrophilia, fever, and hyperfibrogenemia without cardiovascular signs suggest orchitis rather than inguinal hernia with intestinal incarceration.\textsuperscript{29}

Treatment of bacterial orchitis may be attempted with systemic antibiotics and NSAIDs, as well as local hydrotherapy, but is generally unrewarding. Unilateral infections are usually best managed by hemicastration. When bacterial orchitis responds to antimicrobial treatment, the affected testicle will progressively atrophy and become fibrotic.

Viral orchitis has been reported in some horses with equine infectious anemia, EVA, and influenza.\textsuperscript{198,383} Orchitis has also been described in horses with granulocytic leukocytosis.\textsuperscript{120}

Parasitic orchitis may be caused by migratory larval (larva migrans) of Strongylus edentatus.\textsuperscript{45,289,282,277,358}

**Epididymitis**

Infections of the epididymis are rare in stallions and are generally accompanied by orchitis. Therefore the same bacteria and parasites associated with orchitis are associated with epididymitis in the stallion. \textsuperscript{*} Pseudomonas aeruginosa is the most common isolate from bacterial epididymitis in stallions.\textsuperscript{381}

Acute epididymitis is very painful and often accompanied by local swelling and fever. Colic signs may be present even in horses with chronic epididymitis. Periurethral and perirenal abscesses and sperm granulomas may develop following rupture of the epididymis. Systemic signs and palpable changes are often suggestive of the diagnosis. Azospermia is possible. Ejaculates may show oligospermia, hypospermia, and increased numbers of deacrosinated sperm cells with increased numbers of neutrophils in the ejaculate.\textsuperscript{1} Prognosis for fertility is poor in horses with bilateral epididymitis.

**Infections of Accessory Glands**

Infections of the stallion accessory sex glands are relatively rare.\textsuperscript{37,410} Seminal vesiculitis is most common.\textsuperscript{39,146,147,182,364} Bacterial isolates from stallions with seminal vesiculitis include P. aeruginosa, K. pneumoniae, Streptococcus spp., Staphylococcus spp., Proteus vulgaris, Acinetobacter calcoaceticus, and Brucella abortus.\textsuperscript{1} Both descendant routes, from the urinary system, and hematogenous routes of infection are possible. Seminal vesiculitis may be associated with infection of the ampullae of the ductus deferens (ampullitis).\textsuperscript{39}

Clinical signs of seminal vesiculitis are variable. Chronic infection may occur without any systemic signs. Acute infection is characterized by pain during ejaculation or transrectal palpation. Seminal vesiculitis may be suspected in stallions with hemospermia or infertility.\textsuperscript{3} The ejaculate may appear brown or reddish in color and contain a high number of red blood cells and neutrophils.\textsuperscript{39,141,144,364}

Diagnosis of seminal vesiculitis requires evaluation of the gland by transrectal ultrasonography and urethroscopy.\textsuperscript{214,313,383} The inflamed seminal vesicle increases in size and becomes very soft and easily palpable. In some cases the gland may show lobulation and irregular contour.\textsuperscript{141,231,233,310} On ultrasonography, the gland is two to three times the normal size, and its content is densely hyperchoic (normally anechoic).\textsuperscript{231,233,310} Endoscopic examination of the colliculus seminalis may reveal localized inflammation.\textsuperscript{411,383,416} Chronic seminal vesiculitis may not show any changes on endoscopic examination.\textsuperscript{39} The examination of the gland itself is possible with a small-diameter endoscope (Fig. 8-12). Chronic seminal vesiculitis may not show any changes on endoscopic examination.\textsuperscript{39} The examination of the gland itself is possible with a small-diameter endoscope (Fig. 8-12). Culture and cytology of fluid obtained directly from the gland by endoscopic aspiration of the ejaculatory duct allow confirmation of the diagnosis.\textsuperscript{383,390} Microbiologic evaluation may also be performed on samples obtained from preejaculate and postejaculate urethral swabs or sperm.\textsuperscript{41}

The treatment of seminal vesiculitis is very difficult because the majority of antimicrobials cannot reach the gland in sufficient concentration.\textsuperscript{39,41,144} Broad-spectrum antimicrobials with a high volume of distribution, such as trimethoprim-sulfonamide combinations, may be used systemically.\textsuperscript{141} Intravenous antibiotic treatment may also be beneficial in cases of severe infection.\textsuperscript{39,41,144} Local lavage with anikacin and oral treatment with trimethoprim-sulfonamide for 8 days have been successful for the treatment in a stallion with seminal vesiculitis from Proteus vulgaris.\textsuperscript{146}

The use of minimum-contamination breeding technique may be indicated in difficult cases of seminal vesiculitis.\textsuperscript{40,195} Infusion of an extender containing a specific antimicrobial into the uterus of a mare before breeding, combined with postbreeding uterine lavage, has helped prolong the survival of semen and control bacterial growth.\textsuperscript{39,41,57,58,60,221} If artificial insemination is an option, collection of the sperm-rich fraction and dilution with an extender containing the proper antimicrobial are indicated.

A radical treatment of seminal vesiculitis consisting of surgical excision of the affected glands has been described. However, such surgical technique is complicated and often leads to ejaculatory disorders.\textsuperscript{263}

\*References 168, 169, 206, 331, 389, 405.
\*References 30, 40, 140, 182, 184, 189, 205, 251, 364.
\*References 30, 141, 251, 364, 383, 410.
EQUINE VENEREAL DISEASES

The most common equine venereal diseases are CEM (see Chapter 41), coital exanthema (see Chapter 13), EVA (see Chapter 14), and dourine (see Chapter 61). Some bacteria responsible for endometritis in the mares, such as *P. aeruginosa* and *K. pneumoniae*, are also considered venereal. Some of these diseases are subject to strict regulatory guidelines in several countries, and the veterinarian should be aware of the proper procedures for reporting positive or suspect cases.

**Venereral Transmission of *P. aeruginosa* and *K. pneumoniae***

*Pseudomonas aeruginosa* and *Klebsiella pneumoniae* endometritis can be spread between horses by venereal transmission.4 Bacteriologic studies should be routinely performed on recently introduced mares and stallions to prevent such infection. Culture is also indicated if there is an increased incidence of endometritis on a stud farm.5,15,20,66,78,100 Pre-ejaculatory and post-ejaculatory urethral swabs and semen from stallions should be cultured.4

Routine washing of the stallion penis with antiseptic solution before and after breeding is contraindicated because it may disturb the normal bacterial flora of the penile surface and promote growth of pathogenic bacteria such as *P. aeruginosa* and *K. pneumoniae*.5,51,185,190 Washing the penis with sodium hypochlorite solution (5.25%) or dilute hydrogen chloride (HCl, 0.2%) has been suggested for the treatment of stallions with a positive culture of *P. aeruginosa* or *K. pneumoniae*.51,197,200,340

**Coital Exanthema***

Coital exanthema is a very contagious, self-limiting venereal disease caused by equine herpesvirus type 3 (EHV-3). It is characterized by the development of painful purpuric lesions on the external genitalia of stallion and mares.5,140 The direct effect of this disease on fertility remains a subject of debate. The disease is transmitted by coitus, infected artificial insemination equipment, or gynecologic instruments.187,274,290,294,324 In one study in Austria, 27% of Noniker stallions were seropositive.20

The stallion plays an important role in the epidemiology of coital exanthema. Clinical signs develop within a week of infection and consist of multiple circular red nodules on the vulva, vaginal mucosa, clitoral sinus, and perineum in mares and on the surface of the penis in the stallion. The lesions increase in size to 10-15 mm circular erosions, which eventually rupture and become coalescent ulcers (Fig. 8-14). The ulcerative lesions are very painful.390

Prevention of coital exanthema requires examination of mares before breeding or use of artificial insemination. Clinical signs are easily recognized in both stallions and mares. Confirmation of the diagnosis is made by virus isolation from the lesions or histopathologic examination looking for characteristic inclusion bodies.200,204 A highly sensitive and specific PCR test for the detection of virus has been recently described.200,201

**Dourine***

Dourine is defined by the Office international des Epizooties (OIE) as a "chronic or acute contagious disease of breeding stallions that is directly transmitted from animal to animal during coitus." Dourine is probably the oldest equine venereal disease known. It is caused by the trypanosome that is not transmitted by an invertebrate vector, *Trypanosoma equiperdum*.
Fig. 8-14 Perineal area of mare showing old lesions of equine herpesvirus type 3 (EHV-3) infection (coital exanthema) (see Chapter 61). It affects primarily horses and to a lesser degree donkeys.\(^{347}\) Dourine had a global distribution during World War I but has been eradicated from North America and most of Europe. It is still reported in Africa (Botswana, Ethiopia, Namibia, South Africa) and Asia (Kyrgyzstan, Mongolia, Pakistan, Russia, Turkmenistan, Uzbekistan), with suspected cases reported in Germany and the Middle East.\(^{346,349,351}\)

Horses with dourine typically present in one of three clinical phases. Initially, infected horses exhibit edema and fluid accumulation in the genital area starting about 2 weeks after infection. This is followed by development of the characteristic cutaneous lesions from which the disease derives its name, "dourine." The lesions are circular elevated plaques of thickened skin ranging from 1 cm to 10 cm in diameter and resembling money, or "doures." These plaques are observed mostly on the neck, hip, and ventral abdomen. Progressive nervous system compromise leads to paralysis of the hindlimbs, paraplegia, and death.

Clinical signs are highly suggestive of the disease. Dourine can be confirmed by a wide variety of laboratory tests. Complement fixation test (CFT) developed in the early twentieth century remains the internationally recommended test.\(^{317}\) However, recent studies have shown that this test cannot distinguish among *T. equiperdum*, *T. evansi*, and *T. brucei*.\(^{156,344,345,335}\) These cross-reactions are important from an epidemiologic point of view because some clinical signs of infection with *T. evansi* may resemble those of dourine.\(^{344,345,130,141}\)

**CONCLUSION: BIOSECURITY IN BREEDING OPERATIONS**

Biosecurity on horse farms and in veterinary hospitals is essential to prevent introduction and spread of infectious diseases. The general approach to biosecurity and disease outbreaks control is covered in depth in Chapters 66 and 67.

General principles of biosecurity for breeding farms include strict separation of transient and resident horse populations, routine quarantine of all new arrivals on the farm, and segregation of horses according to age and breeding status. Animals returning from events where commingling has occurred (e.g., breeding farms, shows) should be placed in quarantine for a minimum of 3 weeks. Prebreeding uterine culture and cytology should be required for all visiting mares, particularly those that have remained barren in the previous season. Stallions should undergo complete semen evaluation and microbiologic examination of preejaculation and postejaculation urethral swabs as well as semen. Vaccination status and previous exposure to specific disease agents should be determined.

Breeding hygiene should be strictly observed to avoid transmission of contaminants to mares. The surface of the penis can harbor several organisms that may be potentially pathogenic.\(^{341,247,252}\) If artificial insemination is used, particular attention should be paid to the origin of the semen and the health certificate of stallions at collection.\(^{68,87,231}\) Antibiotic-containing extenders do not eliminate risk of transmission of organisms. Quality control of semen processing, particularly shipped cooled semen, is often lacking. Health importation requirements for frozen semen should be verified for each country of origin and strictly adhered to.\(^{156}\) The stallion status with regard to EVA and CEM is of particular importance. Guidelines are available for use of stallions that shed EVA virus (see Chapter 14). The risk of transmission of infectious diseases by embryo transfer in horses has not been thoroughly evaluated.\(^{344}\) Proper screening of the stallion, donor mares, and recipients is therefore very important. Advanced reproductive technologies, such as intracytoplasmic sperm injection (ICSI), cloning, gamete intrafallopian transfer (GIFT), and in vitro fertilization, are becoming accepted in the equine breeding industry and need to be evaluated for risk of disease transmission.

On large stud farms, foaling mares should be grouped by gestational stage. They should be monitored daily for rapid mammary development, premature lactation, or abnormal vaginal discharge. High-risk pregnancy mares should be monitored regularly by transectral and transabdominal ultrasonography. Paddocks should be checked regularly for abortion.

A contingency plan should be elaborated for action to take in case of abortion. This plan should include proper handling (prompt submission to laboratory) of biologic tissues (plaenta and abortus) and measures to isolate the aborting mare from the rest of the herd. On large farms, personnel working with pregnant and parturient mares should have no contact with other horses.

The foaling team should be educated in recognizing abnormal peripartum situations requiring urgent veterinary attention. Hygiene should be emphasized for all personnel attending or assisting in foaling.

On an individual mare level, prevention of reproductive loss from infectious diseases should focus on early diagnosis of sporadic infections that may cause permanent damage to the reproductive tract. Mares that are known to be susceptible to endometritis should be bred using minimum-contamination breeding and monitored for PMF and treated appropriately. Corrective surgery should be performed on all mares with abnormal perineal conformation.

The potential for disease transmission by visitors should not be underestimated. Visitor contact with animals should be limited or discouraged, particularly for high-risk animals (pregnant mares and stallions). A herd by the general public should be disallowed.

Prevention of introduction of diseases into the herd should also take into account other vector animals (insects, birds,
REFERENCES

See the CD-ROM for a list of references linked to the abstract in PubMed.

CHAPTER 9 • Urinary Tract Infections

Urinary Tract Infections

Donna N. Zimmel

ETIOLOGY

Urinary tract infection (UTI) is caused by microbial colonization of the kidney, ureter, urine, or proximal urethra. The incidence of UTIs in the horse is low.1-5 UTIs can be divided anatomically into upper UTI, involving the kidney and ureters, and lower UTI, involving the bladder and urethra. Ascending infections are the most common method of bacterial colonization, with the exception of septicemia-associated nephritis in neonatal foals.6 Upper UTIs occur less frequently and can occasionally be life threatening.5 Lower UTI is generally caused by abnormal urine flow. Urolithiasis and partial obstruction are often the cause of both upper and lower UTI in horses.

The most frequently reported bacteria in UTI include Escherichia coli, Proteus, Klebsiella, Enterobacter, and Pseudomonas aeruginosa.7 Gram-positive infections in horses are less common, but Streptococcus and Corynebacterium spp. have been isolated.8 Enterococcus spp. have been identified in horses with abnormal urine flow or horses that were instrumented with a urinary catheter. Isolation of more than one organism from the urine is common. Neonatal foals receiving broad-spectrum antimicrobials can develop Candida infections in the lower urinary tract.8

The most frequent causes of UTI in the horse are bladder paralysis (Fig. 9-1), urolithiasis (Fig. 9-2), and trauma to the urethra.9-11 Urethritis can result from urethral damage in geldings and stallions secondary to neoplasia, habronemiasis, or trauma to the penis or sheath.9,10 Any alteration or obstruction to urine flow can predispose to infection. Mares are more likely to develop UTI than male horses because of their shorter urethra and the potential for fecal contamination from poor perineal conformation. In addition, mares may sustain damage to the urethra from trauma associated with foaling.

Cystitis may occur secondary to bladder paralysis, bladder neoplasia, or urolithiasis. Neurologic disease, such as equine protozoal myeloencephalitis or equine herpesvirus type 1 (EHV-1), and trauma can result in bladder paralysis. Consumption of Sudan grass and Johnson grass has resulted in ataxia and urinary incontinence in the southwestern United States from sublethal intoxication with hydrocyanic acid in the plants.9,11,12 Conditions that inhibit bladder emptying at regular intervals encourage the growth of bacteria. Urolithiasis in the bladder can damage the mucosa lining, destroying normal defense mechanisms against microbial colonization. Obstruction of the renal pelvis, ureter, or urethra with urinary calculi may result in UTI. Unlike small animal patients, horses rarely develop UTI secondary to urinary catheterization, with the exception of sick neonatal foals.12,13

Pyelonephritis is rare in horses2,4 (Fig. 9-3). The ureters attach dorsally on the bladder, providing a physical barrier to vesicoureteral reflux, which is responsible for ascending infection. Problems that disrupt this normal barrier include ectopic ureter, enlargement of the bladder from paralysis, or obstruction of urine flow from urolithiasis.12

PATHOGENESIS

UTIs are the result of pathogenic bacteria colonizing the urethra and then migrating to the bladder, where they multiply.12,14 Fecal bacteria can adhere to the urothelial cells of the urethra when normal flora is altered by turbulent urine flow.15

Fig. 9-1  Endoscopic image of urinary bladder of 8-year-old Quarter Horse mare with bladder paralysis and recurrent bacterial cystitis secondary to administration of alcohol tail block.
After the pathogenic bacteria colonize in the distal urethra, they must rapidly reproduce between micturition to migrate through the proximal urethra and bladder, which do not have protective flora.

Bacterial virulence properties and host defense mechanisms play a role in the development of UTIs. For example, pathogenic *Escherichia coli* has surface adhesins that can bind to specific glycolipid receptors on uroepithelial cells. Host defense mechanisms include normal flora, normal anatomy, and normal micturition. An intact mucosal defense system includes glycosaminoglycan coating of uroepithelial cells and immunoglobulins in the urine. Normal flora of the UTI can be protective against pathogenic bacteria unless urine flow or an anatomic defect compromises the environment. It has been hypothesized that women with recurrent UTI have decreased immunoglobulin A in their urine. Glycosaminoglycan can coat the uroepithelium, providing a barrier for bacterial attachment. If this layer is damaged by uroliths or neoplastic cells, infections are more likely to occur. Glycosaminoglycan production is directly influenced by estrogen. Prepubertal and postmenopausal women are at an increased risk of UTI because of a decrease in estrogen. Currently, there is no evidence to support an increased risk of UTI in fillies or pregnant mares.

Upper UTI in the horse is uncommon. Infection of the ureter and kidney can occur with compromise of the protective valve, which inhibits vesicoureteral reflux secondary to ectopic ureter, bladder distention, or urethral obstruction. These conditions lead to dilated ureters and vesicoureteral reflux with contaminated urine. The renal cortex is much more resistant to bacterial infection than the renal medulla, decreasing the possibility of hematogenous spread.

**CLINICAL FINDINGS**

Clinical signs of lower UTI may include dysuria, pollakiuria, stranguria, and incontinence. Urine scalding on the perineum in mares or on the dorsal aspect of the hindlimbs in geldings or stallions may indicate chronic UTI (Fig. 9-4). Hematuria occurs with disruption of the mucosal lining associated with accumulation of sanguineous urine sediment or urolithiasis. If hematuria is present only at the end of urination, this suggests that the origin of the problem is the bladder or proximal urethra. If a urolith completely obstructs urine flow, colic may be the presenting complaint.

Clinical signs of pyelonephritis include fever, weight loss, anorexia, depression, and in some cases, mild abdominal pain. Often, upper UTI occurs in conjunction with lower UTI. More frequently, pyelonephritis is accompanied by dysuria manifested as pyuria or hematuria. It is difficult to determine if renal insults result in the formation of uroliths or if the uroliths are the source of the infection.

Rectal examination may confirm the cause of a lower UTI. Common problems detected include a large distended bladder, flaccid bladder, thickened bladder wall, and presence of a bladder mass (neoplasia or cystic calculi). A dilated ureter may be palpable in the caudal abdomen and traceable to the kidney in upper UTIs. An abnormally large or small left kidney may aid in the diagnosis but should be confirmed with ultrasonography.

**DIAGNOSIS**

Analysis of urine confirms the diagnosis of UTI. A sample of urine should be collected by sterile catheterization or
collected midstream during urination. The urine sample should be collected in a sterile container and examined within 30 minutes of collection. Cytologic analysis and a bacterial culture and sensitivity should be performed. If urine is allowed to remain at room temperature, bacteria may multiply, and sediment evaluation and quantitative culture results will be inaccurate. 29 If there is any delay in submission, the sample must be immediately refrigerated.

Interpretation of results varies with the collection method. A normal reference range for horses for a midstream free-catch sample is less than 5 bacteria per high-power field (hpf) on sediment evaluation and less than 20,000 organisms per milliliter (mL). A catheterized urine sample in normal horses has less than 4 bacteria/hpf and less than 300 organisms/mL. 24 Bacteria isolated from normal horses mimics the bacteria isolated in horses with UTI. This fact makes bacterial counts critical to determine the presence or absence of infection. Calcium oxalate and calcium carbonate crystals are normally observed in equine urine and are not correlated with presence of uroliths.

A complete blood count and chemistry profile are unremarkable in most horses with lower UTI that does not involve obstruction of urine flow. A neutrophilic leukocytosis is common in horses with upper UTI. Chronic UTI may be characterized by increased total protein concentration and hyperglobulinemia. Horses with bilateral upper UTI may develop azotemia, low urine specific gravity, and casts in the urine sediment. 8,12

Ultrasoundography of the kidneys can aid in the diagnosis of upper UTI caused by calculi, abscess, or neoplasia (see Fig. 9-3). Ultrasound-guided renal biopsy may be necessary to confirm the diagnosis. Transrectal ultrasonography of the bladder can detect a thickened bladder wall or a bladder mass. Evaluation of dilated ureters may also be possible using transrectal ultrasonography.

Endoscopic evaluation of the urethral mucosa, bladder, and ureteral openings is helpful in diagnosis of UTI (see Fig. 9-1). Advantages of endoscopy include identification of small cystoliths that could not be palpated and visualization of the mucosa. In addition, each ureter can be evaluated by observing urine flow and the diameter of the ureteral opening. If only one ureter and kidney are infected, bacterial culture of that side is indicated. Catheterization of the ureter may be performed endoscopically through the biopsy chamber using a polypropylene catheter. 22 The risks of endoscopic evaluation are minimal when sterile equipment is used.

**THERAPY**

Treatment of UTI consists of correcting the underlying problem and initiating antimicrobial therapy. Factors to consider when choosing an antimicrobial for treatment of UTI should include the concentration of the antimicrobial in the renal tissue and urine, ease of administration, expense, toxicity, activity of antimicrobial at different pH levels, and drug interactions. Many antimicrobials are present in high concentrations in the renal tissue and urine as the result of renal excretion. If the organism is susceptible to an antimicrobial agent, it should be effective if the antimicrobial is excreted in the active form and if renal function is normal. Many antimicrobials may be resistant in vitro but achieve adequate concentrations in the urine to be effective. However, the organism may also be true; for example, *Enterococcus* spp. are susceptible to trimethoprim-sulfonamide in vitro but are often resistant in vivo. 32

Trimethoprim-sulfonamide combinations are the most frequently used antimicrobials for treatment of lower UTI in horses. The spectrum of activity includes both gram-positive
Ocular Infections
Carmen M. H. Colitz and Vanessa Kuonen

Infectious ocular diseases can occur as primary entities or as ocular manifestations of systemic disease. Most cases of surface ocular diseases are primary in origin, whereas intraocular diseases may be either primary or secondary. This chapter discusses the infectious diseases that affect equine eyes, beginning with surface infections and progressing inward.

OCULAR FLORA

Bacterial Isolates from Normal Eyes
The normal ocular microflora is predominantly nonpathogenic gram-positive organisms, although some gram-negative and fungal organisms are also present. Normal ocular flora may vary depending on the environment, husbandry, geographic region, season, and climatic factors. Organisms typically recovered from healthy equine eyes include Bacillus cereus, Streptococcus equi subsp. equi, S. equi subsp. zooepidemicus, other streptococci, Corynebacterium spp., Staphylococcus aureus, and Staphylococcus epidermidis. Gram-negative organisms isolated from healthy equine eyes include Moraxella spp., Neisseria, and Actinobacter. Fungi may be isolated from the conjunctival sac in 95% of equine eyes. The most common fungal flora isolated vary by study, but Aspergillus spp. and Cladosporium spp. are consistently reported, in addition to unidentified and dematiaceous molds, Chrysosporium spp., and Alternaria spp. Fungal organisms may contribute to pathology when the corneal epithelium is ulcerated or eroded.
Bacterial Isolates from Diseased Eyes
In a study of 38 eyes from 37 horses with ulcerative keratitis, *Pseudomonas aeruginosa* was the most common bacterium isolated (10 of 34 isolates), *Enterobacter* spp., *Serratia* spp., and *Citrobacter* spp. were also frequently isolated. In a study of 123 horses with ulcerative keratitis or conjunctivitis, bacteria were isolated from 98 eyes. *Streptococcus* spp. were isolated from 54 eyes (43.9%); β-hemolytic streptococci comprised 32 of the 54 isolates. *Staphylococcus* spp. were isolated from 30 eyes (24.2%) and *Pseudomonas* spp. from 17 eyes (13.8%). Although gram-negative bacteria are often perceived as causing severe corneal infection, *Staphylococcus* and *Streptococcus* infections may also cause severe corneal disease.10-12

Fungal Isolates from Diseased Eyes
Fungal keratitis can be a vision-threatening disease, with reported maintenance of vision in 53% to 64% of affected horses13-18 (Fig. 10-1). Despite these reports, most veterinary ophthalmologists consider prognosis for vision favorable with aggressive surgical and medical management.13,14 *Aspergillus* spp. and *Fusarium* spp. are typically identified as etiologic agents of equine keratomycosis (Fig. 10-2). Fungal keratitis appears to be most common in the summer and fall,19,20,21 although this may vary by geographic location.

PRIMARY OCULAR INFECTION DISSEASES

Blepharitis
Infectious blepharitis, inflammation of the eyelids, may occur secondarily to bacterial, viral, fungal, or parasitic infection.

Regardless of cause, horses with blepharitis present with swollen inflamed eyelid(s). In the horse, bacterial blepharitis is the second most common type of blepharitis after trauma.23 Bacteria implicated as etiologic agents of equine blepharitis include *Moraxella* spp.24 and *S. equi* subsp. *equi*. Bacterial blepharitis is usually unilateral and subacute, with mucopurulent discharge or abscess formation.25 Papovavirus and horse pox can cause unilateral or bilateral blepharitis, chronic papillomas, or pustular dermatosis.25 Numerous fungal organisms cause a blepharitis that is usually unilateral, with chronic alopecia, scaling of the skin, granulomas, draining tracts, or granulation tissue. Specific organisms include *Trichophyton* spp., *Microsporum* spp., *Cryptococcus* *miraudii*, *Aspergillus* spp., *Rhinosporidium* *wetteri*, *Histoplasma* *scarlattii* (epizootic lymphangitis), and phycomycosis.24,25-28 Parasitic blepharitis may be unilateral or bilateral with pruritus and can have a gritty caseous discharge. Aberrant migration of the larvae of *Heligmosoma muscae* in *H. microstoma* or *Dracunculus megastoma* can result in pericorneal or eyelid lesions with a raised, irregular, yellow appearance often referred to as "sulfur granules."29 Biopsy of the affected area can aid in diagnosis to rule out other causes of ulcerative skin lesions, such as neoplasia, proud flesh, and bacterial or fungal granulomas.30 An eosinophilic infiltrate within a fibrous stroma will be evident histologically.31 Other parasites that can cause blepharitis include *Demodex* spp. and *Theelazia* spp.32 Parasitic ocular manifestations are discussed in more detail later in this chapter.

Conjunctivitis
Primary conjunctivitis in the horse is uncommon but associated with numerous infectious etiologies. Differentiation of primary conjunctivitis from secondary conjunctivitis resulting from other diseases (e.g., dacryocystitis, keratoconjunctivitis sicca, keratitis, uveitis, glaucoma) is important.33 Clinical signs associated with conjunctivitis are nonspecific to the underlying cause and include conjunctival hyperemia and chemosis. Other clinical signs may include follicle formation (Fig. 10-3), mucopurulent discharge, and depigmentation of the lateral aspect of the bulbar conjunctiva.
Several bacterial species have been identified as primary etiologic agents of conjunctivitis in horses. *Streptococcus equi* subsp. *equi* is associated with regional lymphadenitis (i.e., strangles), mucopurulent nasal discharge, and conjunctivitis (see Chapter 28). *Moraxella equi* and *Chlamydia and Mycoplasma* spp. have also been identified as causes of primary conjunctivitis in horses. *Histoplasma capsulatum* (epizootic lymphangitis) may result in ulcerative conjunctivitis. *Aspergillus* spp. and *Rhinosporidium seeberi* can cause granulomatous conjunctivitis and blastomycosis has been associated with nasolacrimal disease. Equine herpesvirus types 1 and 2 (EHV-1, EHV-2) can cause recurrent conjunctivitis with or without corneal ulceration (see Chapter 13). Adenoviral infection may result in conjunctivitis with mucopurulent ocular and nasal discharge, keratoconjunctivitis, and systemic disease (see Chapter 16). Equine viral arteritis may cause blepharoceratitis and conjunctivitis (see Chapter 14).

Parasitic conjunctivitis can be caused by *Thelazia lacrimalis*, *Onchocerca* spp., *Habronemla* spp., ophthalmomyiasis externa (*Oestrus ovis*), and *Trypanosoma evansi*. *Thelazia lacrimalis* can cause mild conjunctivitis and epiphora (Fig. 10-4). *Habronemla* results in depigmentation of the lateral aspect of the bulbar conjunctiva with or without uveitis (Fig. 10-5). *Habronemla* results in granuloma formation with mucopurulent discharge (Fig. 10-6).

**Keratitis**

Infectious corneal disease in horses most often occurs secondary to corneal trauma but can also be a manifestation of primary ocular disease or systemic disease. Normal uncomplicated corneal epithelial wound healing in the horse occurs at an average rate of 0.6 mm/day. Healing of corneal stromal wounds is more complicated and involves collagen remodeling and proteoglycan synthesis, eventually resulting in restoration of tensile strength. The prominent anatomic location of equine eyes and the normal opportunistic bacterial and fungal periorcular flora predispose equine corneas to infectious keratitis. Infectious keratitis caused by trauma may or may not be ulcerative and may be caused by opportunistic bacterial or fungal organisms, or a combination of these. Non-specific signs of keratitis include pain (blepharospasm, photophobia, epiphora), serous to mucopurulent ocular discharge, corneal edema, variable corneal vascularization, loss of stromal integrity (melting or keratomalacia), and secondary anterior uveitis (aqueous flare).
hypothesis, miosis). Horses with infectious ulcerative keratitis will have loss of corneal epithelium and variable stromal loss, full-thickness loss of corneal stroma that breaches Descemet's membrane will usually be plugged with fibrin and iris prolapse, with or without aqueous leakage (Fig. 10-7). This is a surgical emergency, and an ophthalmologist should be consulted. Horses with infectious nonulcerative keratitis will have an intact corneal epithelium, but cellular infiltration will be evident within the corneal stroma, that is, corneal abscess (Fig. 10-8). Fungal virulence factors may inhibit corneal vascularization and reduce neutrophil infiltration and cell-mediated phagocytosis.

impeding healing and necessitating aggressive medical and surgical intervention. In horses with progressive or perforated corneal ulceration, keratectomy with a conjunctival pedicle flap will provide diagnostic and therapeutic benefits to the patient. Stromal loss that has progressed beyond three-quarters depth may be treated with debridement, followed by synthetic or heterologous corneal grafts and a conjunctival pedicle flap (Fig. 10-9).

Primary infectious keratitis that is not associated with trauma may be caused by equine herpesvirus (EHV) and other respiratory viruses (e.g., adenovirus, influenza, Borna virus). Each of these diseases is discussed separately elsewhere in this text. EHV keratitis typically presents as superficial punctate or dendritic lesions secondary to EHV-2 infection. Acute cases will be quite painful (blepharospasm, serous epiphora) with chemosis and conjunctival hyperemia. Recurrent cases may exhibit corneal vascularization.

Diagnostic evaluation of infectious ulcerative keratitis may include evaluation of corneal cytology, culture and sensitivity, and histopathology. Nonulcerative keratitis is difficult to assess by cytology and culture and sensitivity because of the intact corneal epithelium. Definitive diagnosis of both these disorders can often be obtained at surgery by biopsy of the infected tissue. A rapid and new diagnostic test available at the author's institution is quantitative polymerase chain reaction (PCR) for fungal deoxyribonucleic acid (DNA). This assay can also be performed on formalin-fixed, paraffin-embedded tissues for retrospective analysis and may ultimately provide a more rapid and precise identification of corneal pathogens. The superficial or punctate lesions of EHV can be identified by rose bengal stain but not always with fluorescein stain. EHV keratitis can also present as anterior stromal or epithelial punctate opacities without ulceration. This makes diagnosis difficult, and other differential diagnoses should be considered, including fungal keratitis. Diagnosis of EHV keratitis is difficult, but cytology early in the course of disease may be helpful.

Infectious ulcerative keratitis that has not progressed beyond one third of the stromal depth can be treated medically. Depending on the underlying cause, topical antifungal medications (e.g., miconazole, natamycin, itraconazole with DMSO) and oral antifungal medications (e.g., fluconazole) may be necessary. All horses with corneal ulceration should be treated with topical cycloplegics (e.g., atropine, q2-24h), oral nonsteroidal antiinflammatory drugs (NSAIDs; e.g., flunixin meglumine).
for pain and secondary uveitis, and topical antibacterial medications (e.g., neomycin-polymyxin-bacitracin, neomycin-polymyxin-gramicidin, chloramphenicol, or ciprofloxacins, q4-6h), to prevent opportunistic bacterial growth.

Melting corneal ulcers can rapidly become surgical emergencies and should be treated aggressively (Fig. 10-10). The underlying infectious causes of melting corneal ulcers include *Pseudomonas* spp., β-hemolytic streptococci, and fungal infections. Neutrophilic infiltrates and previous corticosteroid use can predispose to melting corneal ulcers. Medical management should include compounds with antiproteolytic activity in addition to the medications just listed and appropriate antibacterial medications for the specific bacteria. Several antiproteases have been recommended for treatment of melting corneal ulcers, including 0.2% ethylene-diaminetetraacetic acid (EDTA), 9% to 10% N-acetyllysolecine, autologous serum, and topical or oral tetracycline or doxycycline. If a member of the tetracycline family is used topically, because of its bacteriostatic nature, its administration should be staggered with the bactericidal antibiotic used by at least 1 hour. Most horses with melting corneal ulcers should be examined by a veterinary ophthalmologist and will likely require surgical intervention.

Topical corticosteroids should be avoided in all horses with keratitis. Indolent or nonhealing corneal ulcers should be managed by debridement and topical antimicrobial and cycloplegic medications as well as oral NSAIDs. Grid or punctate keratotony should be avoided because of possible underlying fungal infection.

Therapy for EHV keratitis includes topical antiviral and NSAID therapies. Idoxuridine (0.1%) and trifluridine (0.3%) limit viral replication but do not kill the virus; therefore, they should be used between 4 and 12 times daily for 3 to 5 days until the condition stabilizes, then 3 to 6 times daily thereafter. Some formulations of these medications can be irritating to the eye. Topical NSAIDs include 0.03% flurbiprofen and 0.1% diclofenac and are helpful for secondary uveitis and inflammation, but they should be used with caution because they may cause recurrence of viral keratitis in human patients. Topical corticosteroids should be avoided in horses with EHV keratitis, as well as most horses with keratitis. Oral L-lysine is useful adjunctive therapy in human and feline patients with herpetic keratitis because it limits replication of the virus as a result of its competitive antagonism with arginine. There are no dose guidelines for L-lysine in horses, but empiric supplementary doses of 10 to 30 g once daily indefinitely have been suggested. Viral keratitides that are not associated with EHV are uncommon in the United States but can be treated similarly to EHV keratitis with topical antiviral and NSAID therapy.

Uveitis

Uveitis is inflammation of the uveal tract, which includes the iris, ciliary body, and choroid. Anterior uveitis refers to inflammation of the iris and ciliary body, posterior uveitis refers to inflammation of the choroid, and pars planitis refers to inflammation of all components of the uvea. Clinical signs of active uveitis are nonspecific and include pain (blepharospasm, photophobia, epiphora, ocular discharge), conjunctival hyperemia, scleral injection, corneal edema, keratic precipitates, aqueous flare hypopyon, hypophemia, fibrin in the anterior chamber or vitreous, iris color change, and miosis (Figs. 10-11 and 10-12). Chronic changes include atrophy of the corpora
dilation, and head tilt occur. Systemic clinical signs include fever, consciousness, proprioceptive deficits, and behavioral changes. In the later stages of disease, progressive signs of cerebellar or cerebrocortical and cranial nerve dysfunction may be seen and include facial, lingual, and pharyngeal paralysis, ataxia, hyporeflexia; cataract and proprioceptive deficits or paraplegia of the trunk and limbs; as well as blindness. Diagnosis, treatment, and prognosis for horses with alphahorse encephalitis are discussed in Chapter 20.66,67

Equine Viral Arteritis
Equine viral arteritis (EVA) is caused by a virus of the Arteriviridae family and is spread through inhalation of aerosolized virus or through sexual contact (see Chapter 14). Horses with clinical disease may exhibit signs of upper respiratory disease, edema, fever, and abortion 3 to 8 weeks after infection.68 Ocular signs include serous to mucoid ocular discharge, conjunctivitis, corneal opacity, photophobia, and periorbital edema. Diagnosis, treatment, and prognosis for horses with EVA are discussed in Chapter 14.69

Equine Infectious Anemia
Equine infectious anemia (EIA) is a chronic disease of horses caused by a virus belonging to the Lentivirus genus of the family Retroviridae (see Chapter 23). Although most infected horses show no recognizable clinical signs, other horses may present with signs that includes recurrent fever, weight loss, edema, thrombocytopenia, and anemia.70 Thrombocytopenia can result in ocular lesions, including conjunctival and intracocular hemorrhages. Choroiditis has also been described in horses with EIA.71 Horses with subacute to chronic disease develop anemia and may experience recurrent cycles of disease. Infected horses remain infected for life. Therefore, seropositive horses are considered infected. Diagnosis, prognosis, and prevention of EIA are discussed in Chapter 23.

Rabies
Rabies is a rapidly progressive, fatal disease caused by a neurotropic virus of the family Rhabdoviridae that may affect most warm-blooded mammals (see Chapter 19). Ocular signs rarely occur, or are not noticed, but may include prolapse of the third eyelid, blindness, nystagmus, and strabismus, most likely caused by diffuse cerebrocortical edema and hemorrhage.72 Euthanasia is recommended because no treatment is available. Appropriate caution should be taken with all animals with neurololgic signs, especially those not vaccinated for rabies. The most reliable diagnostic test remains the fluorescent antibody test performed on brain tissue.73

African Horse Sickness
African horse sickness (AHS) is a noncontagious, arthropod-borne orbivirus that affects all Equidae, although mules, donkeys, and zebras are less susceptible than horses (see Chapter 15). It is endemic in sub-Saharan Africa but has not been documented in North or South America. Ocular signs may include chemosis (conjunctival edema) and bulging of the supraorbital fossae.74 Bulging of the supraorbital fossae occurs in 10% to 20% of patients but is considered a hallmark sign of the disease; it is likely caused by retrobulbar edema and increased vascular pressure. Mortality for horses with AHS varies between 50% and 95%. Diagnosis, treatment, and prevention of AHS are discussed in Chapter 15.75

Equine Herpesvirus
Ocular signs have not been described in horses with EHV-1 or EHV-4 (see Chapter 13). EHV-2 is a cytomegalovirus that is not confirmed to have a primary association with systemic

SYSTEMIC DISEASES WITH OCULAR MANIFESTATIONS

Viral Diseases
Alphavirus Encephalitides
Alphaviral encephalitides (eastern, western, and Venezuelan equine encephalomyelitis) are transmitted by mosquitoes and have a typical geographic distribution (see Chapter 20). When the brain stem is involved, nystagmus, strabismus, pupill
disease in horses but is speculated to play a role in the pathogenesis of other diseases through immunosuppression or possible transactivation of EHV-1.9,86 (see earlier discussion). Ocular signs may include serous to mucopurulent ocular discharge, conjunctival hyperemia and chemosis, superficial dendritic or punctate corneal lesions, corneal edema, and variable vascularization.25,81 Therapy is discussed in the earlier section on keratitis.

**Adenovirus**

Equine adenovirus is not considered a pathogen in immunologically competent horses. The most frequent manifestation of adenovirus in the horse is lower respiratory tract disease in Arabian foals with combined immunodeficiency.82 Broncho pneumonitis is accompanied by mucopurulent ocular and nasal discharge. Conjunctival epithelial cells are histologically necrotic with intranuclear inclusions. A neutrophilic infiltrate is present in the uveal vasculature, consistent with panuveitis.25,86

**Equine Influenza**

Equine influenza is an acute respiratory tract disease caused by a virus of the family Orthomyxoviridae. Clinical signs of fever and serous or mucoid nasal and ocular discharge may last up to 10 days with a harsh, dry cough which persists for two to three weeks.83,84 Fever, cough, and a serous or mucoid nasal and ocular discharge are often present along with conjunctival hyperemia.29 Diagnosis, treatment, and prevention of equine influenza are discussed in Chapter 12.88

**West Nile Virus**

West Nile viral encephalitis is caused by a flavivirus and is considered endemic in North America, Europe, Africa, Asia, and the Middle East.86-88 (see Chapter 2). The most common ophthalmic abnormality observed in horses infected with West Nile virus is unilateral or bilateral facial nerve paralysis. Loss of menace response has also been reported, although its pathogenesis is uncertain.89 In an outbreak of West Nile encephalitis in Italy, mild keratitis and protrusion of the third eyelid were noted in horses that recovered from the disease.90 Some infected horses may experience blindness, presumably secondary to encephalitis (Ramiro Toribio, personal communication). In human patients, West Nile virus is reported to cause optic neuritis, uveitis, and choriorretinitis.91,92 Diagnosis, treatment, and prevention of West Nile virus are discussed in Chapter 21.93,94

**Bacterial Diseases**

**Tetanus**

Tetanus occurs following infection of a wound with Clostridium tetani, an anaerobic, spore-forming, gram-positive bacterium found in soil worldwide (see Chapter 47). The bacteria produce three toxins responsible for clinical signs: tetanospsamin, tetanolysin, and a nonsapsmogenic toxin. Tetanospsamin is responsible for the typical clinical signs associated with tetanus and inhibits the release of glycine and γ-aminobutyric acid (GABA), the main inhibitory neurotransmitters in the central nervous system (CNS).93

The characteristic ocular sign of tetanus in horses is rapid retraction of the globe with resulting bilateral prolapse of the third eyelid.54 Ocular signs of advanced tetanus include ventrolateral strabismus and fixed, dilated pupils with normal vision.95 Diagnosis, treatment, and prevention of tetanus in horses are discussed in Chapter 47.96

**Botulism**

The clinical signs of botulism are caused by a neurotoxin of the anaerobic bacterium, Clostridium botulinum (see Chapter 46).57 The toxin blocks the release of acetylcholine from the presynaptic peripheral cholinergic neurons, resulting in a neuromuscular blockade and generalized muscular weakness.98 Ocular signs associated with botulism include enophthalmos secondary to retractor bulbi spasm, upper eyelid ptosis, mydriasis, and slow pupillary light reflexes.57 Sluggish pupillary light reflexes can be detected within 6 to 18 hours of toxin ingestion, ultimately leading to complete mydriasis.57,99,100 Diagnosis, treatment, and prevention of botulism in horses are described in Chapter 46.61,62

**Lyme Disease**

Lyme disease is caused by *Borrelia burgdorferi*, a tick-borne bacterium found throughout North America, Europe, and Asia (see Chapter 35). Lyme disease (*B. burgdorferi*) causes nonspecific ocular signs that include conjunctivitis, anterior uveitis, severe panuveitis, and retinal detachment.97,98 Ophthalmologic signs reported in human patients with Lyme disease include conjunctivitis, keratitis, uveitis, panophthalmitis, papillary edema, retinal hemorrhage, and retinal detachment.97-103 Lyme disease–associated neurologic problems affecting the eye may include facial nerve paralysis and secondary corneal disease.99 In areas where Lyme disease is endemic, it may account for more cases of chronic uveitis than reported Diagnosis, treatment, and prevention of Lyme disease in horses are discussed in Chapter 35.

**Equine Granulocytic Ehrlichiosis**

Equine granulocytic ehrlichiosis is caused by a rickettsial organism, *Anaplasma phagocytophilum* (formerly *Ehrlichia equi*), that is also the causative agent of human granulocytic ehrlichiosis and tick-borne fever of cattle and sheep in Europe (see Chapter 42). Transmission occurs through the tick *Ixodes pacificus*. Ocular signs may include icteric sclera, conjunctival petechia, and uveitis.102 Diagnosis, treatment, and prevention of equine granulocytic ehrlichiosis are discussed in Chapter 42.

**Fungal Diseases**

**Cryptococcosis**

*Cryptococcus neoformans* is a pathogenic fungus that may cause systemic infection in horses and other mammals (see Chapter 57). Ocular signs are not usually reported in horses with cryptococcosis, although there is one report of a frontal sinus granuloma with a retrobulbar mass causing exophthalmos and periocular swelling.103 Diagnosis is based on histopathologic evidence of fungal hyphae in tissue samples or on cytology, as well as a positive culture.

**Epizootic Lymphangitis**

Epizootic lymphangitis, caused by *Histoplasma farciminosum*, a fungal agent found mainly in Africa (see Chapter 57), is manifested as nodules and draining lesions of the subcutaneous lymphatic system.140 A conjunctival form of this disease results from deposition of the organism on the ocular mucous membranes by the biting flies of the *Musca* and *Stomoxys* species. Ocular signs include serous to mucopurulent discharge, blepharohedema, and conjunctival papules.140 Disease progression leads to ulceration of the papules, which may result in obstruction and erosion of the lacrimal duct or secondary keratitis. Diagnosis is mainly by cytology and culture, although serologic assays are also available.141 Amphotericin B is the treatment of choice, and a vaccine is available for horses in endemic areas.140-142

**Aspergillosis**

*Aspergillus* spp. are considered opportunistic fungi that rarely cause systemic disease in immunocompromised horses (see Chapters 56 and 57). Aspergillosis is a cause of guttural
pouch mycosis; ocular manifestations can include Horner’s syndrome, facial nerve palsy, and blindness resulting from ischemic optic neuritis secondary to extension of disease. These organisms are ubiquitous in the environment, and horses are frequently exposed. Treatment with systemic antifungal agents may be attempted; however, the prognosis is always guarded depending on the underlying disease process and the severity of the lesions.

**Equine Leuкоencephalomalacia**

Equine leuкоencephalomalacia (ELM), also called “blind staggers” or “moldy corn disease,” causes central blindness when the midbrain is affected (see Chapter 57). Severe multifocal neurologic signs, including ataxia, agitation, and seizures, may accompany the blindness associated with ELM. Chronic ingestion of moldy corn infected with *Fusarium moniliforme* and its associated mycotoxin, fumonisin B1, results in liquefactive necrosis of the white matter. If one horse on the farm is affected, other horses have likely been exposed, and feed should be checked for the mold. Hepatic enzyme activities are often increased in horses exposed to the toxin and may be used as a screening test. Once neurologic signs have developed, the prognosis is poor. If attempted, treatment should consist of supportive care, fluids, and administration of activated charcoal to decrease absorption of the toxin.

**Parasitic Diseases**

**Equine Protozoal Myeloencephalitis**

*Sarcocystis neurona* is the primary etiologic agent of equine protozoal myeloencephalitis (EPM), one of the most common neurologic disorders of horses in North America (see Chapter 59). A few reports suggest that *Neospora caninum* may cause an identical clinical syndrome. Neurologic signs of EPM vary greatly depending on the area of the CNS that is affected. If the seventh and eighth cranial nerves (CN VII, CN VIII) are affected, horses may present with signs of facial nerve paralysis or vestibular disease, respectively. Ocular signs associated with facial nerve paralysis include ptosis and absence of the palpebral reflex. If the parasympathetic nucleus of CN VII is affected, neurogenic keratoconjunctivitis sicca will occur; predisposing the cornea to ulceration and secondary infectious keratitis. EPM affecting the cervical spinal cord may cause Horner’s syndrome. To the authors’ knowledge, there are no published reports of blindness or fundic lesions in horses with EPM. Diagnosis, treatment, and prognosis for horses with EPM are discussed in Chapter 59.

**Babesiosis (Piroplasmosis)**

Piroplasmosis is a hemolytic disease of horses caused by the tick-borne protozoa *Babesia caballi* and *Babesia equi* (see Chapter 60). Ophthalmic signs of babesiosis include serosanguineous ocular discharge, distention of the superotemporal fossa, blepharohema, icteric conjunctiva and sclera, and petechiae and ecchymoses of the conjunctiva. Diagnosis, treatment, and prevention of piroplasmosis are discussed in Chapter 60.

**Toxoplasmosis**

*Toxoplasma gondii* is a protozoan that can infect the horse, although clinical disease is rare. One study examined three separate horse populations in India and found that in the few horses with ocular lesions, there was no correlation with positive titers for *T. gondii*. Another serologic study of 71 horses with ocular lesions associated with ERU found no correlation with positive titers for *T. gondii*. There are sporadic case reports of horses with ocular lesions associated with toxoplasmosis. *T. gondii* DNA was isolated from the retina, choroid, and sclera of both eyes of a 17-year-old pony from the United Kingdom; however, the presence or absence of ocular lesions or visual deficits was not noted. There is one report of panretinopathy and partial optic nerve atrophy in a horse with toxoplasmosis. In a study of seven horses with choroiditis, five had *T. gondii* titers of 1:64. One of these horses became acutely blind 4 days before presentation and had diffuse, chronic choroiditis in the right eye and acute chorioretinitis in the left eye. At presentation the titer was negative, although 16 days later the titer was 1:64. Postmortem histologic examination of the brain found intracytoplasmic *Toxoplasma* bodies.

**Onchocerciasis**

*Onchocerca volvulus* is spread by *Culicoides* spp. and is a common cause of dermatitis in horses (see Chapters 58 and 62). It is thought that microfilariae migrate along vessels through subcutaneous tissue to the eyelids, then into the conjunctiva, cornea, and uvea. Ocular microfilariae have been reported in horses, and the prevalence varies by geographic location. The most common ocular lesion evident is pigmentary degeneration of the conjunctiva at the temporal limbic region. Similar to systemic onchocerciasis, ocular disease is usually caused by an inflammatory reaction to the antigens of dead parasites releasing antigens. Other ocular manifestations include conjunctivitis, peripheral keratitis, and anterior and posterior uveitis. Conjunctivitis and keratitis are characterized by chemosis, conjunctival follicles, corneal edema and vascularization, and subepithelial yellow-to-white corneal opacities. Keratitis is typically seen at the temporal limbus but can extend axially and may be accompanied by temporal conjunctivitis and anterior uveitis. Clinical signs of uveitis include episclera, blepharospasm, miosis, and aqueous flare. Signs of posterior uveitis can include panretinopathy, chorioretinitis, and choriodoretinal scarring. Although onchocerciasis is often implicated in the pathogenesis of ERU, it is difficult to ascertain the true significance of the association because of the prevalence of the parasite in the normal horse population.

The goal of treatment for onchocerciasis is to reduce ocular inflammation and destroy the microfilariae. Ivermectin is effective at killing microfilariae, but it will not kill the adult parasites. Systemic therapy (e.g., flumioxazin meglumine or phencydylbutazine) and topical antiinflammatory therapy is warranted. Topical corticosteroid and NSAID therapy should not be used if a corneal ulcer is present, except under the advisement of a veterinary ophthalmologist. Treatment may initially worsen clinical signs, and the disease may recur. Lesions are seasonal, and older horses are more likely to be affected than younger horses.

**Habronemiasis**

Cutaneous habronemiasis, also known as "summer sores," is caused by aberrant intradermal migration of the larvae of *Habronema* or *Dracunculus* spp., which are normally found in the stomach (see Chapter 62). Lesions usually develop during the warmer months in traumatized skin and are caused by a hypersensitivity reaction to dying larvae. Granulomas with necrotic centers are typically seen on the lower limbs, the urogenital process, or the eye. Mineralized larvae can be observed in the center of the lesion.

Common ocular locations for habronemiasis include the medial canthus, eyelid, conjunctiva, lacrimal caruncle, nasolacrimal duct, and third eyelid. Periocular or eyelid lesions have a raised, irregular, yellow appearance often referred to as "sulfur granules." The granulomatous lesions are often covered with an exudate and are painful when touched. When the nasolacrimal system is involved, a circular lesion may develop below the medial canthus. Biopsy of the affected area should be performed to aid in diagnosis and to rule out...
other causes of ulcerative skin lesions. Histopathologically, central cavitations (some with nematode larvae) are surrounded by degenerate and degranulating eosinophils and granulomatous inflammation.3.9

Treatment of habronemiasis consists of an adequate deworming program that includes ivermectin, debridement of the lesions, topical and systemic antiinflammatory therapy, and adequate fly control. In severe cases, systemic corticosteroids may substantially lessen the granulomatous reaction.50,143,173

**Thelaziasis**
Ocular disease caused by *Thelazia lucificalis* is uncommon. This tapeworm parasite is a commensal organism that lives in the lacrimal gland, conjunctival fornices, and nasolacrimal duct. It can cause mild blepharoconjunctivitis and dacycystitis.124 Diagnosis of the disease is confirmed by identification of the parasite in conjunctival fluid or nasolacrimal flushes.

**Setariasis**
*Setaria digitata* and *S. equina* are nematodes normally found in the stomach. Aberrant migration of *Setaria* spp. into the eye can occur in horses, resulting in severe intraocular inflammation.79 Clinical signs include photophobia, epiphora, corneal edema, hypopyon, aqueous flare, and miosis.103-104 Successful surgical removal of the nematode from the anterior chamber has been reported.102 In a pilot study, treatment with diethylcarbamazine decreased microfilariaemia in horses.106 Antiinflammatory therapy should be instituted in conjunction with antiparasitic agents.

**Dirofiliariasis**
Intraocular migration of *Dirofilaria immitis* is less common in horses than in carnivores, although successful removal of the nematode from the anterior chamber of a horse has been reported.105

**Echinococcosis**
*Echinococcus granulosus* is a small tapeworm that causes hydatid disease (see Chapter 51). Dogs are the definitive hosts, and horses are considered intermediate hosts. Exophthalmos, blindness, and head shaking caused by retrolubar cysts are the only reported ocular manifestations of hydatid cyst disease in the horse.105-106 The only definitive treatment is surgical excision, although treatment with albendazole can decrease the size of the cyst.128 Diagnosis is based on positive histopathologic or cytologic identification. Cysts are usually an incidental finding at necropsy, but they are of particular concern because they can cause severe disease in humans, another intermediate host.

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**NEURO-OPTHALMIC INFECTIONOUS DISEASES**

**Vestibular Disease**
Vestibular signs may result from either peripheral or central nervous system diseases. Peripheral disease causes ipsilateral head tilt, horizontal or rotary nystagmus with the fast phase occurring away from the side of the lesion, falling, circling, and asymmetric ataxia without conscious proprioceptive deficits or weakness.55,105 Common causes of peripheral vestibular dysfunction include trauma, otitis media, temporomandibular osteoarthropathy, and gullet pouch disease.106-109 Facial nerve paralysis (Fig. 10-14) and Horner's syndrome can occur with peripheral disease because of the facial nerve and sympathetic nerve proximity to the petrous temporal bone.108,109,110

Central (CNS) vestibular disease presents similarly, although conscious proprioceptive deficits, generalized weakness, and involvement of multiple cranial nerves may be present.110 Nystagmus may be rotary, horizontal, vertical, diagonal, or disconjugate (different in each eye). The direction of the nystagmus may change with head position in central vestibular disease.55,105 Paradoxical central vestibular disease may occur with a destructive lesion near the caudal cerebellar peduncle, resulting in clinical signs contralateral to the lesion.105 Bilateral vestibular disease is difficult to differentiate from generalized cerebellar disease; these horses do not have nystagmus or vestibular eye movements and usually exhibit a symmetric ataxia.105 Central vestibular dysfunction is often associated with tumors or abscesses but may also be secondary to protozoal, viral, bacterial, or parasitic encephalitides.105,111

Diagnostic techniques for determining the underlying cause of vestibular disease in the horse should include radiographs of the skull, endoscopy of the pharyngeal region and gullet pouches, and magnetic resonance imaging (MRI) or computed
tonography (CT) scan of the head. Cerebrospinal fluid (CSF) cytology and ancillary testing for viral or protocoll antibodies are indicated if CNS disease is suspected.\textsuperscript{108,109} Caloric testing can be performed, although the test is not always reliable, and most horses will resist the procedure. In caloric testing the ear canal is irrigated with cold water, and a normal response is induction of horizontal nystagmus away from the tested side. A decreased or absent reaction indicates the side of the lesion. Brain stem auditory-evoked responses are also useful in demonstrating damage to the cochlea and CN VIII and can be used to differentiate between central and peripheral disease.\textsuperscript{112,113} This procedure is reliable in the sedated horse. Treatment and prognosis should address the primary disease process.

**Horner’s Syndrome**

Horner’s syndrome is caused by damage or denervation along any portion of the efferent pupillomotor sympathetic nervous system. The sympathetic nervous system originates in the hypothalamus, where the central sympathetic fibers form the tegmentospinal tract (first-order neurons).\textsuperscript{55} This tract descends ipsilaterally through the brain stem and lateral funiculus of the spinal cord to synapse with the preganglionic cell bodies of the first to third thoracic vertebrae (T1–T3) or T4. These preganglionic sympathetic neurons [second-order neurons] leave the spinal cord through the segmental ventral roots to the paravertebral sympathetic chain, continue through the brachial plexus, and travel with the vagosympathetic trunk until they synapse in the cranial cervical ganglion cervicomedial to the tympanic bulla. The postganglionic fibers (third-order neurons) join the tympanic branch of CN IX (glossopharyngeal nerve) within the middle ear and pass over the caudal dorsal aspect of the gullett. After the fibers exit the middle ear, they enter the cavernous sinus and join CN V (trigeminal nerve) and continue rostrally as the nasociliary nerve to innervate the orbital smooth muscles, the eyelids (including the third eyelid), and the ciliary body, iris dilator, and iris sphincter muscles.

Horner’s syndrome in horses is most frequently seen secondary to gullett pouch disease.\textsuperscript{65} Injury to the cranial thoracic spinal cord, brachial plexus avulsions, and traumatic lesions or masses involving the mediastinum, periorbital tissues, or cervical structures may also cause clinical signs of Horner’s syndrome.\textsuperscript{114,115} Intracerebral Horner’s syndrome can result from surgical ligation of the carotid artery. Other causes unique to the horse include polynuromitis equi syndrome, EPM affecting the cervical spinal cord, basilar artery trauma, esophageal rupture, and intravenous injection with various drugs, including phenylbutazone.\textsuperscript{118,119} Clinical signs of Horner’s syndrome in horses include ptosis, relative enophthalmos, subcutaneous miosis, regional hyperesthesia, and excessive sweating on the ipsilateral side of the face.\textsuperscript{114,121,123} Cervical sympathetic nerve damage will cause sweating of the neck, congested conjunctival and nasal mucous membranes, and inspiratory stridor.\textsuperscript{49,122,123}

The location and cause of the lesion will determine which clinical signs are present, and the location will determine what diagnostic tests should be performed. Often, location may provide the diagnosis. Phenylephrine (2% or 10%) or 1:1000 epinephrine are more readily available for the pharmacologic localization of efferent sympathetic lesions. Phenylephrine or epinephrine are direct-acting sympathomimetic drugs that will result in mydriasis within 5 to 8 minutes in postganglionic lesions caused by denervation hypersensitivity of the effector cells.\textsuperscript{55} This test can effectively distinguish between preganglionic and postganglionic lesions during the first few weeks of clinical signs.\textsuperscript{105} One drop of phenylephrine or epinephrine is applied to each eye (the normal eye is used for comparison), and care should be taken to use the same amount in each eye because the response is dose dependent. Mydriasis, retraction of the third eyelid, resolution of the enophthalmos, and ptosis are all positive responses to the phenylephrine test and indicate a postganglionic or third-order lesion. If a lesion localizes to the postganglionic arm of the pathway, endoscopy of the pharynx and gullett pouch should be performed. Alternatively, CT is another diagnostic option when available.

**REFERENCES**

See the CD-ROM for a list of references linked to the abstract in PubMed.
EQUINE TOROVIRUS

Debra C. Sellon

Etiology
Equine torovirus (Berne virus) was originally isolated from a rectal swab of a horse with hepatic and gastrointestinal disease in Berne, Switzerland, in 1972. It is currently classified in the Torovirus genus with bovine, human, and porcine toroviruses, within the family Coronaviridae and order Nidovirales. The enveloped virions are pleomorphic with large protein spikes on the surface, resembling the peplomers of coronaviruses. The nucleocapsid has a tubular appearance with helical symmetry. The positive-sense RNA genome is estimated to be 20 to 25 kilobases in length with six open reading frames (ORFs). Four structural proteins have been identified: spike (S), membrane (M), hemagglutinin-esterase (HE), and nucleocapsid (N) proteins.

Epidemiology
Although originally isolated from a horse with gastrointestinal disease, a causal link between Berne virus and equine disease has not been established. Limited seroepidemiologic studies indicate that the virus is present in Europe and the United States. Neutralizing antibody is also found in the sera of other ungulates (cattle, sheep, goats, pigs), laboratory rabbits, and at least two species of wild mice (Clethrionomys glareolus and Apodemus sylvaticus).

Clinical Findings
Despite widespread evidence of exposure to Berne virus, no evidence indicates that this virus is associated with clinical disease in horses or any other species. Inoculation of the virus into two foals induced neutralizing antibody without associated clinical signs. Bovine torovirus has been associated with gastroenteritis in calves and possibly pneumonia in older cattle. Human and porcine toroviruses are associated with gastroenteritis in people and pigs, respectively.

REFERENCES
See the CD-ROM for a list of references linked to the abstract in PubMed.

CHAPTER 19

Rabies

Pamela A. Wilkins and Fabio Del Piero

Rabies virus (RABV) is an enveloped ribonucleic acid (RNA) rhabdovirus that induces lethal polioencephalomyelitis and ganglionitis in infected animals. The disease is universally endemic in mammals and other warm-blooded vertebrates, except in Australia, where other types of azeotropic lyssaviruses transmitted by flying foxes (bats) are present. The disease has been excluded or eradicated from some countries, or parts of them, especially islands (e.g., Great Britain, New Zealand, Iceland).

ETIOLOGY
Viruses in the Rhabdoviridae family known to infect mammals belong to either the genus Vesiculovirus (vesicular stomatitis virus serotype New Jersey and serotype Indiana, Chandipura virus, and Piry virus) or the genus Lyssavirus (rabies virus and rabieslike viruses). Lyssaviruses include six distinct genotypes that can be classified according to their degree of amino acid homology. Genotypes 2 (Lagos bat virus) and 3 (Makola virus) are the most phylogenetically distant from the vaccinal and classic rabies viruses of genotype 1. Genotypes 4 (Duvenhage virus) and 5 (European bat lyssavirus 1 [EBL1]) are closely related to each other, with the separate genotype 6 represented by EBL2.

RABV virions are enveloped, bullet-shaped, 45 to 100 nm in diameter, and 100 to 430 nm long (Fig. 19-1). Surface projections of the envelope are distinct spikes, dispersed evenly over the whole surface (except for the fusiform end of bullet-shaped viruses). The uncoiled nucleocapsid is filamentous, with regular surface structure, and cross-banded. Virions contain 1% to 2% nucleic acid composed of one molecule of linear, usually negative-sense, single-stranded RNA. Nucleotide sequences of the 5' terminus are inverted and complementary to similar regions on the 3' end and are the same for each gene segment in species of the same genus. Virions contain 65% to 75% protein, most of which are structural. RABVs are recognized and classified through panels of monoclonal
antibodies against nucleocapsid proteins. The pattern of antilycoprotein reactivity of the isolates allows identification of the viral subtype.

**Epidemiology**

RABV is transmitted to warm-blooded animals by bites from infected vectors such as foxes, raccoons, skunks, bats, and vampire bats. In 2003, wild animals accounted for more than 91% of all cases of rabies reported to the Centers for Disease Control and Prevention (CDC). Rabies control programs, including vaccination programs, have significantly decreased, if not eliminated, rabies in humans caused by canine variants. However, ever-increasing numbers of human cases are attributable to bat variants, a group difficult to target for rabies control by traditional methods.

In the United States, rabies infection of terrestrial mammals occurs in geographically defined regions, and transmission is usually within species, with occasional spillover to other species that rarely maintain intraspecific transmission (Fig. 19-2). Sixty-three cases of rabies were reported in horses and mules (including donkeys) in 2003, an 8.9% increase over the 59 cases reported in 2002 (Fig. 19-3). The majority of rabies in horses occurs in animals with no history of vaccination, although it may be recognized in animals not vaccinated within a year of diagnosis. The increase in equine rabies in 2003 was consistent with the increase observed in raccoons, 8.9%, while the number of rabid skunks decreased by about 13%.

**Pathogenesis**

The primary means of transmission of RABV is through the bite of an infected animal that inoculates saliva containing virus into tissues of a receptive animal. The virus likely replicates in muscle tissue at the site of inoculation. Rabies virus is believed to remain near the site of initial inoculation for most of the incubation period. In 1889, DiVesto and Zagari showed that mortality was greatly diminished by severing the sciatic nerves of experimental animals before virus was inoculated in the footpad. This reduction in mortality is seen even when the nerves are severed several days after inoculation of virus. Delayed progression of infection within muscle cells is thought to be responsible for the long incubation period of clinical rabies.

Eventually, RABV binds to nicotinic acetylcholine receptors at the neuromuscular junction, the major site of entry into neurons. The neural cell adhesion molecule, the low-affinity p75 neurotrophic receptor, and perhaps the N-methyl-D-aspartate NR1 receptor may also function as RABV receptors.

The virus then travels in an ascending fashion through the spinal cord to the brain or from the cranial nerves directly to the brain stem. Once transit in peripheral nerves begins, it progresses rapidly through transynaptic neuronal spread. Virus can be observed in peripheral nerve myelin late in infection. Clinical signs appear to result primarily from neuronal dysfunction secondary to drastically diminished synthesis of proteins required for maintenance of normal neuronal function. After it reaches the brain, RABV is passed centrifugally to tissues and organs. It reaches the salivary glands and nasal secretions after passage down appropriate cranial nerves.
CLINICAL FINDINGS

Several authors have described clinical signs of rabies in horses in detail. These signs range from poor racing performance to bizarre behavior and may include spinal cord, cerebellar, and cranial nerve signs; apparent lameness; gastrointestinal signs; and genitourinary signs (Fig. 19-4). Clinical signs are progressive from onset until death, which usually occurs by day 10. Average survival from the onset of clinical signs is approximately 5 days. Clinical chemistry and hematologic results are nonspecific and nondiagnostic. Cerebrospinal fluid (CSF) analysis reveals increased protein and lymphocytes but is not diagnostic.

Spinal cord signs are frequently observed in horses with rabies and may include subtle hindlimb lameness or shifting of weight in the hindlimbs, progressing to knuckling of one or both fetlocks. Ataxia or weakness usually follows, with paresis advancing to total pelvic limb paralysis when spinal cord signs are present. Associated signs may be constipation, tenesmus, paraparesis in males, dribbling of urine from bladder paralysis, and flaccid tail and anus.

The classic description of encephalitis signs includes evidence of progressive depression ("dumb" form) or aggression ("furious" form). Depression is often characterized by extreme obtundation, whereas aggression often includes hyperesthesia and self-mutilation. Other accentuated cerebral responses observed in rabies patients are hypersexuality with frequent mounting behavior, localized or generalized pruritus leading to self-injury, tremors, seizures, alert eyes and ears despite paralysis or ataxia, blindness, head pressing, bellowing, and opisthotonos. Dysphagia, salivation, and a weak tongue may occur, often accompanied by an inability to drink, which may reflect laryngeal paralysis.

Several common diseases should be considered as differential diagnoses of rabies. In the paralytic form with spinal cord signs predominating, sacral injuries from estrous activities and spinal cord neoplasms or abscesses should be considered. In advanced rabies cases approaching coma, many encephalitides and toxic central nervous system (CNS) diseases should be considered.

PATHOLOGIC FINDINGS (FIGS. 19-5 THROUGH 19-13)

Gross CNS lesions of rabies are rare in horses and may consist of focal to multifocal, mild to moderate hemorrhages. Self-trauma or aspiration pneumonia may be seen. Histologic

http://www.cdc.gov/ncidod/dvrd/rabies/professional/publications/DFA_diagnosis/DFA_protocol-b.htm
lesions of rabies in horses are similar to lesions in cattle, although with more frequent neuronal vacuolization, and much less frequent Negri body formation.\(^4\) There is a clear viral tropism for gray matter, neuronal cell bodies, and glial cells. Less virus antigen is found in animals euthanized early in the disease process. Histologic lesions observed in rabid animals, which died or were euthanized, consist of nonsuppurative perivascular encephalomyelitis with ganglionitis. Moderate to severe lymphocytic perivascular inflammation in gray and white matter of cerebral hemispheres with mild lymphocytic leptomeningitis is often present. In the basal nuclei, gray matter of the thalamus, and the brain stem, there is prominent inflammation with diffuse gliosis and the presence of lymphocytes in the neuropil. In these areas and in the hippocampus, neuronophagia, neuronal chromatolysis, microglial cell nodules, and proliferation of rod cells tend to be constant features. Moderate lymphocytic inflammation infiltrates the subependymal tissue of the lateral ventricles and fornix. The cerebellum contains mild perivascular lymphocytic inflammation in the molecular layer, mild lymphocytic leptomeningitis, and moderate inflammation of the white matter. Negri bodies, eosinophilic

intracytoplasmic inclusions associated with accumulations of viral and cell protein (see Fig. 19-7), are observed in pyramidal cells of the hippocampus, extensively in Purkinje cells and infrequently in the neocortex, without inflammatory changes. Mild ring hemorrhages are occasionally observed multifocally. Trigeminal ganglia are affected by severe lymphocytic inflammation with neuronal degeneration, neuronophagia, and formation of Negri bodies, which are aggregates of glial cells replacing a neuron (see Figs. 19-11 and 19-12).

Using indirect peroxidase IHC with monoclonal antibodies, RABV can be identified within neural cell cytoplasm and processes.\(^4\) Often the distribution of RABV is prominent, with marked intracytoplasmic immunoreactivity of almost all neurons in every brain area and diffuse granular positivity of the neuropil of cerebral and cerebellar cortices, the thalamus, and the gray matter of the brain stem and spinal cord. RABV forms fine to large granules and 3- to 10-micron inclusion
Fig. 19-9  Rabies; horse, cerebellum. Purkinje cells and granular cells contain variously sized, round to oval, often prominent, rabies virus aggregates. (IPIHC and HE stain.)

Fig. 19-10  Rabies; horse, brain stem. The cytoplasm of this nuclear neuron is heavily colonized by rabies virus, which extends within the visible dendrite and the axon; surrounding fibers also contain rabies virus, and there is moderate focal gliosis (left). (IPIHC and HE stain.)

Fig. 19-11  Rabies; horse, trigeminal ganglion. Severe, diffuse lymphocytic ganglionitis. (HE stain.)

Fig. 19-12  Rabies; horse, trigeminal ganglion. Abundant intracytoplasmic rabies virus within ganglionic neurons and trigeminal nerve fibers (right); there is a gathering of glial cells replacing a necrotic phagocytized neuron (Negri body) and lymphocytic ganglionitis. (IPIHC and HE stain.)

Fig. 19-13  Rabies; horse, retina. In absence of histologic lesions, the entire retinal layers contain variable quantity of granular intracytoplasmic rabies virus; particularly colonized are the ganglion cells, the inner plexiform layer, and the outer nuclear layer. (IPIHC and HE stain.)

bodies that are single or multiple and distributed homogeneously within the cytoplasm. RABV is predominantly observed in neuronal cell bodies, axons, and dendrites, which appear morphologically normal. There is prominent immunostaining of cortical neurons, pyramidal cells, and neurons of gyrus dentatus as well as nuclei of the thalamus and brain stem. In the cerebellum, RABV is primarily localized within the Purkinje cells and some neurons of the granular and molecular layers. The spinal cord often contains abundant RABV in dorsal and ventral horns, with sparing of the white matter. RABV is also observed in some astrocytes and oligodendrocytes, ganglion cells of the retina and trigeminal ganglia cells, and autonomic ganglia of celiac-mesenteric ganglia. Negri bodies are reported in less than 30% of cases, and their absence should not rule out rabies as a diagnosis.
### Table 19-1

**Approved Rabies Vaccines for Use in Horses (as of 2004)**

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>MANUFACTURER</th>
<th>DOSE</th>
<th>RECOMMENDED BOOSTER</th>
<th>ROUTE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monovalent (Rabies Inactivated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RABVAC 3</td>
<td>Fort Dodge Animal Health (Lic. #112)</td>
<td>2 mL</td>
<td>Annually</td>
<td>IM</td>
</tr>
<tr>
<td>RABVAC 3 TF</td>
<td>Fort Dodge Animal Health (Lic. #112)</td>
<td>2 mL</td>
<td>Annually</td>
<td>IM</td>
</tr>
<tr>
<td>IMRAB 3</td>
<td>Merial Inc. (Lic. #298)</td>
<td>2 mL</td>
<td>Annually</td>
<td>IM/SC</td>
</tr>
<tr>
<td>IMRAB</td>
<td>Merial Inc. (Lic. #298)</td>
<td>2 mL</td>
<td>Annually</td>
<td>IM/SC</td>
</tr>
<tr>
<td>Large animal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination (Rabies Inactivated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equine</td>
<td>Merial Inc. (Lic. #298)</td>
<td>1 mL</td>
<td>Annually</td>
<td>IM</td>
</tr>
<tr>
<td>POTOMOVAC + IMRAB</td>
<td>Merial Inc. (Lic. #298)</td>
<td>1 mL</td>
<td>Annually</td>
<td>IM</td>
</tr>
<tr>
<td>MYSTIQUE II POTOMOVAC+</td>
<td>Intervet Inc. (Lic. #286)</td>
<td>1 mL</td>
<td>Annually</td>
<td>IM</td>
</tr>
</tbody>
</table>

*IM, Intramuscular; SC, subcutaneous.

### THERAPY

No known therapy is effective for treatment of unvaccinated or vaccinated horses with clinical rabies. Horses presenting with clinical signs of rabies should be isolated to prevent possible human exposure. Healthy, vaccinated horses suspected of being exposed to rabies may be quarantined for a period of observation for development of clinical signs. All species of livestock are susceptible to rabies; horses are among the most frequently infected. Horses exposed to a confirmed rabid animal and currently vaccinated with a vaccine approved by the U.S. Department of Agriculture (USDA) for that species should be revaccinated immediately and observed for 45 days (Table 19-1). Unvaccinated horses should be euthanized immediately. If the owner is unwilling to have this done, the horse should be kept under close observation for 6 months. More than one rabid horse in a herd, or herbivore-to-herbivore transmission, is uncommon. Therefore, if a single animal has been exposed to or infected by rabies, quarantine of the rest of the herd is not necessary.

### PREVENTION

The mainstays of rabies prevention are vaccination and exposure avoidance. Parenteral animal rabies vaccines should be administered only by, or under the direct supervision of, a veterinarian. Any veterinarian signing a rabies certificate should ensure that the person administering the vaccine is identified on the certificate and is appropriately trained in vaccine storage, handling, administration, and management of adverse events. This practice ensures that a qualified and responsible person can be held accountable to make certain the animal has been properly vaccinated.

A peak rabies antibody titer is reached within 28 days of primary vaccination. An animal is currently vaccinated and is considered immunized if the primary vaccination was administered at least 28 days previously and vaccinations have been administered appropriately.

Regardless of the age of the horse at initial vaccination, a booster vaccine should be administered 1 year later (Box 19-1). Because a rapid anamnestic response is expected, an animal is considered currently vaccinated immediately after a booster vaccination. Rabies is rare in vaccinated animals. If suspected, such an event should be reported to state public health officials, the vaccine manufacturer, and the USDA’s Animal and Plant Health Inspection Service (APHIS), Center for Veterinary Biologics.4 The laboratory diagnosis should be confirmed and the virus characterized by a rabies reference laboratory. A thorough epidemiologic investigation should be conducted.

### PUBLIC HEALTH CONSIDERATIONS

Rabies is considered a zoonotic disease. Although the authors were unable to find a single case of documented transmission of rabies from horse to human, the possibility is real, and all equine rabies suspects* must be handled as if a significant threat to human health exists. Animals with suspected rabies should only be handled by individuals who have had appropriate rabies preexposure vaccination. A list of all “in-contact” and potential in-contact individuals, including owners and

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*Based on vaccination guidelines of the American Association of Equine Practitioners (AAEP).
private parties, should be developed and kept current. It is convenient to place a clipboard near the stall housing a rabies suspect and require individuals to sign the list if they enter the stall, handle the patient, or handle biologic material from the patient. If rabies is a differential diagnosis, laboratory personnel handling body fluids obtained for diagnostic purposes should be informed of this potential. This is best accomplished by labeling all specimens obtained as “rabies suspect” on their containers and clearly stating this on any submission paperwork. Details of the CDC preexposure vaccination protocols can be found below* (at 700556176.htm).

Horses suspected of having rabies should be handled carefully, with examiners using protective gear that includes eye goggles, face shields/masks, and gloves during all examinations. Persons performing necropsy examinations on horses with suspected rabies are at increased risk of exposure to baby, although more extensive protective measures should be considered. Individuals who move the bodies of rabies suspects should wear rubber boots, a scrub suit, double gloves (the outer glove being heavy vinyl) with gauntlets, and a face shield for splash protection. Additionally, individuals who decontaminate and remove brains of rabies suspects should use the protection of a Tyvek coverall (or surgical gown at a minimum) and a mist mask rated for biohazards (N95 rating or better, routine surgical masks are unacceptable for this purpose). The brain half that is submitted for rabies testing should be placed in a sealed plastic container, the external surface thoroughly cleaned with an appropriate disinfectant, and the container then placed in a second clean plastic container. Samples for rabies testing should be transported in rigid, LEAKPROOF containers with the samples stabilized within the container by frozen gel packs or similar materials. The outer container should meet the federal standards for transport of diagnostic or dangerous goods.

The carcass and other specimens obtained at necropsy should not be submitted for additional studies until a negative rabies test result is obtained from the appropriate testing facility. If a positive test result is reported, all interested parties should be notified immediately, including the state veterinarian. Exposed individuals should consult their physician and local and state health authorities regarding postexposure treatment, which will vary depending on suspected level of exposure and preexposure vaccination status.

**ACKNOWLEDGMENTS**

The authors would like to acknowledge the assistance of John Krebs, MS, from the CDC, in the preparation of the manuscript. We would also like to acknowledge the CDC for allowing free use of their images.

**REFERENCES**

See the CD-ROM for a list of references linked to the abstract in PubMed.

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**CHAPTER 20 • Equine Alphaviruses**

E. Paul J. Gibbs and Maureen T. Long

The first recorded epidemic of eastern equine encephalitis (EEE) in horses likely occurred in Massachusetts in 1831; the first recorded human case occurred in that state in 1838. In 1933, EEE virus was isolated from a horse, and it was established that epidemics of encephalitis in horses in North America were caused by two separate viruses, EEE and western equine encephalitis (WEE), that were segregated geographically. A related virus, Venezuelan equine encephalitis (VEE), causes outbreaks of encephalitis in horses in Central America, South America, Mexico, and occasionally the southern United States. Although widespread vaccination has reduced the severity of outbreaks of EEE, WEE, and VEE in horses, the impact of these diseases is still significant because of the fulminating nature of clinical signs and high mortality rate in affected horses.

**ETIOLOGY**

The genus *Alphavirus* belongs to the family *Togaviridae* and includes a large number of viruses that have been isolated from horses with neurologic disease. Of these alphaviruses, eastern, western, and Venezuelan equine encephalitis viruses are the most frequently isolated from epidemics of encephalitis in horses and humans in the Western Hemisphere. The other genus in the family *Togaviridae*, *Rubivirus*, contains no viruses of known equine significance. Togaviruses are single-stranded, linear positive-sense ribonucleic acid (RNA) viruses that are enveloped and measure 60 to 70 nm in diameter. Within the envelope there is a nucleocapsid withicosahedral symmetry composed of peplomers arranged as trimers. Each peplomer is a heterodimer composed of two glycoproteins, E1 and E2.

The glycoproteins E1 and E2 are immunodominant proteins that induce neutralizing antibody. Both glycoproteins have hemagglutinating properties, the activity of which is highly modulated by pH. Both hemagglutination inhibition (HI) activity and neutralizing specificity have historically been used to differentiate viral species and their antigenic types (Table 20-1). Although these techniques are now being rapidly replaced by molecular
bone marrow suppression. Unfortunately, previously infected
animals may not develop immunity and may relapse when
favorable conditions are present.

PREVENTION

The most effective method for prevention of equine
dermatophilosis is to minimize exposure to excessive moisture
and insects. Insect repellents [e.g., 2% permethrin, FlyPel]
should be applied at least once daily in tropical climates where
high humidity and rainfall are present. Topical antibacterial
therapy with antibacterial shampoos [e.g., benzoyl peroxide] is
also helpful to decrease the bacterial load on the skin.

PUBLIC HEALTH CONSIDERATIONS

Dermatophilis is a rare zoonosis. In people it can cause
pitted keratolysis, painful or pruritic folliculitis, or subcutaneous
nodules. Immunosuppressed individuals may be more
susceptible to disease.

REFERENCES

See the CD-ROM for a list of references linked to the abstract
in PubMed.

CHAPTER 32 • Rhodococcus equi

Rhodococcus equi

Melissa T. Hines

Rhodococcus equi infection was first described in horses
in 1923. It is now recognized worldwide as a major
cause of disease in foals 3 weeks to 6 months of age.
The most common clinical manifestation is pyogranulomatous
encephalitis, although a variety of other clinical problems
may be identified. The disease has the potential to cause
significant losses, especially on farms where it is enzootic.
Infrequently, R. equi causes infection in adult horses, generally
thought to be associated with immunosuppression. R. equi
has been isolated from a wide variety of species, including
cats, dogs, goats, cattle, camels, pigs, crocodiles, and other
indigenous animals. Clinical disease is uncommon in these
species, and infection is often localized. R. equi is now consid-
ered an important pathogen in immunocompromised human
patients, particularly those infected with human immunoodefici-
cy virus (HIV).

ETIOLOGY

Rhodococcus equi, previously known as Corynebacterium equi
and Mycobacterium equi, is a facultative intracellular bacterium
that resides within macrophages. Rhodococci belong to
the family Nocardiae, order Actinomycetales. R. equi is a
pleomorphic, gram-positive organism with a rod-coccus life
cycle. Depending on growth conditions and the phase of
the life cycle, it may appear either cocccoid or as long rods
or short filaments with rudimentary branching. The organism
is aerobic, nonmotile, asporogenous, and partially acid-fast.
In vitro, optimal growth occurs at 30°C (86°F) and at a pH
between 7.0 and 7.5.

Rhodococcus equi is a member of a unique phylogenetic
group within the Actinomycetales, known as the mycolata. This
group contains a number of pathogenic genera in addition to
Rhodococcus, including Mycobacterium, Corynebacterium,
and Nocardia. The distinguishing feature of the mycolata is their
distinct, lipid-rich cell envelope that contains mycolic acids,
a large proportion of which are linked to the peptidoglycan-
arabinogalactan cell wall polysaccharide and (glyco)lipids. This
characteristic cell envelope forms a permeability barrier to
hydrophilic compounds, which makes some type of permeabili-
ity pathway necessary for the bacteria. Two channel-forming
proteins, or pili, have been identified in R. equi.7 The unique
mycolic acid−containing cell envelope of R. equi is of clinical
significance because it is thought to play a role in survival of
the bacteria under harsh conditions, such as those within
macrophages, and may also influence antibiotic susceptibility
patterns.

The numerous different strains of R. equi include both
virulent and avirulent variants. Strains may be identified by
a variety of characteristics, including the degree of virulence,
serotyping, and restriction endonuclease digestion of genomic
and plasmid deoxyribonucleic acid (DNA). In one study, 44
strains were identified among 209 isolates, with five strains accounting for more than half the isolates.17
It was determined that a small number of strains account for
clinical disease, and that in some cases, disease may be caused
by simultaneous infection with multiple strains.

Virulent strains of R. equi are characterized by their ability
to survive and replicate within macrophages (Fig. 32-1). This
ability is associated with the presence of a large virulence
plasmid of approximately 80 to 90 kilobases (kb), which
was initially identified in isolates from diseased foals.12-14-18
A number of different strains carry the virulence plasmid,
and these strains appear to be geographically widespread.17
The DNA from the virulence plasmids of various isolates have
been analyzed by RE digestion, and based on the digestion
patterns, at least 10 distinct but closely related plasmids have
been identified.19-22

The virulence plasmid has been sequenced and contains
69 open reading frames in three functional regions. Two of
these regions contain genes that are similar to those encoding
proteins involved in conjugation and in plasmid replication,
stability, and segregation. The presence of genes resembling
if the severely immunocompromised status of the majority of human patients with *R. equi* allows relatively avirulent organisms to produce disease or if there are distinct, species-specific virulence determinants.

### EPIDEMIOLOGY

*Rhodococcus equi* is widespread in soil samples and in the feces of herbivores, especially horses. Because *R. equi* is present on virtually all horse farms, exposure of horses is common worldwide, and the majority of horses have antibodies to *R. equi*. In soil samples the greatest numbers of organisms are found in surface soil, with almost no bacteria found at a depth of 30 cm (1 foot) or more. *Rhodococcus equi* can be isolated from the feces of adult horses, reaching numbers of 10^6 to 10^8/g of feces. This generally represents acquisition from contaminated soil and passive intestinal carriage in adult horses, rather than actual colonization of the intestine. The bacteria of *Rhodococcus equi* are highly adapted to avian intestinal environments and may be isolated from various avian lesions and environmental sources.

In foals, *R. equi* can be first isolated from the feces at about 1 to 2 weeks of age, with most foals becoming positive by 4 weeks of age. Up to the age of about 3 months, *R. equi* can actively multiply in the intestine of foals, reaching concentrations of 10^4 to 10^6/g of feces or higher and then declining to adult concentrations. Foals with rhodococcal pneumonia often swallow sputum infected with large numbers of virulent organisms, which may then multiply in the intestine, resulting in high numbers in the feces and significant environmental contamination.

Under suitable conditions, *R. equi* can multiply further in the environment. *Rhodococcus equi* grows substantially better in soil enriched with feces than in soil alone, and it is hypothesized that the organic acids in manure, such as acetate and propionate, support growth. The organism tends to replicate better at a relatively warm temperature and in a neutral soil (pH 7.3) compared with an acidic soil (pH < 5.5). In addition, decreased soil moisture and decreased pasture cover have been associated with high numbers of environmental *R. equi*. In some cases, a single gram of soil may contain millions of virulent *R. equi*. Inhalation of dust particles containing virulent *R. equi* is the major route of infection in foals. Experimentally, aerosolized bacteria and intratracheal inoculation of bacteria in foals can produce pulmonary lesions similar to those of natural infection. One study, *R. equi* was isolated from the air in stables, with the number of organisms in the air increasing on dry, windy days. A study of six farms found poor correlation between the numbers of virulent *R. equi* in air samples and soil samples on a given farm. Inhalation is a common route of exposure, in most cases it does not result in clinical disease. Rarely, *R. equi* infection is acquired through contamination of a wound. Once infection is established, *R. equi* may disseminate to distant sites by hematogenous spread.

Foals are generally exposed to *R. equi* early in life, but the time when foals actually become infected has not been well established. It has long been thought that the age of onset of clinical disease is associated with the period of waning maternal antibody. However, one study concluded that foals are infected much earlier, during the first several days of life. This study was based on a retrospective analysis of the age at onset of clinical signs and the age at death caused by *R. equi* pneumonia using Sartwell's model to determine if there was a logarithmic normal distribution consistent with a point source of infection. The interpretation of these data is controversial, and although it is accepted that foals developing *R. equi* pneumonia can be infected in the first...
a week of life, it has been proposed that infection is not limited to this period.\textsuperscript{39} Experimental studies show that foals remain susceptible over a wider age range.\textsuperscript{44,61-63,70} Currently, no experimental data support the long incubation period (30-90 days) that would be necessary in some cases if all foals that develop rhodococcal pneumonia after natural exposure were infected in the first few days of life.\textsuperscript{4,61,63,65,70}

Exposure of foals to \textit{R. equi} is common because the organism is present on most horse farms, but the prevalence of clinical disease is highly variable. On many farms the disease is unrecognized, whereas on others it is either sporadic or enzootic. The prevalence varies widely between farms and years, with rates ranging from 0% to 100%.\textsuperscript{50-75} Many enzootic farms have prevalence rates of 13% to 25%. The mortality rate is also highly variable, with death or euthanasia occurring in 0% to approximately 30% of cases.\textsuperscript{71,75,76,78}

A number of theories have been proposed to explain the difference in prevalence between farms. Although it was initially proposed that the prevalence of rhodococcal pneumonia correlated with the number of \textit{R. equi} bacteria in soil, this was not supported by soil cultures.\textsuperscript{50,70-82} Subsequently, it was hypothesized that farms with enzootic disease were more heavily infected with virulent strains of \textit{R. equi} than those farms where the disease was not present. Although initially supported by Talai et al.,\textsuperscript{57} other studies have not supported this theory.\textsuperscript{53,83} Martens et al.\textsuperscript{83} compared 33 farms with \textit{R. equi} and 33 farms without a history of \textit{R. equi} and found no significant associations between disease status and isolation of \textit{R. equi} from soil or detection of VapA in soil isolates. These findings suggest that it cannot be determined whether foals on a given farm are at increased risk of developing rhodococcal disease based on soil culture and VapA results.

Several epidemiologic studies have assessed risk factors for the development of rhodococcal disease, evaluating variables such as soil geochemistry, breeding-farm characteristics, management and preventive health practices, and farm-related factors.\textsuperscript{72,84,87} Although study results have varied somewhat, some general risk factors have been identified: Farms with large acreage, large numbers of mares and foals, and a population of transient mares and foals are at high risk for foals developing rhodococcal pneumonia.\textsuperscript{84,87} High fetal density is associated with an increased risk of farms being affected by \textit{R. equi} in one study, but a subsequent study found no associations.\textsuperscript{85,88} There has been no evidence that poor farm management or lack of attention to preventive health practices contributes to the probability of rhodococcal pneumonia.\textsuperscript{85,87}

The role of housing has been evaluated, but the significance of the findings is unclear. In one study, having concrete floors in the foaling stalls was associated with an increased risk of developing disease, whereas in a second study, housing foals in stalls with dirt floors appeared to increase risk.\textsuperscript{85,87} The investigators recommend that these results be interpreted with caution until more data are available. One study evaluated soil samples from affected and unaffected farms for multiple factors, including pH, salinity, and nitrate, and found no association between any soil factor and the \textit{R. equi} disease status of the farms.\textsuperscript{72} In another study, rhodococcal pneumonia was associated with an environment that participating veterinarians subjectively determined to be moderately to severely dusty.\textsuperscript{85} One theory currently under investigation is that foals developing rhodococcal pneumonia are born to mares that shed high numbers of organisms in their feces, but as yet, no data support this hypothesis.

Limited studies have attempted to identify host factors of foals that influence the outcome of exposure to \textit{R. equi}. To identify differences between foals that become affected and those that remain healthy on enzootic farms, Chaffin et al.\textsuperscript{88} evaluated hematologic and immunophenotypic parameters in foals at 2 and 4 weeks of age before the onset of clinical disease.\textsuperscript{88} Foals with a CD4/CD8 ratio of less than 3.0 appeared to have a higher risk of developing rhodococcal pneumonia. In addition, the number of segmented neutrophils was lower in foals that subsequently became affected compared with foals that remained healthy. However, the significance of these findings is unclear because the data were confounded by farm-related differences, and there was considerable overlap between values for affected and unaffected foals. Flaminio et al.\textsuperscript{89} found that absolute and proportional B-cell concentrations were greater in foals with active \textit{R. equi} pneumonia than in healthy foals of the same age. It has also been suggested that genetic factors may play a role in susceptibility to \textit{R. equi}, because limited data suggest an association between foal death caused by \textit{R. equi} and the type of transferrin, an iron-binding protein with differing genotypes and variable bacteriostatic properties.\textsuperscript{89,90} Another hypothesis is that infection of foals with equine herpesvirus type 2 (EHV-2) is a predisposing factor for invasion of the respiratory tract by \textit{R. equi}.\textsuperscript{91,92} At this time, host factors that influence susceptibility to \textit{R. equi} in foals are poorly understood.

**PATHOGENESIS**

**Mechanisms of Disease**

The infectivity of \textit{R. equi} is limited to cells of the monocyte/macrophage lineage, and the basis of this organism's pathogenicity is its ability to replicate in and eventually destroy macrophages.\textsuperscript{85,87} \textit{R. equi} strains cured of the virulence plasmid are unable to survive and replicate in macrophages and are avirulent for foals and mice.\textsuperscript{12,13,15,63} Specifically, it has been demonstrated by targeted "knockout" mutants that VapA is necessary for full virulence in mice, as well as for multiplication in ex vivo murine macrophages.\textsuperscript{94} Thus, although the function of the virulence plasmid is not fully understood, it appears to be essential for full virulence. Defining the precise mechanisms by which rhodococci survive and replicate within macrophages, as well as the role of the virulence plasmid, is key to understanding the pathogenesis of the disease.

The means by which \textit{R. equi} enters the macrophage may influence survival within the cell. Bacteria interact with a surface receptor on the macrophage and are internalized by phagocytosis, becoming enclosed in a portion of the macrophage plasma membrane, forming a phagosome. The specific phagocytic receptor involved mediates differences in internalization mechanisms and macrophage activation. \textit{R. equi} appears to bind primarily to macrophages through fixation of complement after activation of the alternative complement pathway, then binding to the macrophage-complement receptor type 3 (CR3), also known as Mac-1 (CD11b/CD18).\textsuperscript{39,94} In general, complement receptor-mediated phagocytosis is not associated with a high level of production of reactive oxygen intermediates and proinflammatory mediators, possibly allowing the organism to avoid antibody-associated macrophage-killing pathways.\textsuperscript{95} Brumbaugh et al.\textsuperscript{96} reported that phagocytosis of \textit{R. equi} by equine macrophages was not associated with a functional respiratory burst. In contrast to complement receptor-mediated phagocytosis, entry into the cell through the Fc receptor after opsonization with specific antibody is associated with significantly enhanced killing of \textit{R. equi} by equine macrophages.\textsuperscript{97,98} The presence of the virulence plasmid does not appear to influence the uptake of \textit{R. equi} by macrophages because both virulent and avirulent strains are phagocytosed to a similar extent.\textsuperscript{99}
Once within the macrophage, virulent strains of *R. equi* continue to multiply within the membrane-enclosed vacuoles, whereas avirulent strains multiply at low levels initially and cease to grow after approximately 6 hours. The means by which virulent *R. equi* avoids the killing mechanisms of macrophages are not fully understood. Initially, a lack of phagosome-lysosome fusion was reported. It now appears that there is a complex alteration of the normal phagocytic maturation process, which is at least in part regulated by the virulence plasmid. Based on studies with murine macrophages, Toyooka et al. reported that phagosome-lysosome fusion occurred with both virulent and avirulent *R. equi*, but that the phagolysosomes containing virulent organisms were not as acidic as those containing avirulent organisms. Also in murine macrophages, Fernandez-Mora et al. demonstrated that *R. equi*-containing vacuoles progressed normally through the early stages of phagosome maturation, but that maturation was ultimately blocked. This block in maturation was regulated by the presence of the virulence plasmid. Strains with the virulence plasmid maintained a nonacidified compartment for 48 hours, whereas strains lacking the plasmid acidified progressively more.

Ultimately, the replication of *R. equi* within macrophages results in the death of the host cell. In vitro, macrophage degeneration is apparent by approximately 8 hours after infection and is marked by 24 hours. The cytotoxicity is linked to virulence, although the exact mechanisms are unclear. Virulent *R. equi* bacteria are cytotoxic for murine macrophages, and the cytotoxicity is strongly upregulated by the presence of VapA-expressing plasmids. Isolates with a VapB-expressing plasmid are less virulent and have a lower cytotoxic potential, whereas isogenic strains without a plasmid are avirulent with a very low cytotoxic potential. The cytotoxicity requires viable bacteria. Cell death occurs by necrosis rather than apoptosis.

A number of additional factors may play a role in the pathogenesis of *R. equi*. The polysaccharide capsule, the presence of lipopolysaccharides, mechanisms of iron acquisition, and the enzyme cholesterol oxidase, termed "equi factor," may all contribute to virulence. Some evidence suggests that the length of the mycolic acid carbon chain in the cell envelope influences virulence, because strains of *R. equi* with longer mycolic acid carbon chains are more lethal in mice and cause greater granuloma formation than those with shorter mycolic acid carbon chains. The modulation of cytokine production by virulent strains may contribute to pathogenicity. Virulence is linked to resistance to β-lactam antibiotics in a study of non-plasmid-containing *R. equi* strains isolated from humans. However, a study of *R. equi* isolated from infected foals and soil from affected and control farms found no significant correlation between β-lactam resistance and either the presence of VapA or the disease status.

Large numbers of cells migrate to the site in response to infection with *R. equi*, ultimately resulting in granuloma formation. There is an influx of neutrophils, and an early hypothesis stated that a defect in neutrophil function contributed to disease; however, neutrophils from foals are fully bactericidal. The precise signals that influence granuloma formation are largely unknown, but it is clear that a complex network of cytokines and chemokines is involved. Granulomas may help contain and control infection but may also contribute to the pathology of disease; they are associated with the secretion of several inflammatory mediators and may allow proliferation of organisms and cause the loss of pulmonary function.

**Immunity to Rhodococcus equi**

The mechanism of protective immunity to *R. equi* has important implications for the control of disease. Although the outcome of exposure to *R. equi* is clearly affected by the dose and virulence of the organism, the host immune response is also important. Virtually all foals are exposed to *R. equi* early in life, but most do not develop disease. Adult horses are essentially resistant to infection because of the acquisition of protective immunity. Thus, it appears that most foals are capable of developing effective immune responses, which subsequently protect them for life. The mechanisms of this protective immunity are not fully understood. Because *R. equi* is a facultative intracellular pathogen, much emphasis has been placed on the role of cellular immunity. However, it appears that all aspects of the immune system are involved in protection from *R. equi*.

**Role of Innate Immunity**

The replication of *R. equi* in nonactivated resident macrophages is critical to the pathogenesis of disease, but at the same time the killing of *R. equi* by activated macrophages can be important in the control of infection. Myeloid macrophages that are sufficient in either of two pathways or both have an increased susceptibility to infection with *R. equi*. Macrophage activation by *R. equi* in mice involves toll-like receptor 2 (TLR-2) and myeloid differentiation primary response 88 (MyD88). The ability of bone marrow myeloid cells or plasmacytoid dendritic cells to clear *R. equi* from the site of infection is associated with TLR-2 signaling.

Neutrophils may also be important in controlling *R. equi* early in the course of infection. The induction of a neutrophil deficiency in mice during the first week after experimental rhodococcal infection resulted in more severe disease and an significantly increased tissue concentrations of *R. equi*.

**Role of Antibody**

As noted earlier, the unique age-related susceptibility of foals to *R. equi* has long been thought to be associated with the waning of maternal antibody. Although the explanation is probably more complex, antibody does appear to play a role in immunity to *R. equi*. Some mechanisms by which antibody may contribute to immunity include blocking the initial stages of cellular infection, altering the route by which bacteria enter the macrophage, and decreasing the bacteria's ability to arrest maturation of the phagosome.

Several lines of evidence support a role for antibody in protection against *R. equi*. In addition to the observation that the age of onset of disease in foals typically coincides with the waning of maternal antibody, Antibodies to *R. equi*, including antibodies to the 15- to 17-kDa antigen of virulent *R. equi*, are widespread in horses and are found in the majority of foals within the first 3 months of age. An inverse correlation may exist between antibody concentrations and disease severity and prevalence. After challenge of immune or nonimmune adult horses with virulent *R. equi*, an antibody response is characterized predominantly by increases in concentrations of immunoglobulin G subtypes IgG and IgG, which are important antibody isotypes in opsonization and complement fixation. During in vitro experiments by Hietala and Andrews, opsonization with *R. equi*-specific antibody increased phagosome-lysosome fusion and significantly enhanced the killing of *R. equi* by alveolar macrophages from foals. Additional evidence supporting a role for humoral immunity in protection against *R. equi* comes from studies of passive immunization through the administration of hyperimmune plasma (Box 32-1). Several studies investigating the protective effect of hyperimmune plasma have been performed in both mice and foals. The results in mice have been variable, with some studies indicating that hyperimmune serum was not.
Box • 32-1

Commercial Sources of R. equi Hyperimmune Plasma

Lake Immunogenics, Inc.
348 Berg Road
Ontario, NY 14519
585-265-1973 or 800-648-9990
lakeimmunogenics.com

Plasvac USA, Inc.
1535 Templeton Road
Templeton, CA 93465
805-434-0321 or 800-654-9743
plasvacusa.com

Veterinary Immunogenics, Ltd.
Carleton Hill
Penrith
Cumbria
CA11 8TZ
United Kingdom
+44 (0) 1768 863881
veterinaryimmunogenics.com

PRO-SER S.A.
Av. N. Alem 1698
(2752) Copitlan Sarmento
Buenos Aires, Argentina
(054-11) 15-4420-1757
labproser.com.ar

protective against experimental challenge and others indicating a protective effect. 24,10,130 Similarly, studies in foals have had mixed results. The administration of hyperimmune plasma does not always have a significant protective effect, but it does prevent or reduce the severity of pneumonia in foals that are either experimentally or naturally R. equi infected. 24,75,121,125 Hyperimmune plasma does not alleviate clinical signs or alter the course of the disease when administered to foals 7 days after experimental challenge with R. equi; thus it appears that the protective components in immune plasma are primarily effective in the prevention of infection. 123,124

It is uncertain which specific components of hyperimmune plasma are responsible for enhancing protection against R. equi. In addition to immunoglobulin, hyperimmune plasma contains a number of substances, including fibrinogen, interferon, complement factors, and cytokines. In a study by Hooper-McGregor et al., 124 the same degree of protection was provided by purified immunoglobulin specific for VapA and VapC as by hyperimmune plasma, suggesting that immunoglobulin was the primary component of hyperimmune plasma that conferred protection, and that specific antibodies against VapA and VapC were protective. In contrast, Perkins et al. 123 found no difference in the incidence and severity of disease after experimental challenge with R. equi in colostrom-derived foals given either normal equine plasma or hyperimmune plasma. Because the survival rate for foals in both groups was approximately 70% without antibiotic therapy, both normal and hyperimmune plasma were thought to provide some protective effect, although there was no untreated control group. The researchers therefore concluded that either only a small amount of antibody was sufficient to enhance protection, or that factors in the plasma other than immunoglobulin were responsible for the protective effect.

Several studies have evaluated the protection provided by the ingestion of colostrum from mares immunized against rhodococcus. Martens et al. 127 found that the passive immunization of foals by ingestion of colostrum from mares immunized with live R. equi did not provide protection against experimental challenge. Similarly, in field studies by Madigan et al. 128 in which pregnant mares were immunized with an R. equi bacterin, and by Prescott et al. 129 in which pregnant mares were immunized with a VapA extract, foals were not protected from natural infection with R. equi. In contrast, in a field study by Cauchard et al. 130 in which pregnant mares were immunized with either VapA protein antigen or whole killed R. equi, vaccination did appear to provide protection. In general, the protection provided by colostrum has not been as consistent as that with hyperimmune plasma. One possible explanation for this difference is that factors in plasma other than antibody significantly contribute to protection. An alternative explanation is that the isotypes of antibody necessary for protection may not be present in high concentrations in colostrum. Furthermore, the specific immunogens or immunization protocols employed may not induce sufficient concentrations of antibody or antibody with the appropriate antigen specificity.

Although antibody contributes to protective immunity, by itself it does not afford complete protection. The humoral response appears to be most important in the initial stages of infection. The immune response to R. equi is complex, and ultimately, optimal control of the disease involves cell-mediated immunity, as would be expected for an intracellular pathogen.

Role of Cellular Immunity

Considerable evidence supports the importance of cell-mediated immunity in the control of R. equi infection. Much of this evidence comes from a mouse model of rhodococcal disease, although there are some data in horses. In mice, both CD4+ and CD8+ T lymphocytes contribute to immune clearance of R. equi from the lung. 129,131 Mice that lack CD8+ but not CD4+ T lymphocytes are able to clear infection completely in the period studied, whereas mice lacking CD4+ but not CD8+ T lymphocytes are able to decrease bacterial numbers significantly in the lung. 132

Studies have emphasized the role of CD4+ T lymphocytes because these cells appear to be both necessary and sufficient for clearance of R. equi. 129-131 CD4+ T lymphocytes are further characterized as Th1 cells (CD4+ Th1 cells) and Th2 cells (CD4+ Th2 cells) depending on their cytokine secretion patterns. 132 These CD4+ subtypes have been best defined in mice. CD4+ Th1 cells secrete primarily interferon-gamma (IFN-γ), a potent activator of macrophage microbicidal activity. In comparison, CD4+ Th2 lymphocytes secrete predominantly the interleukins IL-4, IL-5, and IL-13, which potentiate the humoral immune response. In mice, secretion of IFN-γ by CD4+ Th1 lymphocytes appears to be absolutely required for clearance of R. equi. 130 Adoptive transfer of a R. equi-specific CD4+ Th1 cell line mediates clearance in immunodeficient nude mice that normally are unable to control pulmonary bacteria. 131 In contrast, nude mice that receive an R. equi-specific CD4+ Th2 cell line are unable to clear bacteria and develop prototypic pulmonary lesions.

CD4+ T lymphocytes are critical in the control of rhodococcal infection, but CD8+ T lymphocytes contribute as well. These CD8+ cells probably act through multiple mechanisms to decrease bacterial numbers. One of their effector functions is the ability to produce IFN-γ. Another possible important
function is the recognition and lysis of R. equi-infected cells, as demonstrated for the related pathogen, Mycobacterium tuberculosis.12,13

Limited data in horses support the observations in mice that protective immunity to R. equi involves both CD4+ and CD8+ T lymphocytes. Adult horses challenged intrabronchially with virulent R. equi do not develop clinical disease and effectively clear bacteria from the lung in association with increased numbers of CD4+ and CD8+ lymphocytes at the site of infection.13 T lymphocytes from bronchoalveolar lavage (BAL) fluid of challenged horses proliferate when stimulated with R. equi antigen, and both CD4+ and CD8+ T lymphocytes from the site express IFN-γ. In addition, T lymphocytes from the blood and BAL fluid of adult immune horses have R. equi-specific cytolytic activity.13 These cytotoxic T lymphocytes (CTLs) appear to be primarily CD8+ and have the ability to kill in a major histocompatibility complex (MHC) class I, unrestricted fashion.

**CLINICAL FINDINGS**

Clinical disease caused by R. equi is most common in foals 3 weeks to 6 months of age, with signs most often developing before age 4 months.52,70,73,77,79-81 Respiratory tract disease occurs most often, although other systems may be affected as well, either independently or in conjunction with lung involvement. In a retrospective study of 61 foals seen at a referral center for rhodococcal pneumonia, the prevalence of extrapulmonary disorders was 66%, although this percentage is higher than what some clinicians recognize.138 General clinical signs often associated with rhodococcal disease, regardless of the site of infection, include fever, lethargy, and decreased appetite.

Rhodococcal infection may remain subclinical in some cases. When clinical disease develops, it is often insidious in nature. Because of the foal’s ability to compensate and the slow spread of infection, early clinical signs are often subtle, making the disease difficult to detect. Although infection is generally chronic, clinical signs often appear acutely when the disease becomes severe, leading to the description of an “acute on chronic” disease. A small percentage of foals exhibit a subacute form of the disease, in which they may be found dead or in acute, severe respiratory distress with high fever. These foals often have a poor prognosis.91

**Pulmonary Disease**

The most common manifestation of R. equi infection in foals is chronic pyogranulomatous bronchopneumonia with abscessation and associated suppurative laryngitis.52,70,80,81 Zink et al.137 confirmed the presence of suppurative pneumonia in 115 of 131 cases of R. equi infection. In a review of 40 cases of equine lung abscesses, 32 cases were identified in foals 6 months of age or younger, with R. equi cultured from 13 of 34 cases and Streptococcus zooepidemicus cultured from 20 of 34.138 Occasionally, R. equi is cultured with other pathogens, including Pasteurella multocida.140 Rhodococcus equi has rarely been cultured from foals with the syndrome of bronchointerstitial pneumonia and respiratory distress, but it is not believed to be the primary cause of this condition.141

It is important to minimize stress during the physical examination of foals with suspected rhodococcal pneumonia so as not to exacerbate respiratory distress. The most prominent clinical signs include tachypnea and increased respiratory effort, characterized by abdominal effort and nostril flaring. Tachycardia is often present. In severe cases, mucous membranes may be cyanotic. The presence of a cough and mucoid to mucopurulent nasal discharge is variable. Generally, affected foals are in good body condition, although weight loss may be present in some chronic cases.

Findings on auscultation of the lung are variable and often do not correlate well with the severity of pneumonia. The sensitivity of auscultation may be enhanced by inducing the foal to breathe deeply using a rebreathing bag or cupping a hand over the nostrils for a few seconds if the foal is stable enough to tolerate this procedure. Inspiratory and expiratory crackles and wheezes may be audible and are often most prominent cranioventrally. In some cases, only large airway sounds are present, suggesting consolidation. With severe consolidation or extensive peripheral abscess formation, lung sounds may be decreased. This may also indicate pleural effusion, although effusion is seen only occasionally in association with rhodococcal pneumonia.139 In one case, respiratory distress was identified in association with a focal mediastinal abscess without concurrent pulmonary involvement.10 Thoracic percussion, as well as ancillary diagnostic aids such as radiography and ultrasonography, may help detect areas of consolidation, abscessation, or pleural fluid.

**Abdominal Disease**

Enterocolitis, typhilitis, abdominal abscesses, peritonitis, and adhesions have been reported in association with R. equi.1 In the review of 131 cases by Zink et al.,137 approximately 50% of foals with R. equi that had bronchopneumonia on necropsy also had intestinal lesions, and an additional 4% of foals had intestinal lesions without pneumonia. However, of the foals with intestinal lesions, only 38% had any history or clinical signs related to intestinal disease.

The predominant signs in those foals with intestinal involvement that do manifest clinical signs are colic and diarrhea. In chronic or severe cases, there may be a loss of body condition. Some foals develop significant ascites, resulting in a marked “pot-bellied” appearance. These foals generally have extensive granulomatous inflammation of the colonic mucosa and submucosa with involvement of the mesenteric lymph nodes causing lymphatic obstruction with an increased concentration of protein in the abdominal fluid and circulating hypoalbuminemia. Chances for survival decrease with extensive abdominal disease.

**Nonseptic Polysynovitis**

An immune-mediated polysynovitis has been documented in approximately one third of R. equi cases.72,138 (Fig. 32-2). Although all joints may be affected, this condition appears to be most common in the tibiotalar and stifle joints.77 Degree of joint effusion is variable, but unlike cases of septic arthritis, there is no or minimal lameness. Evaluation of synovial fluid reveals a nonseptic mononuclear pleocytosis with no bacterial growth.77,140,141 Histologic examination of the synovium reveals a lymphoplasmacytic synovitis.140,141 Horses with nonseptic arthritis, the effusion generally resolves as the rhodococcal infection clears.

It is hypothesized that the presence of immune complexes in the joint leads to an acute reactive arthritis.140 Immunoglobulin was demonstrated within the synovial membrane using fluorescein-labeled antiequine IgG in three affected foals.138 Additionally, rheumatoid factor activity, which results from antibodies directed against the Fc portion of autoantibodies or heterologous immunoglobulin, was identified in the synovial fluid of a foal with R. equi pneumonia and reactive arthritis.140

*References 76, 137, 138, 142, 144, 145.*
Bone and Joint Disease

Septic arthritis and osteomyelitis may be observed either alone or with other signs of rhodococcal disease. These conditions can be distinguished from immune-mediated polyarthritis by the degree of lameness along with cytologic evaluation and culture of joint fluid or aspirates. Some foals have an associated cellulitis. Treatment includes aggressive local therapy in addition to systemic antibiotics.

Several cases of *R. equi* vertebral osteomyelitis have been reported, and the question has arisen whether this condition is becoming more common. In general, early signs of vertebral osteomyelitis may include a stiff gait, reluctance to move, and pain on palpation. However, the diagnosis is usually not made until the infection extends to the epidural space, causing signs of spinal cord or nerve root compression, such as paresis, ataxia, paraplegia, or cauda equina syndrome. The specific signs will vary depending on the severity and site of the lesion. Although radiography may be useful in the diagnosis, in four of six cases, radiographs were normal despite the presence of extensive lesions on necropsy. Therefore, nuclear scintigraphy, computed tomography, or magnetic resonance imaging may be indicated.

Diseases of Other Body Systems

A variety of other conditions have been sporadically recognized in association with *R. equi*. These include ulcerative lymphangitis, cellulitis, subcutaneous abscesses, abscesses of the submandibular lymph nodes, nephritis, renal abscesses, and hypopyon (Fig. 32-3). Some cases of cellulitis without any internal involvement may be secondary to wounds or damage to the skin by the larvae of *Strongyloides westeri*. Hepatitis, cholangitis, and hepatoencephalopathy as well as uveitis and panophthalmitis have also been reported.

*R. equi* has rarely been isolated from aborted equine fetuses and infertile mares. The significance of isolating the organism has been unclear in some cases, but *R. equi* has been confirmed as a cause of placentitis and abortion with fetal pneumonia. However, despite the frequent occurrence of *R. equi* in equine feces and soil samples, it is rarely recognized as a cause of equine abortion.

Infection in Adult Horses

Rhodococcal disease is uncommon in adult horses because most adults are immune to infection. However, sporadic cases have been reported. As in foals, the most common clinical signs are related to suppurative bronchopneumonia (Fig. 32-4). Occasionally, pleuritis may be recognized. Other reported signs include intestinal disease, lymphadenitis, wound infections, and osteomyelitis. In both cases in which the organism isolated from adult horses was assessed, the virulence plasmid was present. It is thought that adult horses...
with *R. equi* infection are immunocompromised, and although the immune status has not been assessed in every case, immunodeficiency was reported in two cases.\(^{169,173}\)

**DIAGNOSIS**

The ability to make a rapid, accurate diagnosis of rhodococcal pneumonia is important because early recognition and treatment of the disease can improve the prognosis. Based on clinical signs alone, it is difficult to distinguish pneumonia caused by *R. equi* from that caused by other pathogens. The isolation of *R. equi* by culture or the identification of *R. equi*-specific DNA by polymerase chain reaction (PCR) provides definitive diagnosis. However, a variety of additional tests can be supportive.

**Cytology**

The presence of intracellular gram-positive pleomorphic rods on cytologic evaluation of fluid specimens supports a diagnosis of rhodococcal infection (Fig. 32-5). However, the organisms may be present in low numbers and may be difficult to detect. Sweeney et al.\(^{174}\) reported that organisms were seen on cytology of tracheobronchial fluid in 61% of 48 culture-positive foals, whereas in 22% of these foals, no bacteria were seen, and in 17%, only bacteria other than *R. equi* were identified. An indirect fluorescent antibody (IFA) technique has been described for acetone-fixed specimens; 33 of 53 (62.3%) tracheal aspirates from foals with experimentally induced rhodococcal pneumonia had a positive IFA result.\(^{175}\)

**Culture**

Culture and subsequent phenotypic analysis of the isolate by classic morphologic and biochemical tests has been the "gold standard" for the diagnosis of *R. equi*. Typically, the organism is cultured from a tracheobronchial aspirate, which may be obtained by a variety of techniques.\(^{174,175}\) When collecting the sample, the clinician must consider stress to the patient because some foals are in severe respiratory distress. Other samples, such as joint fluid or peritoneal fluid, can be cultured as appropriate based on the case.

Colonies of *R. equi* will usually appear on solid media within 48 hours of aerobic culture, although in some cases, longer incubation is necessary, especially for samples collected from foals that have been treated with antibiotics.\(^{3,76,177,178}\) Occasionally, the organism may be isolated only under anaerobic conditions after antimicrobial therapy.\(^{179}\) Colonies of *R. equi* generally appear irregularly round, smooth, semitransparent, and mucoid (Fig. 32-6). They typically have a characteristic salmon-pink color, which may not develop until 4 to 7 days in culture. Other pathogens may be isolated concurrently with *R. equi*.\(^{177,179}\)

It is generally assumed without further testing that the isolates of *R. equi* from clinically ill foals are virulent strains. However, isolates can be analyzed for the presence of virulence plasmids and virulence-associated antigens.\(^{3,75,178,179}\)

The reliability of culture of tracheobronchial aspirates in the diagnosis of rhodococcal pneumonia has varied among studies.\(^{4}\) In some studies, essentially all foals in which *R. equi* was isolated from the lung parenchyma at necropsy had positive antemortem cultures from tracheobronchial fluid, but in other studies the results have not been as consistent. Combining the results of three studies, Giguere et al.\(^{180}\) reported that 86% of foals with positive *R. equi* cultures at necropsy had positive antemortem cultures of tracheobronchial fluid. Sellon et al.\(^{181}\) compared PCR, serology, and culture for the diagnosis of *R. equi* pneumonia in 56 foals with respiratory tract disease. Using the final clinical diagnosis of the attending clinician as the reference standard for diagnosis of *R. equi*, microbiologic culture was found to have a sensitivity of 57.1% and a specificity of 93.8%, making it less sensitive than PCR. In a study of experimentally induced rhodococcal pneumonia in foals, *R. equi* was consistently isolated by culture of tracheal aspirations, and culture was found to be more sensitive than either PCR targeting VapA or IFA staining of tracheobronchial aspirate cells using a monoclonal antibody against VapA.\(^{174}\)

*References 64, 70, 78, 139, 180, 181.*
R. equi may occasionally be isolated from the trachea as a contaminant. In one study on a farm with enzootic rhodococcal pneumonia, 77 of 216 foals with no signs of respiratory disease had positive cultures of tracheobronchial fluid. These data raise the possibility that PCR tests may also be positive in cases where R. equi is not causing clinical disease. Therefore, it is important to interpret culture and PCR results in the context of the entire case, including the physical examination findings, laboratory evaluation, and diagnostic imaging.

Samples in addition to the tracheobronchial aspirate may be positive for R. equi in some cases of rhodococcal pneumonia. Although blood cultures are not routinely performed in foals with suspected R. equi infection, cultures have occasionally been positive in horses with natural or experimental infection. In contrast, blood culture appears to be a sensitive means of diagnosis in human patients with R. equi. Positive cultures of nasal swabs or feces cannot be taken as evidence of rhodococcal disease. The inhalation of dust from the environment may result in contamination of the upper airways and positive nasal swabs. R. equi can be cultured from the feces of many normal horses. Negative fecal cultures are not helpful in ruling out infection. Despite that infected foals often swallow contaminated spumum, in one study only 5 of 30 foals (17%) with confirmed R. equi pneumonia had positive fecal cultures. Based on another study, weekly quantitative fecal cultures have been advocated as an aid in the early diagnosis of R. equi enteritis because the bacterial count per gram of feces increased at the onset of clinical signs.

Nucleic Acid Amplification and Polymerase Chain Reaction

A number of PCR techniques have been developed to amplify either chromosomal or plasmid DNA of R. equi in a variety of samples. Using primers for VapA, virulent strains of R. equi can be rapidly identified. It is also useful to identify chromosomal DNA because the virulence plasmid is present in many strains isolated from environmental samples or from species other than horses, particularly human patients. Although PCR can be a valuable diagnostic test, it should be used in conjunction with standard microbial culture because multiple bacterial pathogens may be present.

The PCR has generally been shown to be rapid and reliable, although the results of individual studies assessing its accuracy have varied. With as few as 10 to 100 organisms, R. equi can be identified and virulent strains differentiated from avirulent strains within 12 to 24 hours. In the study of 50 foals with respiratory tract disease by Sellon et al., in which the reference standard was the final clinical diagnosis of the attending clinician, the PCR of tracheal wash fluid using primers that recognized the VapA virulence plasmid had a diagnostic sensitivity of 100% and a specificity of 90.6%, making it a more sensitive diagnostic test than culture or serology. Analysis of serum samples had a sensitivity of only 12.5% and a specificity of 88.9%, whereas analysis of nasal swabs had a sensitivity of 50% and a specificity of 88.9%. In the study of experimentally induced rhodococcal pneumonia by Anzai et al., PCR of tracheal aspirates, although more rapid than culture, was less sensitive in the diagnosis of R. equi. Recently, Harrington et al. evaluated a real-time quantitative PCR for detection and quantification of virulent R. equi in experimental studies and found it to be highly specific and more sensitive than standard PCR for the detection of R. equi in tracheobronchial fluid. The increased sensitivity of this method could facilitate the rapid and accurate diagnosis of R. equi pneumonia in foals, and evaluation in clinical cases is warranted.

Serologic Tests

Serologic assays developed to detect R. equi-specific antibodies include several enzyme-linked immunosorbent assays (ELISAs), an agar-gel immunodiffusion (AGID) test, and synergistic hemolysis inhibition (SHI) assays. Variations among the assays are primarily based on differences in the test antigen preparation. These assays have been used in various studies to assess the humoral immune response to R. equi. It has also been proposed that serologic testing could be used in the diagnosis of rhodococcal infection.

Sellon et al. and Giguerre et al. assessed an AGID test in the diagnosis of R. equi; both studies found the sensitivity to be 62.5%, and the specificity was 75.9% and 58.8%, respectively. Two studies critically evaluated the performance of several serologic assays for the diagnosis of R. equi in foals; the first evaluated three ELISAs, an AGID, and a SHI assay, and the second evaluated four ELISAs and the AGID assay. None of the serologic assays in either study differentiated between disease and clinically normal foals. One study evaluated the testing of paired sera, but this failed to improve the diagnostic accuracy. In both studies, antibodies, including those specific for VapA, were found in many foals regardless of their disease status. Some antibody could be maternal derived, but because titers increased significantly over time in all assays, this suggests that foals are routinely exposed to R. equi, including virulent strains. It has been suggested that serologic tests may be of more value as a diagnostic test if used on nonenzootic farms, but this has not been assessed.

Ancillary Diagnostic Tests

Clinical Pathology

A complete blood count (CBC), fibrinogen, and serum biochemistry profile can provide useful information in the evaluation of patients with suspected rhodococcal infection. However, the abnormalities generally are nonspecific, reflecting the presence of inflammation. Hyperfibrinogenemia is the most consistent laboratory finding, although rare cases may have normal fibrinogen concentrations. Neutrophilic leukocytosis with or without monocytosis is also common. Most studies show significant variation in fibrinogen concentrations and white blood cell (WBC) counts both within foals known to be infected with R. equi and compared to foals infected with another pathogen, limiting the value of these tests as specific diagnostic tests or prognostic indicators. Thyroid function, which is often associated with acute or chronic inflammation, has also been reported in conjunction with R. equi infection, but this finding is variable. Hypergammaglobulinemia may be seen in some foals. The CBC and serum chemistry profile also allow for evaluation of the patient's hydration status.

Serum amyloid A (SAA) is an acute-phase protein that has been proposed as a useful inflammatory marker in infectious disease. In one limited study, foals with R. equi had increased concentrations of SAA. Concentrations of SAA decreased in recovered foals before fibrinogen concentration and neutrophil count decreased, suggesting that SAA concentrations could be used in monitoring treatment response. A study that evaluated SAA concentrations in foals before and during clinical signs of rhodococcal pneumonia found that concentrations of SAA were variable among foals with R. equi pneumonia and could not be used reliably either as an ancillary diagnostic tool or as a screen for early detection of disease during the first month postpartum.
Thoracic radiographs from two foals with rhodococcal pneumonia. A, Severe, structured interstitial pattern with multiple, large, cavitating masses (arrows) typical of R. equi. B, Mild to moderate, diffuse, structured interstitial pattern, with numerous small nodules and masses and at least two moderate-sized cavitary lesions (arrow). (Courtesy Dr. Greg Roberts.)

**Fig. 32-7**

**Diagnostic Imaging**

Thoracic radiography is frequently used to evaluate foals with suspected *R. equi* pneumonia. Typically, there is a prominent alveolar pattern with regional consolidation. Often, discrete nodular and cavitary lesions compatible with pulmonary abscessation are seen, and in some cases, gas is detectable within the abscesses (Fig. 32-7). Evidence of tracheobronchial lymphadenopathy may be present, characterized by nodular densities displacing the trachea dorsally. Although the results of studies correlating the severity of radiographic lesions and prognosis have varied, radiographic findings generally should not be used as a primary prognostic indicator because many surviving foals have had severe lesions.\(^{76,77,174,177,211}\)

Radiographic evidence of pulmonary abscessation in foals strongly suggests *R. equi* infection. However, other pathogens, such as *Streptococcus zoonaepticus*, can also cause abscessation and should be considered, especially in foals over 3 months of age.\(^{190}\) In addition, radiographic evidence of abscessation may be absent in some cases of rhodococcal pneumonia, and only a mild to severe bronchointerstitial pattern may be recognized. In foals with severe respiratory distress and a marked bronchointerstitial pattern, the syndrome of sporadic bronchointerstitial pneumonia should be considered. The cause of this syndrome is not known, and although occasional cases have cultured *R. equi*, its role in the pathogenesis is unclear.\(^{141}\) A hilar pattern characterized by distinct reticuloendymal nodules was described in three of five foals concurrently infected with *R. equi* and *Pseudomonas aeruginosa*.\(^{140}\)

**Fig. 32-8** Magnetic resonance imaging (MRI) of left tarsus of foal with septic physitis, metaphysitis, and epiphysitis caused by *R. equi* (coronal proton-density image). There is a decrease in signal from the medial aspect of the tarsus and extending beyond the midline. Fluid in the soft tissue on the medial aspect most likely represents purulent material. The lesion in the tarsus demonstrated by MRI was much more extensive than that visualized radiographically. (Courtesy Drs. Kelly Farnsworth and Pat Gavin.)

**Thoracic ultrasonography (US)** is a practical means of assessing the thorax and can yield valuable information in the evaluation of *R. equi* pneumonia.\(^{76,212,213}\) Because US does not image lesions with overlying aerated lung, the technique is primarily useful in identifying peripheral lung involvement and may not evaluate the full extent of the lesions as accurately as radiography. In most affected foals, however, peripheral lesions are present.\(^{212,213}\) When thoracic US was compared with radiography in 17 foals with confirmed *R. equi* pneumonia, the findings were essentially in agreement in 15 of 17 foals.\(^{212}\) Lesions were identified by US in the remaining two foals, but were less severe than those identified by radiography. It was concluded that US may be an accurate imaging modality for detection of pulmonary pathology caused by *R. equi*.\(^{212}\)

Advanced imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), and scintigraphic imaging, may be indicated in some foals with *R. equi* infection, especially when there is extrapulmonary involvement. High-resolution CT has been used to define lesions in human patients with *R. equi* pneumonia.\(^{214}\) CT was used to diagnose a mediastinal abscess causing severe respiratory distress in a 4-month-old foal with an atypical clinical presentation of *R. equi*.\(^{143}\) MRI and CT have been used to diagnose septic physitis in foals (Fig. 32-8). Scintigraphic perfusion imaging
was used to demonstrate pulmonary perfusion defects in affected areas of the lung in four foals with experimental rhodococcal pneumonia. The findings correlated well with radiographic and necropsy lesions.

**PATHOLOGIC FINDINGS**

The gross lesions characteristic of *R. equi* pneumonia are multiple firm nodules separated by congested and partly atelectatic lung (Fig. 32-9). The nodules vary in size, with some coalescing to form large lesions. Occasionally, multiple miliary pyogranulomatous foci are present. Although the distribution of lesions may be variable, lesions are bilateral in most cases and are most severe in the cranioventral regions, as is typical of bronchopneumonia. In some cases, however, lesions are distributed widely throughout the lung, especially in rapidly progressive cases. The lesions are often described as abscesses when circumscribed and as suppurative bronchopneumonia when less well defined. They consist of areas of caseous necrosis, and in most cases there is no distinct fibrous capsule around the necrotic tissue. The presence of pleural fluid is uncommon. Grossly, the bronchial lymph nodes are often swollen and edematous, and caseous necrotic foci may be present.

Histologically, the lesions are predominantly pyogranulomatous. Early lung lesions are characterized by a cellular influx into the alveolar spaces, consisting largely of macrophages and multinucleate giant cells with fewer neutrophils. Intact bacteria are typically observed within macrophages and giant cells. Lymphocytes and plasma cells are present in moderate numbers, primarily in the alveolar septa and other interstitial zones. As the disease progresses, necrosis involves the alveolar septa and spreads to affect large areas of the pulmonary parenchyma, producing the caseous necrotic foci observed macroscopically. Numerous degenerate bacteria-laden macrophages are present. Frequently, a pyogranulomatous lymphadenitis is also present histologically.

The most common sites involved in *R. equi* infection other than the lung are the intestinal tract and mesenteric lymph nodes. There is a multifocal enterocolitis and typhilitis, associated primarily with Peyer’s patches in the ileum and areas of lymphoid tissue in the cecum and colon. Similar to the bronchial lymph nodes, mesenteric and colonic lymph nodes may be enlarged and have caseous necrotic foci. Occasionally, a large abdominal abscess will form, most often in a mesenteric node. Peritonitis and adhesions may be present. Histologically, the intestinal lesions consist of pyogranulomatous inflammation of lymphoid tissue with fibrinonecrotic ulceration of the overlying epithelium.

The lesions of *R. equi* infection may be more widespread, suggesting hematogenous dissemination of the organism. Some of the lesions identified include septic arthritis, vertebral osteomyelitis, hypophysitis (see Fig. 32-9), and ulcerative lymphangitis. Abscesses may develop at almost any site, and dental, hepatic, renal, and splenic abscesses have been described, among others. Lesions of placentitis and fetal pneumonia in an aborted fetus have been reported in association with *R. equi* infection.

*R. equi* can be isolated from tissues at necropsy in most cases. When only formalin-fixed tissue specimens are available for diagnostic evaluation, immunohistochemistry can be used as a diagnostic aid. An immunohistochemical method is useful in the rapid detection of *R. equi* in impression smears obtained postmortem from tissues at necropsy. This method is as sensitive as bacterial culture. To identify virulent *R. equi* specifically in tissues, monoclonal antibodies directed against the 15- to 17-kDa antigens associated with virulence have been used.

**THERAPY**

**Antimicrobial Therapy**

*Rhodococcus equi* is sensitive to a wide variety of antimicrobial agents in vitro, but in vitro susceptibility does not always correlate with efficacy in vivo. For example, aminoglycosides appear to be highly active against *R. equi* in vitro. However, in one case series, none of the 17 foals treated with gentamicin and penicillin survived despite all isolates being susceptible to gentamicin in vitro, whereas 13 of 18 treated with erythromycin had survived. Because *R. equi* is a facultative intracellular pathogen that causes pyogranulomatous inflammation, effective antimicrobials must have good tissue and macrophage penetration and function in a relatively acid environment.

Treatment of foals with the macrolide antibiotic erythromycin in combination with rifampin began in the late 1980s (Table 32-1). The use of this combination significantly improved the success of treatment from a survival rate of approximately 20% to 30% to 60% to 90%. Rifampin and to a lesser extent erythromycin are lipid-soluble antibiotics capable of intracellular penetration. Both erythromycin and rifampin are concentrated in granulocytes and macrophages by an active mechanism. The drugs are usually bacteriostatic but may be bactericidal at high concentrations. Use of erythromycin and rifampin in combination is recommended because they are synergistic in vitro and in vivo and because the development
Table 32-1

Antibiotics Frequently Used to Treat Rhodococcus equi in Horses

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin (estolate,</td>
<td>25 mg/kg orally (PO)</td>
</tr>
<tr>
<td>stearate, phosphate,</td>
<td>every 6 to 8 hours</td>
</tr>
<tr>
<td>ethylsuccinate, lactobionate)</td>
<td>(q6-8h) or 37.5 mg/kg</td>
</tr>
<tr>
<td>PO q12h</td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>10 mg/kg PO q24h</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>7.5 mg/kg PO q12h</td>
</tr>
<tr>
<td>Rifampin</td>
<td>5-10 mg/kg PO q12h or</td>
</tr>
<tr>
<td></td>
<td>10 mg/kg q24h</td>
</tr>
</tbody>
</table>

In most cases, erythromycin, azithromycin, or clarithromycin is given in combination with rifampin. In one study, clarithromycin-rifampin was found to be the most effective therapy.11

of resistance to either drug is decreased when used in combination.70,220,225

Two drugs closely related to erythromycin, azithromycin, an azalide, and clarithromycin, a semisynthetic macrolide, have been investigated as alternatives to erythromycin for the treatment of R. equi infections in foals. Compared with erythromycin, these drugs are more chemically stable, have a greater bioavailability after oral administration, and achieve higher concentrations in tissues and phagocytic cells. Studies of the pharmacokinetics and in vitro susceptibility of R. equi have been performed with both antimicrobials.221,220,226

The efficacy of azithromycin, clarithromycin, and erythromycin were compared in a retrospective study of foals admitted to a referral hospital.71 Foals were treated with erythromycin stearate (n = 24; 25 mg/kg every 6 hours [q6h], 25 mg/kg q8h, or 37.5 mg/kg q12h), azithromycin (n = 20; 10 mg/kg q24h), or clarithromycin (n = 18; 7.5 mg/kg q12h). All foals except one in the azithromycin group were treated concurrently with rifampin (5 mg/kg q12h, 10 mg/kg q12h, or 10 mg/kg q24h). The results indicated that clarithromycin-rifampin was superior to erythromycin-rifampin or azithromycin-rifampin. There was no advantage of azithromycin-rifampin over traditional therapy with erythromycin-rifampin except for the convenience of once-daily dosing. These results may not necessarily apply to a situation where foals are screened and treatment is started early before establishment of severe lung lesions. Differences in the duration of therapy among treatment groups were not evaluated in this study, but many horses with rhodococcal infection require prolonged antibiotic therapy regardless of the treatment protocol. Treatment is frequently continued for 4 to 8 weeks, although a shorter duration of therapy may be sufficient if the disease is recognized early.6,77,229 In some affected foals, such as those with well-established abscesses or osteomyelitis, a longer treatment period may be indicated. Criteria often used for the cessation of therapy include resolution of clinical signs, normalization of plasma fibrinogen concentrations, and radiographic or ultrasonographic resolution of lung lesions.

The use of erythromycin in foals is associated with a number of adverse effects, including diarrhea, hyperthermia, and respiratory distress.220,225 In a study of 145 pneumonic foals, the risk of adverse effects was greater in foals treated with erythromycin than in foals treated with trimethoprim-sulfamethoxazole or penicillin.230 Of the 73 foals treated with erythromycin, either alone or in combination with rifampin or gentamicin, 26 (36%) developed diarrhea, 18 (25%) develop hyperthermia, and 11 (15%) developed respiratory distress. Colitis has been observed in mares of foals being treated orally with erythromycin-rifampin, and in one study, Clostridium difficile was cultured from 5 of 11 (45%) of such mares with diarrhea.233,234 Although many cases of antibiotic-associated colitis are self-limiting in both foals and mares, occasional cases are severe and fatal. In the study comparing erythromycin, azithromycin, and clarithromycin, diarrhea was observed in 17% of foals treated with erythromycin, 5% of foals treated with azithromycin, and 28% of foals treated with clarithromycin.71 No difference was found between the groups in the proportion of foals that developed severe diarrhea requiring fluid therapy. The incidence of hyperthermia and respiratory distress resulting from antimicrobial therapy was not critically evaluated because both are common clinical signs in foals affected with R. equi.

The majority of R. equi isolates are sensitive to erythromycin, clarithromycin, azithromycin, and rifampin, but resistant strains have been encountered.14,220,222,223,235-240 Resistance to erythromycin and especially rifampin can develop rapidly, particularly when these drugs are used as monotherapy. There is significant cross-resistance between the macrolides.241 R. equi isolates from foals have been documented to develop resistance to rifampin after monotherapy with rifampin and to both erythromycin and rifampin during therapy.236,237 Anecdotally, the development of resistance to clarithromycin and azithromycin in treated foals has also been observed.

It is occasionally necessary to consider alternative antimicrobials to the macrolide/rifampin therapy because of diarrhea, resistance, or financial concerns. In some horses, especially those with mild R. equi pneumonia, a trimethoprim-sulfonamide combination (15-30 mg/kg q8-12h) has been effective.242 A combination of trimethoprim-sulfonamide and rifampin has been suggested, but pharmacokinetic and efficacy data are not available. Enrofloxacin (5 mg/kg orally q24h) alone or in combination with other antibiotics (rifampin or oxytetracycline) has been used successfully to treat a limited number of foals with culture-confirmed R. equi pneumonia.70 However, administration of enrofloxacin to foals may result in lameness, joint effusion, and cartilage lesions.243,244 In foals in which significant diarrhea develops, intravenous erythromycin lactobionate (5 mg/kg diluted in saline and administered as a slow infusion q6h) has been recommended.245 The use of an amino-glycoside in combination with either erythromycin or rifampin is controversial; it was demonstrated in vitro that activity against R. equi was diminished when these drugs were used in combination.76,220,229 In a clinical study of 72 foals, however, the survival rate and ability to race as 3-year-olds were similar for foals treated with gentamicin and rifampin as for those treated with erythromycin and rifampin.246

Many antimicrobial agents have been used in the treatment of human patients with rhodococcal infections.46,247 Protocols for immunocompromised human patients with serious infections often include two or three drug regimens. Antimicrobials typically used include vancomycin, imipenem, amoxicillin, ciprofloxacin, rifampin, and erythromycin.

Additional Therapy

Additional therapy may be required depending on the specifics of the case. If a pathogen is isolated in addition to R. equi, a third antimicrobial may be indicated depending on the susceptibility of the organism. Supportive care is important, including maintaining adequate nutrition and hydration, as well as maintaining foals in a cool, well-ventilated environment. Arterial blood gas (ABG) assessment will help determine if
oxygen therapy is indicated. Bronchodilators, such as aminophylline, theophylline, clenbuterol, and albuterol, are rarely helpful clinically. In addition, concurrent administration of erythromycin and to a lesser extent clarithromycin, with either aminophylline or theophylline, may result in increased plasma concentrations of these bronchodilators, potentiating their toxicity. Nonsteroidal antiinflammatory drugs should be used judiciously to reduce fever and improve attitude and appetite. Although data are limited, based on an experimental model of R. equi pneumonia in foals, specific hyperimmune plasma was ineffective in treating disease once infection was established. In cases with infection at a site other than the lungs, such as septic arthritis or osteomyelitis, local therapy may be indicated.

**Prognosis**

The survival rate for foals with *R. equi* pneumonia varies from 60% to 90% with current antimicrobial therapies. Clinical and hematologic variables associated with survival from rhodococcal pneumonia have varied widely between studies. In a retrospective study of 115 cases from six veterinary medical teaching hospitals, the overall survival rate was 72%. Foals that did not survive were more likely to have extreme tachycardia (heart rate >100), to be in respiratory distress, and to have severe thoracic radiographic abnormalities than were foals that survived. Clinico-pathologic abnormalities were not associated with survival. The proportion of foals that survived was significantly higher in Standardbreds (80%) than in Thoroughbreds (61%). In a study of 81 foals, overall survival was 69%. Radiographic scores, heart rate, and fibrinogen concentrations were significantly higher in nonsurviving foals, whereas arterial oxygen and platelet counts were significantly higher in survivors. Only fibrinogen concentration was retained in the logistic regression model. There was no significant difference in survival among breeds. In another study of 39 foals, respiratory rate, temperature, WBC count, and fibrinogen concentration were higher in nonsurvivors.

The prognosis has generally been poor in cases of rhodococcal osteomyelitis. However, some horses respond to aggressive treatment. A 4-month-old colt that presented for urinary incontinence associated with a *R. equi* diskospondylitis of S5-S4 responded to treatment with erythromycin, rifampin, bethanechol, and cutaneous treatment of the lesion. Similarly, in adult horses the prognosis has generally been poor, possibly because of delayed identification of the problem and underlying immunosuppression. A 2-year-old Quarter Horse with osteomyelitis of the pelvis did respond to treatment with erythromycin and rifampin.

Several studies have attempted to evaluate the long-term effects of *R. equi* pneumonia on pulmonary function and athletic performance. In one study by Ainsworth et al., five horses recovered from rhodococcal pneumonia, and five healthy control horses were evaluated by endoscopy, radiography, histologic and BAL analyses, and pulmonary function testing. There were no significant differences in these parameters between groups, suggesting that horses that recover from *R. equi* pneumonia do not have detectable evidence of residual lung damage. The pulmonary function of seven Standardbreds that had recovered from *R. equi* pneumonia was evaluated during intense treadmill exercise, and gas exchange was not compromised compared with reference values for normal Standardbreds.

A number of studies have evaluated racing performance. In one study of 11 horses previously affected with *R. equi* pneumonia, seven of them eventually raced, and four of the seven won races. In a subsequent study by Ainsworth et al., 54% of foals (45/83) surviving *R. equi* infection eventually raced at least once, compared with 65% of foals in the general population. No physical examination, laboratory, or radiographic findings were identified that were predictive of whether foals went on to race. The racing performance of foals that went on to race was not significantly different from that of the general U.S. population of racing horses. Thus, although *R. equi* infection was associated with a decreased chance of racing as an adult, the performance of those foals that did go on to race was not impaired. Similarly, in a study by Bernard et al., *R. equi* in foals did not have a negative influence on racing performance, as evaluated by 2- and 3-year-old race earnings.

**PREVENTION**

**Decreasing the Size of Infective Challenge**

The outcome of exposure to *Rhodococcus equi* is partially determined by the size of the infective challenge, as with most infectious diseases. Therefore, practices targeted at decreasing the number of organisms in the environment could decrease the incidence of disease. Although a number of management practices have been recommended theoretically to decrease exposure to *R. equi*, data supporting their efficacy are limited. In addition, studies aimed at identifying practices that influence the risk of disease have often had conflicting results, making it difficult to make specific management recommendations.

Farmers affected with *R. equi* pneumonia tend to have large numbers of mares and foals. One explanation for this is that because *R. equi* is frequently present in horse manure and may reach high numbers in the feces of foals, where it can replicate in the intestinal tract, a larger number of mares and foals may result in greater environmental contamination with *R. equi*. Additionally, a larger number of mares and foals may simply increase the probability that a farm has a foal that develops *R. equi* pneumonia. Studies evaluating whether an association exists between high foal density and disease, as well as between mare and foal numbers and disease, have had varying results. However, it has been suggested that both decreasing the number of mares and foals on a farm and decreasing the density could minimize *R. equi* infection.

Horse manure is believed to contribute to environmental contamination not only because it often contains bacteria, but because it contains volatile fatty acids that enhance the growth of *R. equi* in the environment. Therefore, it has been recommended to remove horse manure frequently from stalls, paddocks, and pastures and either not to spread manure on pastures as fertilizer or to compost the manure before spreading. In epidemiologic studies, however, manure removal programs did not significantly alter the risk for development of *R. equi* pneumonia. There were no significant differences between control farms and affected farms in whether horse manure was spread on pastures or composted before spreading. The highest concentrations of bacteria in manure are generally found in the feces of infected foals, because these foals swallow sputum with large numbers of virulent organisms, which may then multiply within the intestine. Thus, although *R. equi* is not thought to be highly contagious between horses, preventive recommendations include isolating infected foals and removing their manure promptly to decrease environmental contamination. *R. equi* infection has anecdotally been linked to raising foals in a dusty environment, but it has been difficult to document this objectively. Cohen et al. demonstrated an association between *R. equi* pneumonia and the veterinarians' report of a dusty environment, whereas Chaffin et al. failed to show such an association. However, it has been theorized that
efforts to reduce dust in the environment, such as reseeding and irrigating to promote growth of grass, as well as using water sprinklers in paddocks, may reduce aerosolization of dust particles that might be laden with *R. equi* and may help decrease the incidence of rhodococcal infection.

One study demonstrated that foals from farms with enzootic *R. equi* were significantly less likely to have foaled in a paste than in a stall or small paddock. Stalled confinement may expose foals to high concentrations of microorganisms and poor ventilation, contributing to the development of disease. Further investigation is needed to evaluate the effects of environmental management procedures on the prevalence of *R. equi* infection.

**Early Detection of Disease**

The early recognition of *R. equi* pneumonia may reduce losses and limit the duration, and thus the costs, of therapy. Because obvious clinical signs are often not apparent until the disease is advanced, a number of approaches have been recommended for early diagnosis. Higuchi et al. suggested that physical examination of foals at 30 and 45 days of age was useful for early diagnosis of *R. equi* infection on enzootic farms. Similarly, Prescott et al. found that twice-weekly complete physical examinations with careful auscultation of the thorax was successful in the early diagnosis of infection and in preventing mortality. Serologic surveillance has also been recommended, but it is unreliable.

Other strategies for early detection of *R. equi* pneumonia include serial monitoring of WBC count and fibrinogen concentration and thoracic US. A prospective study of 162 foals from a farm with enzootic *R. equi* infection evaluated the efficacy of WBC count, fibrinogen concentration, and the AGID test for early identification of *R. equi*-infected foals. Although both WBC count and fibrinogen concentration were useful in detecting early *R. equi* infection, the WBC count was more sensitive and specific. It was recommended that WBC counts of foals should be evaluated monthly on farms with enzootic *R. equi* infection. Foals with WBC concentrations of 13,000 cells/µL or greater should receive a careful physical examination, and foals with WBC concentrations of 14,000/µL or higher should be considered candidates for additional diagnostic testing, such as thoracic radiography or US. Serologic testing using the AGID was not accurate in predicting disease.

Thoracic US of foals starting at 30 days of age and repeated at 2-week intervals until 16 to 20 weeks of age may be effective in reducing subclinical and clinical disease associated with *R. equi*.

Prophylactic antibiotic use has been anecdotally recommended to reduce disease caused by exposure to *R. equi*. This practice is controversial in part because of concerns about the selection of antibiotic-resistant bacteria. The efficacy of this recommendation in preventing disease is currently under investigation, but no data are yet available.

**Passive Immunization**

Hyperimmune plasma is often administered intravenously to foals in an effort to prevent *R. equi* pneumonia. In some studies, this practice has been effective in significantly reducing the incidence of rhodococcal pneumonia after experimental or natural challenge. However, other studies have failed to document a statistically significant protective effect. For example, in a randomized clinical trial of 165 Thorobred foals on a farm with enzootic pneumonia, 19.1% of foals receiving plasma developed *R. equi* pneumonia compared with 30% of nontreated foals. This difference was not statistically significant. Despite the somewhat varying results, the generally beneficial effects and relative safety of administering hyperimmune plasma have made its use relatively common. In a study of 65 enzootic farms, 36 (50%) administered hyperimmune plasma.

The optimal protocol for the administration of hyperimmune plasma has not been determined, and differences in the timing of administration may account for some of the variability between studies. Optimally, plasma should be given before exposure to *R. equi*, based on studies that demonstrated no benefit when hyperimmune plasma was administered after experimental challenge. The exact time of exposure of most foals is unclear but likely occurs early in life, especially on enzootic farms. Administration of hyperimmune plasma too early may result in a waning of passively transferred antibodies to nonprotective concentrations when some foals are still susceptible.

Most studies have administered approximately 1 liter of plasma between 30 and 60 days of age. In the study of 165 foals on an enzootic farm, 950 mL of plasma was administered at 1 to 10 days of age and again at 30 to 50 days of age. Because the majority of treated foals that developed pneumonia did so before the administration of the second dose, it was postulated that administration of the second dose at an earlier age may have been more beneficial. The ideal time for hyperimmune plasma administration may vary from farm to farm.

**Active Immunization**

The development of an effective vaccine for *R. equi* would clearly be beneficial to the equine population and has been an area of active research. Most foals exposed to virulent *R. equi* mount a protective immune response and remain immune as adults, which suggests that the induction of protective immunity by active immunization should be possible. However, the development of an efficacious vaccine has proved difficult despite the use of multiple strategies for active immunization of mares and foals.

One major challenge in developing an effective vaccine is the ability to stimulate the correct type of immune response (i.e., the protective phenotype) in a neonatal foal. Because of immunologic naiveté, foals may have a diminished ability to mount a protective immune response of the required magnitude quickly enough to prevent infection. Although specific information related to neonatal immunity in foals is limited, the immune responses of neonates appear to differ both quantitatively and qualitatively from those of adults. The differences in the immune system during the first few weeks of life have been variously described as a state of immunologic immaturity, a relative immunodeficiency, or immunodeviation. With respect to cellular immunity, neonates are thought to have a Th2 bias and a diminished ability to generate the type 1 responses necessary for clearance of intracellular pathogens. Another possible challenge to immunization of neonatal foals is overcoming potential interference by maternal antibody. However, this may be of less importance with *R. equi* than with some other pathogens, because the T-lymphocyte responses that play a significant role in immunity to *R. equi* may be less affected by maternal antibody than humoral responses.

Several candidate vaccines have been investigated, but as yet none has been developed for widespread use. Killed virulent *R. equi* did not elicit protective immunity in mice. Similarly, killed virulent *R. equi* given intramuscularly did not protect foals from experimental infection. Immunization of foals with two exoenzymes produced by *R. equi*, cholesteryl oxidase and phospholipase C, did not prevent the development of lung abscesses after experimental challenge, although severe clinical signs did not develop in either vaccinated or control foals in this study. A number of vaccines
have been evaluated for the prevention of *R. equi* under field conditions, including an inactivated *R. equi* vaccine with and without EHV-2, a preparation of soluble antigens of *R. equi* that include Vapa and "equi factor" exoenzymes, and an EHV-2 subunit vaccine. Although studies have suggested that these vaccines could provide some protection against *R. equi*, data are limited and further study is needed.

Infection with avirulent *R. equi* does not result in protection, suggesting that the virulence plasmid encodes antigens critical to protective immunity. Several studies have focused specifically on the potential of Vapa as an immunogen. Vaccination with Vapa results in the production of Vapa-specific antibodies in both horses and mice. A study in mice demonstrated that immunization with partially purified Vapa also resulted in significantly enhanced clearance of organisms from the liver and spleen after experimental challenge. Other studies, however, have suggested that Vapa vaccines are unable to prevent bacterial replication during natural infection with *R. equi* despite the presence of an opsonizing antibody. Limited data from a study in pregnant mares suggest that the use of a Vapa candidate vaccine could result in passive antibody-mediated protection of foals and warrants further investigation.

Exposure to live virulent *R. equi* elicits protective immunity in both foals and mice. Specifically in foals oral immunization with live virulent *R. equi* protected foals against experimental challenge, confirming that young foals can mount a highly effective protective immune response. Feals that were orally immunized developed high concentrations of antibody specific to Vapa and VapC but not to other Vap proteins, indicating that Vap A and Vap C are highly immunogenic. Although oral immunization with live virulent bacteria is protective, it is not considered a practical means of widespread administration because of the risks of developing disease in some individuals and disseminating large numbers of organisms into the environment.

Efforts to develop a safe, effective vaccine for *R. equi* are ongoing. Even at a young age, most foals are probably capable of mounting a protective immune response, as supported by the observations that the majority of foals do not develop clinical disease after natural exposure and that foals are protected after oral immunization with live virulent bacteria. An effective vaccine will most likely induce both humoral and cellular immunity and will direct the immune response to the protective phenotype. Some strategies under investigation include the development of attenuated strains of *R. equi* by transposon mutagenesis, DNA vaccination, and the use of a recombinant bacille Calmette-Guérin (BCG) vaccine expressing Vapa antigen.

**PUBLIC HEALTH CONSIDERATIONS**

*Rhodococcus equi* is an emerging pathogen in human medicine and is most often recognized as an opportunistic infection in immunocompromised patients. The first case of *R. equi* infection in a human patient was not reported until 1967, and only about 12 additional cases were reported during the next 15 years. However, coincident with the emergence of HIV infection and advances in organ transplantation and cancer treatment, the incidence of *R. equi* in humans has greatly increased since the early 1980s. Improvements in laboratory diagnosis and enhanced awareness of the disease have also contributed to the increase in reported cases. In the past 15 years, at least 100 cases of *R. equi* infection in humans have been reported in the medical literature. Approximately 85% to 90% of human patients with *R. equi* are immunocompromised, with these patients being divided between those with HIV infection and those who are otherwise immunocompromised as a result of disease, immunosuppressive medications, or both. These immunocompromised patients often have concurrent infections with other opportunistic pathogens. Only about 10% to 15% of *R. equi* infections occur in seemingly immunocompetent hosts.

*Rhodococcus equi* infection in human patients is thought to be acquired by inhalation, inoculation into a wound or mucous membrane, or ingestion. The soil is believed to be the most common source of infectious organisms. The possible role of other routes of *R. equi* acquisition, including human colonization and person-to-person transmission, is poorly understood. It is believed that *R. equi* does not colonize the intestine of human patients. Because rhodococcal species other than *R. equi* are among the species that dominate the nasal microbiota of healthy adults, it has been speculated that nasal colonization with *R. equi* could occur. Unlike in foals, where essentially all isolates from clinical cases express Vapa, only 20% to 25% of isolates recovered from human infections express Vapa.

The clinical manifestations of *R. equi* infection in human patients are varied, and the organism has been isolated from almost every body site. As in foals, pulmonary infection, often resulting in pyogranulomatous pneumonia, is common, being recognized in approximately 84% of immunocompromised patients and approximately 42% of immunocompetent patients. Localized infections, often associated with wounds, represent about 50% of reported cases in immunocompetent hosts. Combination antibiotic therapy is the mainstay of treatment, and empiric two-drug regimens typically include erythromycin, rifampin, and/or ciprofloxacin. Vancomycin, imipenem, aminoglycosides, and a number of other antibiotics have also been recommended. Surgical drainage of abscesses in sites of poor antibiotic penetration is probably beneficial. The mortality rate among immunocompetent patients is approximately 11%, compared with rates of 50% to 65% among HIV-infected patients and 20% to 25% among non-HIV-infected immunocompromised patients.

Exposure to domesticated animals, especially horses and pigs, may play a role in some cases of *R. equi* infection in humans, although only one third of all patients have a history of exposure to horses or pigs. However, it is recommended that immunocompromised patients with significant exposure to domesticated animals be cautioned regarding the possible risk of *R. equi* infection.

**REFERENCES**

See the CD-ROM for a list of references linked to the abstract in PubMed.
**RESPIRATORY PROBLEMS**

**Cough**
- Pleuropneumonia (1)
- Pharyngeal or laryngeal abscess (1)
- Pulmonary abscess (1)
- Guttural pouch empyema or mycosis (1, 28)
- Bacterial pneumonia (1, 28)
- Equine influenza (12)
- Equine herpesvirus (13)
- Equine viral arteritis (14)
- African horse sickness (15)
- Equine rhinovirus (16)
- Equine adenovirus (16)
- Hendra virus (16)
- Strangles (28)
- Nocardiosis (30)
- *Rhodococcus equi* (32)
- Tuberculosis (33)
- Glanders (39)
- Pneumocystis carinii infection (50)
- Coccidioidomycosis (51)
- Pythiosis, zygomycosis (55)
- Pulmonary aspergillosis (56)
- Cryptococcosis (57)
- *Parascaris equorum* larval migration (62)
- Lungworms (62)

**Nasal Discharge**
- Lymphoid pharyngeal hyperplasia (1)
- Bacterial pneumonia (1)
- Pleuropneumonia (1)
- Guttural pouch mycosis (1)
- Lung abscess (1)
- Guttural pouch empyema, chondroids (1, 28)
- Equine influenza (12)
- Equine herpesvirus (13)
- Equine viral arteritis (14)
- African horse sickness (15)
- Equine adenovirus (16)
- Equine rhinovirus (16)
- Hendra virus (16)
- Strangles (28)
- Nocardiosis (30)
- *Rhodococcus equi* (32)
- Tuberculosis (33)
- Glanders (39)

*Numbers in parentheses refer to chapters in which diseases are discussed.*

**Respiratory Noise**
- Arytenoid chondritis (1)
- Guttural pouch empyema (1)
- Guttural pouch mycosis (1)
- Strangles (28)
- Conidiobolomycosis (55)

**Rhinitis, Sinusitis**
- Glanders (39)
- Conidiobolomycosis (55)
- Aspergillosis (56)

**Pleural Effusion**
- Pleuropneumonia (1)
- African horse sickness (15)

**Lower Respiratory Tract Inflammation**
- Pneumonia (1)
- Pleuropneumonia (1)
- Aspiration pneumonia (1)
- Interstitial pneumonia (1)
- Endocarditis (2)
- Myocarditis (2)
- Neonatal septicemia (6)
- Influenza (12)
- Equine herpesviruses (13)
- Adenovirus (16)
- Hendra virus (16)
- Rhinovirus (16)
- Streptococcal diseases (28)
- Corynebacterium pseudotuberculosis (30)
- *Rhodococcus equi* (32)
- Mycobacteria (33)
- Glanders (39)
- Anaerobic infection (48)
- Pneumocystis (50)
- Pulmonary aspergillosis (56)
- Pulmonary habronemiasis (62)
Lungworms (62)  
Ascarid migration (62)

**GASTROINTESTINAL PROBLEMS**

**Diarrhea in Adult Horses**  
*Aeromonas* spp. (3)  
Mycobacterial infections (33)  
Endotoxemia (37)  
Salmonellosis (38)  
Potomac horse fever (43)  
Enteric clostridiosis (44)  
Histoplasmosis (57)  
Cryptosporidiosis (61)  
Giardiasis (61)  
Parasitism (62)  
Cyathostomiasis (62)  
Cestodes (63)

**Diarrhea in Foals**  
*Aeromonas* spp. (3)  
Neonatal septicemia (6)  
Rotavirus (17)  
Coronavirus (18)  
*Rhodococcus equi* (32)  
*Lawsenia intracellularis* (36)  
Endotoxemia (37)  
Salmonellosis (38)  
*Clostridium perfringens* type A, B, or C (44)  
*Clostridium difficile* (44)  
Tyzzer’s disease (45)  
Cryptosporidiosis (61)  
Giardiasis (61)  
Gastrointestinal parasites (61, 62)  
Strongyloidosis (62)

**Abdominal Pain**  
Peritonitis (3)  
Abdominal abscess (3)  
Neonatal septicemia (6)  
Oophoritis (8)  
Equine viral arteritis (14)  
African horse sickness (15)  
Rabies (19)  
West Nile virus (21)  
Purpura hemorrhagica (*Streptococcus zooepidemicus* subsp. *equi*) (28)  
*Corynebacterium pseudotuberculosis* (30)  
Anthrax (30)  
*Rhodococcus equi* (32)  
*Lawsenia intracellularis* (36)  
Endotoxemia (37)  
Salmonellosis (38)  
Potomac horse fever (43)  
Enteric clostridiosis (44)  
Botulism (46)  
Tetanus (47)  
Pythiosis (55)  
Piroplasmosis (60)  
Ascarid impaction (62)  
Strongylosis (62)  
Cestodes (63)

**Dysphagia**  
Guttural pouch mycosis (1)  
Guttural pouch empyema (1, 28)  
Pharyngeal or laryngeal infection or abscess (1)  
Oral infection (3)  
Bacterial meningitis or encephalitis (4)  
Rabies (19)  
Alphaviruses (20)  
West Nile virus infection (21)  
Strangles (28)  
Botulism (46)  
Tetanus (47)  
Equine protozoal myeloencephalitis (59)  
Sarcocystosis (61)  
Tick paralysis (64)

**Icterus**  
Cholangiohepatitis, cholangitis (3)  
Hepatic abscess (3, 28, 30)  
Equine viral arteritis (14)  
Equine infectious anemia (23)  
Leptospirosis (34)  
Ehrlichiosis (42)  
Tyzzer’s disease (45)  
Piroplasmosis (60)  
Surra (61)  
Dourine (61)  
Ascarids (62)

**Oral Ulcerations or Vesicles**  
Equine herpesvirus (13)  
Equine viral arteritis (14)  
Vesicular stomatitis (24)  
Jamestown Canyon virus (26)  
Mycobacterial infections (33)  

**Hepatomegaly, Hepatic Inflammation**  
Equine infectious anemia (23)  
*Rhodococcus equi* (32)  
Mycobacterial infections (33)  
Leptospirosis (34)  
Endotoxemia (37)  
Tyzzer’s disease (45)  
Echinococcosis (61)

**Abdominal Abscess**  
Abdominal abscess (3)  
Strangles (28)  
Corynebacterium *pseudotuberculosis* (30)  
*Rhodococcus equi* (32)  
Mycobacterium spp. (33)  
Echinococcus infection (61)

**Abdominal Effusion**  
Abdominal abscess (3)  
Peritonitis (3)  
Streptococcal infections (28)  
*Rhodococcus equi* (32)  
Coccidiodomycosis (51)  
Verminous arteritis (62)  
*Corynebacterium pseudotuberculosis* (30)

**CENTRAL NERVOUS SYSTEM PROBLEMS**

**Cortical Signs**  
Parasite migration (4, 61)  
Brain abscess, meningitis (4, 28)  
Neonatal septicemia (6)  
Equine herpesvirus type 1 (13)  
Rabies (19)  
Eastern equine encephalitis (20)
Western equine encephalitis (20)
Venezuelan equine encephalitis (20)
Japanese encephalitis virus (21)
West Nile virus (21)
Borna disease (22)
Main Drain virus (26)
Snowshoe hare virus (26)
Jamestown Canyon virus (26)
Equine encephalosis (26)
Glanders (39)
Candidiasis (53)
Aflatoxicosis (56)
Cryptococcus neoformans (57)
Equine protozoal myeloencephalitis (59)
Piroplasmosis (60)

**Brain Stem Signs**
Temporohyoid osteoarthropathy (1)
Guttural pouch mycosis or empyema (1, 28)
Parasite migration (4, 61)
Brain stem abscess (4, 28)
Equine herpesvirus type 1 (13)
Rabies (19)
West Nile virus (21)
Borna disease (22)
Equine protozoal myeloencephalitis (59)

**Spinal Cord or Peripheral Nerve Signs**
Vertebral body abscess (4)
Discospondylitis (4)
Equine herpesvirus type 1 (13)
Rabies (19)
West Nile virus (21)
Borna disease (22)
Equine infectious anemia (23)
*Rhodococcus equi* (32)
Lyme disease (35)
Granulocytic ehrlichiosis (42)
Botulism (46)
Tetanus (47)
Equine protozoal myeloencephalitis (59)
Dourine (61)
Surra (61)
Tick paralysis (64)

**URINARY TRACT PROBLEMS**

**Dysuria, Stranguria, Pollakiuria**
Cystitis (9)
Urethritis (9)
Pyelonephritis (9)
Urinary calculi (9)
Habronemiasis (62)

**Incontinence**
Parasite migration (4, 62)
Equine herpesvirus type 1 (13)
Rabies (19)
Equine protozoal myeloencephalitis (59)

**Hematuria**
Seminal vesiculitis (8)
Cystitis (9)
Urinary tract infection (9)
Urolithiasis (9)
*Corynebacterium pseudotuberculosis* (30)
Leptospirosis (34)
Endotoxia (37)
Salmonellosis (38)
Enteric clostridiosis (44)
Habronemiasis (62)

**Renal Failure**
Pyelonephritis (9)
Urolithiasis (9)
Leptospirosis (34)
Endotoxia, sepsis (37)
Piroplasmosis (60)

**MUSCULOSKELETAL PROBLEMS**

**Myositis, Increased Muscle Enzyme Activity**
Sarcocystosis (5, 61)
Equine influenza (12)
Equine herpesviruses (13)
African horse sickness (15)
Strangles (28)
Streptococcal infections (28)
Clostridial myonecrosis (45)
Anaerobic bacterial infections (48)
Surra (61)

**Lameness, Stiffness, Arthritis**
Aortoiliac thrombosis (2)
Septic arthritis (5)
Osteomyelitis (5)
Bacterial tenosynovitis (5)
Neonatal septicemia (6)
Rabies (19)
West Nile virus (21)
Borna disease (22)
Purpura hemorrhagica (strangles) (28)
Streptococcal infections (28)
Staphylococcal infections (29)
*Corynebacterium pseudotuberculosis* (30)
*Rhodococcus equi* (32)
Lyme disease (35)
Endotoxia (37)
Brucellosis (40)
Potomac horse fever (43)
Clostridial myonecrosis (45)
Tetanus (47)
Coccidioidomycosis (51)
Candidiasis (53)
Equine protozoal myeloencephalitis (59)

**Muscle Fasciculations**
Rabies (19)
West Nile virus (21)
Borna disease (22)
Anthrax (30)
Endotoxia (37)
Botulism (46)
Tetanus (47)

**CARDIOVASCULAR PROBLEMS**

**Cardiomyopathy, Myocarditis, Endocarditis**
Bacterial endocarditis (2)
Inflammatory valvulitis (2)
Equine influenza (12)
Equine herpesvirus (13)
African horse sickness (15)
Streptococcal infections (28)
*Rhodococcus equi* (32)
Granulocytic ehrlichiosis (42)

**REPRODUCTIVE PROBLEMS**

**Abortion, Infertility, Early Embryonic Loss, Birth of Weak Foals**
Endometritis (8)
Pyometra (8)
Oophoritis (8)
Salpingitis (8)
Neosporosis (8)
Nocardioform placentitis (8)
*Aeromonas hydrophila* (8)
Chlamydiosis (8)
*Mycoplasma* infection (8)
Bacterial placentitis (8)
Fungal placentitis (8)
Equine herpesvirus type 1 (13)
Equine viral arteritis (14)
Equine infectious anemia (23)
Streptococcal infections (28)
*Rhodococcus equi* (32)
Mycobacterial infections (33)
Leptospirosis (34)
Salmonellosis (38)
Brucellosis (40)
Contagious equine metritis (41)
Potomac horse fever
*Neorickettsia risticii* (43)
Coccidioidomycosis (51)
Candidiasis (53)
Aspergillosis (56)
Piroplasmosis (60)
African animal trypanosomiasis (61)
Surra (61)
Dourine (61)

**Scrotal/Preputial Enlargement**
Epididymitis (8)
Equine herpesvirus type 3 (8)
Orchitis (8)
Streptococcal infections (28)
*Corynebacterium pseudotuberculosis* (30)
Glanders (39)
Dourine (61)
Habronemiasis (62)
Onchocerciasis (62)

**HEMOLYMPHATIC PROBLEMS**

**Enlarged Lymph Nodes**
Upper respiratory tract infection (1)
Equine influenza (12)
Equine herpesviruses (13)
Equine rhinovirus (16)
Equine adenovirus (16)
Strangles (28)
*Corynebacterium pseudotuberculosis* (30)
*Rhodococcus equi* (32)
Mycobacterial infections (33)
Glanders (39)
Pythiosis (55)
Histoplasmosis (57)
Cryptococcosis (57)
Blastomycesis (57)
Epizootic lymphangitis (57)

**Lymphangitis**
*Corynebacterium pseudotuberculosis* (30)
*Rhodococcus equi* (32)
Glanders (39)
Sporotrichosis (52)

**Anemia**
Equine infectious anemia (23)
Chronic infections (28)
Streptococcal infection (28)
*Corynebacterium pseudotuberculosis* (30)
Granulocytic ehrlichiosis
*Anaplasma phagocytophilum* (42)
Clostridial myonecrosis (45)
Piroplasmosis (babesiosis) (60)
Dourine (61)
Surra (61)
African animal trypanosomiasis (61)
Gastrointestinal parasitism (61, 62, 63)

**Petechial Hemorrhages**
Neonatal septicemia (6)
Equine viral arteritis (14)
Equine infectious anemia (23)
Purpura hemorrhagica (strangles) (28)
Endotoxemia, septicemia, bacteremia (37)
Salmonellosis (38)
Granulocytic ehrlichiosis (42)
Potomac horse fever (43)
Piroplasmosis (60)
African animal trypanosomiasis (61)
Surra (61)

**Ventral Abdominal or Limb Edema**
Pleuritis, pleuropneumonia (1)
Pericarditis (2)
Thrombophlebitis (2)
Bacterial endocarditis (2)
Equine herpesvirus (13)
Equine viral arteritis (14)
Equine infectious anemia (23)
Purpura hemorrhagica (strangles) (28)
*Corynebacterium pseudotuberculosis* (30)
Anthrax (30)
Mycobacterial infections (33)
Endotoxemia (37)
Granulocytic ehrlichiosis (42)
Monocytic ehrlichiosis (43)
Piroplasmosis (60)
Dourine (61)
Surra (61)
African animal trypanosomiasis (61)
Gastrointestinal parasitism (61, 62, 63)

**Hypoalbuminemia**
Mycobacterial infections (33)
Equine infectious anemia (36)
*Lawsonia intracellularis* (36)
Salmonellosis (38)
Enteric clostridiosis (44)
Gastrointestinal parasitism (61, 62, 63)
Cyathostomiasis (62)
Immunodeficiency
Equine herpesvirus type (2, 13)
African animal trypanosomiasis (61)

Thrombocytopenia
African horse sickness (15)
Equine infectious anemia (23)
Endotoxemia (37)
Salmonellosis (38)
Granulocytic ehrlichiosis (42)
Potomac horse fever (43)
Enteric clostridiosis (44)
Babesiosis (60)
Trypanosomiasis (61)

Ocular Problems

Uveitis
Neonatal septicemia (6)
Viral infection (10)
Setaria infection (10)
Verminous migration (10)
Uveitis (10, 34)
Streptococcal infections (28)
Rhodococcus equi (32)
Leptospiriosis (34)
Lyme disease (35)
Granulocytic ehrlichiosis (42)
Onchocerciasis (62)

Keratitis
Temporohyoid osteoarthropathy (1)
Neonatal septicemia (6)
Bacterial keratitis (10)
Fungal keratitis (10, 56)
Equine herpesviruses (13)
Dourine (61)
Onchocerciasis (62)

Conjunctivitis
Chlamydiosis (10)
Thelazia (10)
Equine influenza (12)
Equine herpesviruses (13)
Equine viral arteritis (14)
African horse sickness (15)
Equine adenovirus (16)
Streptococcal infections (28)
Lyme disease (35)
Blastomycosis (57)
Epizootic lymphangitis (57)
Piroplasmosis (60)
Surra (61)
Dourine (61)
Besnoitiosis (61)
Onchocerciasis (62)
Habronemiasis (62)

Corneal Edema
Equine herpesvirus type 2 (13)
Leptospiriosis (34)
Aspergillosis (56)
Onchocerciasis (62)

Blindness
Guttural pouch empyema (1)
Brain abscess (4)
Meningitis (4)
Toxoplasmosis (10)
Echinococcosis (10, 61)
Equine leukoencephalomalacia (10)
Rabies (19)
Alphavirus encephalitides (20)
Japanese encephalitis (21)
West Nile virus (21)
Aspergillosis (56)
Equine protozoal myeloencephalitis (59)

Integumentary Problems

Hair Loss
Dermatophilosis (31)
Dermatophytosis (54)
Besnoitiosis (61)
Pinworms (62)
Onchocerciasis (62)
Lice (64)
Mite infestation (64)
Culicoides hypersensitivity (64)

Pruritus
Malassezia infection (7)
Folliculitis (7)
Besnoitiosis (7, 61)
Rabies (19)
Dermatophilosis (31)
Dermatophytosis (54)
Onchocerciasis (62)
Pinworms (62)
Culicoides hypersensitivity (64)
Pediculosis (64)
Lice (64)
Mites (64)

Crusting, Scaling
Bacterial folliculitis (7)
Malassezia infection (7)
Poxvirus (7)
Besnoitiosis (7, 61)
Dermatophilosis (31)
Dermatophytosis (54)
Onchocerciasis (62)
Culicoides hypersensitivity (64)
Mite infestation (64)

Ulcers, Fistulas, Granulomatous Lesions
Leishmaniasis (7)
Equine sarcoid (25)
Staphylococcal infections (29)
Corynebacterium pseudotuberculosis (30)
Nocardiosis (30)
Mycobacterial infections (33)
Glanders (39)
Brucellosis (40)
Sporotrichosis (52)
Pythiosis (55)
Basidiobolomycosis (55)
Mucormycosis (55)
Habronemiasis (62)
Myiasis (64)
Papulonodular Lesions
- Bacterial furunculosis (7)
- Molluscum contagiosum (7)
- Leishmaniasis (7)
- Papillomatosis (25)
- Dermatophytosis (54)
- Fly or tick bites (64)
- Warbles (64)
- Straw itch mites (64)

Large Nodular Dermatoses or Abscesses
- Equine sarcoid (25)
- Streptococcal infections (28)
- Staphylococcal infections (29)
- Corynebacterium pseudotuberculosis (30)
- Nocardiosis (30)
- Rhodococcus equi (32)
- Mycobacterial infections (33)
- Glanders (39)
- Coccidioidomycosis (51)

Sporotrichosis (52)
Zygomycosis (55)
Pythiosis (55)

SUDDEN DEATH

Collapse and Sudden Death
- Guttural pouch mycosis (acute hemorrhage) (1)
- Septic thromboembolism (2)
- Ruptured pulmonary or abdominal abscess (3)
- Neonatal septicemia (6)
- Hendra virus (16)
- Anthrax (30)
- Salmonellosis (38)
- Potomac horse fever (43)
- Enteric clostridiosis (44)
- Clostridial myonecrosis (45)
- Tyzzer’s disease (foals) (45)
- Botulism (46)
APPENDIX B

Vaccination Guidelines for Horses in North America
<table>
<thead>
<tr>
<th>DISEASE/VACCINE</th>
<th>FOALS/WEANLINGS</th>
<th>YEARLINGS</th>
<th>PERFORMANCE HORSES</th>
<th>PLEASURE HORSES</th>
<th>BROODMARES*</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus (inactivated toxoid)</td>
<td>Foal of vaccinated mare: First dose: 6 months Second dose: 7 mo Third dose: 9-10 mo</td>
<td>Annual</td>
<td>Annual</td>
<td>Annual</td>
<td>Annual, 4-8 wk before foaling</td>
<td>Booster at time of penetrating injury or surgery if last dose of tetanus toxoid was not administered within past 6 mo.</td>
</tr>
<tr>
<td></td>
<td>Foal of nonvaccinated mare: First dose: 3-4 mo Second dose: 4-5 mo Third dose: 6-8 mo</td>
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<tr>
<td>Encephalomyelitis (EEE, WEE, inactivated vaccine)</td>
<td>Foal of vaccinated mare: First dose: 6 months Second dose: 7 months Third dose: 9-10 mo</td>
<td>Annual, spring</td>
<td>Annual, spring</td>
<td>Annual, spring</td>
<td>Annual, 4-8 wk before foaling</td>
<td>For VEE, follow same protocol as for WEE/EEE if indicated by threat of exposure or requirements for interstate or international transportation. VEE may be available only as a combination vaccine with EEE and WEE.</td>
</tr>
<tr>
<td></td>
<td>Foal of nonvaccinated mare: First dose: 3-4 mo Second dose: 4-5 mo Third dose: 6-8 mo</td>
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<tr>
<td></td>
<td>EEE: (in low-risk areas)</td>
<td></td>
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</tr>
<tr>
<td>West Nile virus (WNV) (inactivated or canarypox-vectored recombinant vaccine)</td>
<td>Foal of vaccinated mare: First dose: 3-4 mo Second dose: 4-5 mo Third dose: 6-8 mo</td>
<td>Semiannual (twice annually) or annual depending on regional duration of season for challenge by WNV-infected mosquitoes.</td>
<td>Semiannual or annual depending on regional duration of season for challenge by WNV-infected mosquitoes.</td>
<td>Semiannual or annual; time one booster 4-8 wk before foaling. Avoid administration to mares during the first 60 days of gestation if possible.</td>
<td>Peak seasonal exposure to WNV is in summer and fall. In areas with prolonged season for WNV-infected mosquitoes, time one booster in early spring to precede local mosquito activity and second booster in middle to late summer to precede expected peak local incidence of disease. Mosquito control is important for effective WNV prevention in both</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Foal of nonvaccinated nonexposed mare: First dose: ≤3 mo Second dose: 1 mo later</td>
<td></td>
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<tr>
<td></td>
<td>For the inactivated vaccine, administration of third dose, 2-3 mo</td>
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</tr>
</tbody>
</table>
after second, is recommended.

### Influenza

**Inactivated injectable:**
- **Foal of vaccinated mare:**
  - First dose: 9 mo
  - Second dose: 10 mo
  - Third dose: 12-13 mo
  - Fourth dose: 2-3 mo after second dose


<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Frequency</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated injectable</td>
<td>Semiannual</td>
<td></td>
</tr>
</tbody>
</table>

**Rhinopneumonitis (EHV-1 and EHV-4)**
- Add to core as outlined for influenza.

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Frequency</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhiopneumonitis</td>
<td>Every 4-6 mo if elected</td>
<td></td>
</tr>
</tbody>
</table>

**Modified live virus:**
- First dose: 11 mo
- Optional second dose: 3 mo later

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Frequency</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Live Vaccine</td>
<td>Semiannual</td>
<td></td>
</tr>
</tbody>
</table>

### Annual before breeding (see comments).

- Use inactivated injectable influenza vaccine for prepartum booster.

### Rhino-pneumonitis (EHV-1 and EHV-4)

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Frequency</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhiopneumonitis</td>
<td>Every 4-6 mo if elected</td>
<td></td>
</tr>
</tbody>
</table>

**Use inactivated EHV-1 vaccine during first, seventh, and ninth month of gestation (additional dose during third month of gestation optional).**

**Vaccination of mares with an EHV-1/4 combination vaccine before breeding is recommended. Vaccinate breeding stallions semiannually, with one of the doses timed before start of breeding season.**
<table>
<thead>
<tr>
<th>DISEASE/ VACCINE</th>
<th>FOALS/WEANLINGS</th>
<th>YEARLINGS</th>
<th>PERFORMANCE HORSES</th>
<th>PLEASURE HORSES</th>
<th>BROODMARES*</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strangles. Add to care when risk of exposure is high, particularly on breeding farms.</td>
<td><strong>Intranasal live vaccine</strong>: First dose: 4-6 mo Second dose: 2-3 wk later Third dose: 7-10 mo</td>
<td>Semiannual</td>
<td>Optional: semiannual if risk is high</td>
<td>Optional: semiannual if risk is high</td>
<td>Semiannual, but use M-protein injectable vaccine for prefoaling booster 4-8 wk before foaling</td>
<td>Use when endemic conditions exist or risk is high. Fosals as young as 6 mo have been vaccinated with intranasal product, but a third dose should be administered before weaning.</td>
</tr>
<tr>
<td>Rabies (inactivated vaccine) Add to care when significant risk of exposure to wildlife vectors of rabies exists.</td>
<td><strong>Injectable inactivated vaccine</strong>: First dose: 4-6 mo Second dose: 5-7 mo Third dose: 7-9 mo (depending on product used) Fourth dose: 12 mo</td>
<td>Semiannual</td>
<td>Optional: semiannual if risk is high</td>
<td>Optional: semiannual if risk is high</td>
<td>Semiannual, with one dose of inactivated M-protein vaccine 4-8 wk before foaling</td>
<td>Use when endemic conditions exist or risk is high. Vaccination of seropositive horses with SeM ELISA titers &gt;1:1600 is not recommended because it may increase risk of purpura.</td>
</tr>
<tr>
<td>Potomac horse fever (inactivated vaccine)</td>
<td><strong>Foals of vaccinated mares</strong>: First dose: 3-4 mo Second dose: 12 mo</td>
<td>Annual</td>
<td>Annual</td>
<td>Annual</td>
<td>Annual, before breeding</td>
<td>Vaccination is recommended in endemic areas where potential exists for contact with wildlife vectors such as skunks, raccoons, foxes, badgers, and bats.</td>
</tr>
<tr>
<td>Botulism (shaker foal; inactivated type B toxoid)</td>
<td><strong>Foal of vaccinated mare</strong>: Three-dose series at 30-day intervals is best delayed until foals are 6 mo old, but can be started as early as 2 mo of age.</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Initial three-dose series at 30-day intervals with last dose 4-6 wk before foaling. Annually thereafter, 4-6 wk before foaling.</td>
<td>Only in endemic areas on breeding farms where risk of infection is high. Protection of foal is best accomplished by vaccinating the mare. Vaccination of young foals from nonvaccinated mares is often practiced but may not protect them during first few months of life, when they are most susceptible.</td>
</tr>
<tr>
<td>Condition</td>
<td>Vaccination Schedule</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>--------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Equine viral arteritis</strong></td>
<td>- Intact colts intended for future use as breeding stallions: One dose at 6-12 mo of age</td>
<td></td>
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<tr>
<td><strong>Special circumstances only</strong></td>
<td>- Annual for colts intended for use as breeding stallions</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>- Annual for colts intended for use as breeding stallions</td>
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</tr>
<tr>
<td></td>
<td>- Annual for colts intended for use as breeding stallions</td>
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<tr>
<td></td>
<td>- Annual for seronegative, open mares before breeding to carrier stallions; isolate mares for 21 days after breeding to carrier stallion.</td>
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<tr>
<td></td>
<td>- Use only under special circumstances. Annual for breeding stallions and teasers, 28 days before start of breeding season. Vaccinated mares do not develop clinical signs after breeding to carrier stallions even though they become transiently infected and may shed virus for a short time. Vaccination will render horses seropositive and may complicate exportation. Use on endemic farms or when risk of infection is high. Check concentrations of immunoglobulins at 24 hours of age to verify adequate passive transfer.</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Vaccination Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rotavirus A</strong></td>
<td>- Little value to vaccinate foal because there is insufficient time to develop antibodies to protect during susceptible age</td>
</tr>
<tr>
<td><strong>Special circumstances only on breeding farms</strong></td>
<td>- Not applicable</td>
</tr>
<tr>
<td></td>
<td>- Not applicable</td>
</tr>
<tr>
<td></td>
<td>- Not applicable</td>
</tr>
<tr>
<td></td>
<td>- Vaccinate mares at 8, 9, and 10 mo of gestation, each pregnancy. Passive transfer of colostral antibodies aid in prevention of rotaviral diarrhea in foals.</td>
</tr>
</tbody>
</table>

Compiled by W. David Wilson, University of California, Davis, 2006.

Appropriate application of these guidelines depends on specific assessment of risk on your particular premises by your veterinarian. As with the administration of all medications, the label and product insert should be read before administration of all vaccines.

*Schedules for stallions should be consistent with the vaccination program of the adult horse population on the farm and modified according to risk.

†When a third dose is recommended in the primary immunization series, this should be administered 8 to 12 weeks after the second dose.

EEE, Eastern equine encephalomyelitis; WEE, western equine encephalomyelitis; EHV, equine herpesvirus; SeM, M protein of Strepococcus equi; ELISA, enzyme-linked immunosorbent assay.
### Antimicrobial Drug Formulary

<table>
<thead>
<tr>
<th>DRUG</th>
<th>BRAND NAME</th>
<th>DOSING INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>Amiglyde-V</td>
<td>Adult: 8-10 mg/kg IM or IV q24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Foals: 20-25 mg/kg IM or IV q24h</td>
</tr>
<tr>
<td>Ampicillin sodium</td>
<td>Amp-Equine, generic</td>
<td>22 mg/kg IM q12h, or 22 mg/kg IV q8h; lower doses may be used for highly susceptible organisms such as streptococci.</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Amoxil, Amoxi-ject, Amoxitabs</td>
<td>10-20 mg/kg IV or IM q6h, 20-30 mg/kg PO q4-6h; not absorbed well orally, except in foals.</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Zithromax</td>
<td>For Rhodococcus equi: 10 mg/kg PO q24h for 7 days, then q48h for 21 days; may cause diarrhea in adult horses.</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>Cefa-Tabs</td>
<td>30 mg/kg PO q12h; oral absorption is adequate only in young foals, not adults.</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Ancef, Kefzol</td>
<td>10-22 mg/kg IV or IM q6-8h</td>
</tr>
<tr>
<td>Cefepime</td>
<td>Maxipime</td>
<td>Adult: 2.2 mg/kg IV or IM q8h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Foals: 11 mg/kg IV q8h</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>Mefoxin</td>
<td>20 mg/kg q4-6h IV or IM</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Cliforan</td>
<td>Foals: 40 mg/kg IV q6h</td>
</tr>
<tr>
<td>Cefpodoxime proxetil</td>
<td>Simplicef</td>
<td>Foals: 10 mg/kg PO q8-12h; more frequent dosing should be used for Salmonella or E. coli infections.</td>
</tr>
<tr>
<td>Ceftiofur</td>
<td>Naxcel</td>
<td>Gram-positive infections: 2.2 mg/kg IV or IM q12h E. coli infections: 4.4 mg/kg IV or IM q12h Doses up to 11 mg/kg/day have been used for refractory infections (see Chapter 71).</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>Keflex, generic</td>
<td>30 mg/kg PO q8h, or 10 mg/kg IV q8h</td>
</tr>
<tr>
<td>Cephapirin</td>
<td>Cefadyl, generic</td>
<td>20-30 mg/kg IM or IV q4-8h</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Chloromycetin, generic</td>
<td>35-50 mg/kg PO q6-8h, or 25 mg/kg IV q6-8h</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Biaxin</td>
<td>For Rhodococcus equi: 7.5 mg/kg PO q12h; may cause diarrhea in adult horses.</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Vibramycin, generic</td>
<td>10 mg/kg PO q12h, or 20 mg/kg PO q24h; do not administer IV; variable oral absorption (see Chapter 71).</td>
</tr>
<tr>
<td>Enrofloxacin</td>
<td>Baytril, Baytril-100</td>
<td>5-7.5 mg/kg IM or IV q24h, or 7.5-10 mg/kg PO q24h</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Generic</td>
<td>Erythromycin base alone is poorly absorbed. For Rhodococcus equi: Erythromycin estolate: 25 mg/kg PO q6-8h Erythromycin phosphate: 37.5 mg/kg PO q12h Erythromycin gluceptate injection: 5 mg/kg IV q4-6h</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Gentocin</td>
<td>Adult: 4.4-6.6 mg/kg IV or IM q24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Foal (&lt;2 wk): 12-14 mg/kg IV or IM q24h</td>
</tr>
<tr>
<td>Marbofloxacin</td>
<td>Zenequin</td>
<td>2 mg/kg IV, IM, SC, or PO q24h; injectable formulation not available in United States (see Chapter 71).</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Flagyl, generic</td>
<td>10-20 mg/kg PO q6-8h</td>
</tr>
<tr>
<td>Orbifloxacin</td>
<td>Orbx</td>
<td>5-7.5 mg/kg PO q24h</td>
</tr>
<tr>
<td>DRUG</td>
<td>BRAND NAME</td>
<td>DOSING INFORMATION</td>
</tr>
<tr>
<td>--------------------------</td>
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<td>--------------------</td>
</tr>
<tr>
<td><strong>Antibiotics—cont’d</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Oxytetracycline          | LA-200, other forms             | *Ehrlichiosis*: 3.5 mg/kg IV q12h, or up to 10 mg/kg IV or IM, q24h (give IV slowly)  
|                          |                                 | *Foals* (flexural limb deformities): As much as 44 and up to 70 mg/kg IV (2-3 g per foal), with two doses 24 hr apart, has been used.  
|                          |                                 | *Foals* (flexural limb deformities): As much as 44 and up to 70 mg/kg IV (2-3 g per foal), with two doses 24 hr apart, has been used.  
| Penicillin G             | Generic                         | Sodium or potassium penicillin: 22,000 U/kg IV q6-8h  
|                          |                                 | Procaine penicillin: 22,000 U/kg IM q12h  
|                          |                                 | Doses up to 44,000 U/kg q6h have been used for refractory cases.  
| Rifampin                 | Rifadin                         | 10 mg/kg PO q24h  
|                          |                                 | For *Rhodococcus equi*: 5-10 mg/kg PO, q12h; always use in combination with a macrolide or azalide.  
| Sulfonamides             | Generic                         | See *Trimethoprim-sulfonamides*.  
| Ticaricillin             | Ticar                           | 44 mg/kg IV or IM, q6-8h  
|                          |                                 | Ticaricillin also is used intrauterine in mares.  
| Tilmicosin               | Micotil                         | 15 mg/kg IV q12h, or 20-30 mg/kg PO q12-24h; formulations contain a sulfonamide/trimethoprim ratio of 5:1.  
| *Trimethoprim- sulfadiazine or trimethoprim-sulfamethoxazole* | *Bactrim* | 4.3-7.5 mg/kg as IV infusion q8h  
| Vancomycin               | Vancocin                         | 4.3-7.5 mg/kg as IV infusion q8h  
| **Antifungals**          |                                 |                    |
| Amphotericin B           | Fungizone                        | 0.1-0.6 mg/kg as IV infusion q24h; start at low doses and increase gradually.  
| Fluconazole              | Diflucan, generic                | Loading dose of 14 mg/kg PO, followed by 5 mg/kg PO q24h; liver enzymes should be monitored.  
| Griseofulvin             | Fulvicin U/F                     | 5 mg/kg PO q24h  
| **Antibiotics**          |                                 |                    |
| Itraconazole             | Sporanox                         | Oral solution: 5 mg/kg PO q24h  
|                          |                                 | Oral capsules: 7.5-10 mg/kg PO q24h; absorption is low and variable.  
|                          |                                 | IV solution: 1.5 mg/kg IV q24h  
| Voriconazole             | Vfend                            | 2-4 mg/kg PO q24h, or 1 mg/kg IV q24h; use higher doses for *Fusarium* spp.  
| **Antiprotozoals**       |                                 |                    |
| Pyrimethamine            | Daraqrim                         | 1 mg/kg PO q24h; used in combination with a sulfonamide for the treatment of EPM.  
| Trimeprsim-sulfonamide combinations | *Tribrissen, Uniprim, Bactrim* | See under Antibiotics.  
| Ponazuril                | Marquis                          | 5 mg/kg PO q24h; treatment recommended for a minimum of 28 days for EPM.  
| Diclazuril               | Clinacox                         | 5 mg/kg (500 g of Clinacox) PO q24h; treatment recommended for a minimum of 28 days for EPM.  
| Nitazoxanide             | Navigator                        | Starting dose of 25 mg/kg (11.36 mg/lb) PO q24h for 5 days, followed by 50 mg/kg (22.72 mg/lb) PO q24h for 23 days for EPM; monitor for possible gastrointestinal complications.  

*IM*, Intramuscularly; *IV*, intravenously; *PO*, orally; *SC*, subcutaneously; *q24h*, every 24 hours; *EPM*, equine protozoal myeloencephalitis.