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BACTERIAL PNEUMONIA

The two most important bacterial pathogens affecting older foals are *Streptococcus zooepidemicus* (*Strep. zooe.*) and *Rhodococcus equi* (*R. equi*). *Strep. zooe.* is a Gram-positive opportunistic microbe that takes advantage of mucosal membrane damage (viral, parasitic infections, noxious gases) to cause pulmonary disease. Infections are also enhanced in horse bands with high stocking densities and other associated stressors. In one study of 1-8 month old foals exhibiting respiratory tract infections, *S. zooe.* was isolated in 87% of the cases either as the single agent (49/101 cases) or in combination with Gram-negative organisms such as *Klebsiella*, *Actinobacillus* or *Bordetella* spp. (*Mycoplasma* was rarely isolated.) *Strep. zooe.* differs greatly from *S. equi*, in its pathogenicity. Most notably is the absence of the anti-phagocytic SeM protein found in *S. equi*. However *Strep. zooe.* does produce an acid- and heat-resistant M-like protein (SzP) that binds fibrinogen and interferes with phagocytosis of the organism in vivo. In addition to SzP, capsule formation by the organism *in vivo* inhibits neutrophil phagocytosis and bacterial clearance. Nucleotide variations in the gene encoding SzP contribute to phenotypic diversity of *S. zooe.* found in the tonsils of healthy horses. However, usually a single SzP phenotype is isolated from the pneumonic lungs of affected foals or horses. It is uncertain whether invasion of the bronchi and lung parenchyma results from failure of the mucociliary escalator to remove aspirated *Strep. zooe.* or whether the number of organisms of a single strain becomes so excessive in the nasopharynx that it overloads the normally efficient clearance mechanisms of the lower respiratory tract following their aspiration. Clinical signs of streptococcal pneumonia include fever, depression, nasal discharge, cough, tachypnea and accentuated breathing effort. Adventitious lung sounds (crackles, wheezes) and fluidly tracheal sounds are ausculted. Laboratory work typically reveals a neutrophilic leukocytosis, hyperfibrinogenemia and anemia. Thoracic radiographs demonstrate an airspace pattern with or without abscessation and/or an accentuated bronchial pattern. Ultrasonography reveals comet tails and abscesses if the latter are located in the lung periphery. Interestingly, lung abscesses due to *Strep. zooe.* have been reported to occur in a frequency equal to that of *R. equi* making it difficult to distinguish the two etiological agents based on imaging studies and clinical pathology data. Tracheobronchial aspirates (TBA) demonstrate the presence of intracellular Gram-positive cocci, degenerative neutrophils and mucus. Mixed (polymicrobial) infections are possible. Culture of the TBA and secondary determination of antimicrobial sensitivity patterns enables a definitive diagnosis to be made as well as the recognition of resistance development. *Strep. zooe.* is typically sensitive to the β-lactams, chloramphenicol, rifampin and erythromycin but resistance to trimethoprim-sulfa has been reported in an experimental study of *Strep. zooe.* abscesses in ponies. Foals should be treated for 10-14 days and then re-evaluated.
clinically and by blood work analysis. In addition, some foals benefit from nebulization therapy. If pneumonia has improved but not resolved, treatment is continued for an additional 7-14 days. Treatment is discontinued when the foal appears clinically normal—is afebrile, lacks a cough, nasal discharge, tachypnea—and has a normal leukogram and serum fibrinogen concentration (< 300 mg/dL). If no response to treatment occurs with 4-5 days, antimicrobials should be stopped for 36-48 hours (if possible) and a repeat TBA obtained.

No vaccine is currently available against Strep zooe so preventative measures should be implemented to reduce or eliminate environmental stressors, viral and parasitic infections through husbandry alterations and vaccination protocols (pre-partum mares). Note that Strep zooe is also a zoonotic pathogen: Bacteremia, meningitis and nephritis have been reported in individuals who have had close contact with horses or with dogs infected with Strep zooe. In household dogs living on horse farms, the organism has been isolated from canine cases of severe pneumonia and chronic rhinitis as well as from an asymptomatic dog. Rhodococcus equi is an important cause of subacute to chronic pneumonia in foals 1 to 6 months of age with most infections found in foals 3 months of age. This Gram-positive coccobacillus is also a zoonotic pathogen that poses a risk predominantly for immunocompromised humans. Rare infections of immunocompetent individuals have also been reported. In foals, the specific factors that cause clinical disease to be sporadic on some farms but enzootic and devastating on other farms (mortality rates can exceed 40%) are not understood. This ubiquitous soil organism is frequently isolated from the feces of mares and foals. However, not all isolates of R. equi are pathogenic—only those organisms that contain a large plasmid which encodes virulence associate proteins (with VapA being the most important) cause disease in foals. In one study it was found that compared to dams of unaffected foals, fecal concentrations of total or virulent R. equi shed by dams of foals with R. equi pneumonia were not greater. However, organisms shed in the feces following replication within the intestinal tract of young foals, along with bacteria shed from exhalates of infected foals, contribute to environmental build-up of virulent organisms as the foaling season progresses.

In the foal, disease is thought to result from exposure to the organisms during the first few days of life either by inhalation from the environment or by repeated ingestion of organisms in the manure or soil. The pathogenesis of the bacteria—that is the formation of pyogranulomatous abscesses—is related to its ability to survive and replicate within alveolar macrophages which are eventually killed, releasing more organisms. Opsonizing antibodies against R. equi enhance intracellular killing by phagocytes and this observation serves as the basis for hyperimmune plasma administration to neonatal foals.

**Clinical signs.** Both pulmonary and extrapulmonary manifestations of infection with R. equi occur. Typically, pneumonia is insidious, becoming recognized in foals as exercise intolerance, tachypnea, poor growth and nasal discharge. Other clinical signs include cough, fever and adventitious lung sounds. Some affected foals develop acute onset respiratory distress with high fevers while others may be found dead without any premonitory signs or a history of respiratory disease. Multiple pyogranulomatous lesions are typically found throughout the lungs although a single lung lobe may be involved. Extrapulmonary sites of infections involve the abdominal cavity (mesenteric lymphadenitis, ulcerative enterotyphlocolitis, peritonitis, abscesses; pyogranulomatous hepatitis; nephritis); the musculoskeletal system (immune-mediated polyarthritis; septic arthritis; osteomyelitis; subcutaneous abscesses; cellulitis); the central nervous system (intracranial abscesses, vertebral body abscesses and cord compression); the hematological system (anemia, thrombocytopenia); the ocular tissues (uveitis; hypopyon; hyphema) and the thoracic cavity (septic pleuritis, pericarditis, mediastinal lymphadenitis). Involvement of extrapulmonary sites is presumed to result from...
bacteremic spread of the organisms from the gastrointestinal tract or the pulmonary tissues. In one retrospective study, 74% of *R. equi* cases referred to a university teaching hospital had at least one extrapulmonary infection primarily involving musculoskeletal or intestinal sites. Those investigators, like others, noted that 5-10% of foals with extrapulmonary manifestations of *R. equi* lacked overt evidence of pneumonia either following clinical or post-mortem examination. Foals with extrapulmonary infections had significantly greater WBC (median= 19,700) and neutrophil counts (median = 17,700) compared to foals with only pneumonia (median WBC count = 14,000; median neutrophil count = 10,600).

**Diagnosis** of *R. equi* is dependent upon detection of the organism in a foal with clinical signs. Bacteriological culture and PCR amplification of the vapA gene from a tracheobronchial aspirate (TBA) in concert with cytological examination of the TBA (presence of degenerative neutrophils, intracellular bacteria, Gram-positive coccobacilli) is the diagnostic method of choice. Bacterial culture allows identification of other bacterial pathogens and *in vitro* antimicrobial susceptibility testing. (NB: Foals without clinical disease may have *R. equi* in their trachea as a result of subclinical disease or from inhaling the organism in contaminated environments.) Note that blood cultures are rarely positive for the organism, being found positive in 7% of cases with extrapulmonary disorders. In cases with extrapulmonary infections, the same diagnostic approach is taken: bacteriologic culture and PCR amplification of vapA gene in samples obtained from the site of infection. In foals with polysynovitis (25-30% of cases), cytological examination of the synovial fluid demonstrates a non-septic mononuclear pleocytosis. As bacterial culture of the fluid is negative, the polysynovitis is thought to represent an immune-mediated disorder that resolves with treatment.

The diagnosis here is usually based on isolation of *R. equi* from TBA or other primary site of infection. Diagnosis of enterocolitis caused by *R. equi* is problematic because isolation of the organism from the feces cannot be taken as evidence of causality. Furthermore a negative fecal culture should not be used to exclude *R. equi* pulmonary infections since so few infected foals have positive fecal cultures. The current serological assays (ELISAs, AGID) fail to differentiate between diseased and clinically healthy foals and are thus of little diagnostic utility. The overlap in antibody titers between healthy and diseased foals is likely due to widespread exposure of foals to the organism without developing overt infections as well as due to the confounding effects of maternal antibody concentrations. Supportive diagnostic tests include alterations in the CBC and serum chemistry panel (anemia; a neutrophilic leukocytosis (WBC> 20,000); hyperfibrinogenemia (> 700 mg/dL); hyperglobulinemia); imaging abnormalities (alveolar pattern with regional consolidation or focal or multifocal nodules or cavitary lesions or hypoechogenic lesions in the peripheral portion of the lung consistent with abscession or consolidation). Imaging modalities are useful in monitoring the response to therapy as the number and size of abscesses should decrease within 2-3 weeks of initiating therapy.

**Treatment.** The combination of rifampin and erythromycin, which achieve high concentrations in phagocytes, has traditionally been used to treat rhodococcal infections. More recently, erythromycin has been supplanted by newer macrolides, azithromycin and clarithromycin that exhibit broader spectrum antimicrobial coverage. Nevertheless, there drugs are bacteriostatic and exert time-dependent activity. In a retrospective study, the combination of rifampin and clarithromycin was more effective than rifampin and erythromycin or rifampin and azithromycin in treating foals with severe radiographic lesions.

In polymicrobial infections (20% of cases), an additional antibiotic (selected based upon culture and sensitivity results of the TBA), is needed: Chloramphenicol is often used as the single antimicrobial for treatment. Culture/sensitivity testing is critical in detecting the development of antimicrobial resistance to the macrolides or rifampin in either single cases or in farm outbreaks. A recent
multi-center study found that approximately 4% of all R. equi isolates evaluated over a 10 year period were found to have antimicrobial resistance. Of the 38 R. equi isolates re-examined in their study, the investigators found that 22 were all resistant to azithromycin, erythromycin, clarithromycin and rifampin and that this resistance pattern correlated with a reduced survival rates. In foals, macrolide administration often produces diarrhea which can be self-limiting, but hydration status and electrolyte balance should be monitored in affected foals. If necessary, metronidazole is added to the treatment regimen to decrease the incidence or severity of diarrhea. Recall that exposure to macrolides is associated with severe life threatening colitis in adult horses so residual drug on the foal’s mouth or muzzle should be removed and feed buckets and water pails should be frequently cleaned to eliminate drug contamination. Erythromycin and the newer macrolides (based upon anecdotal reports) interfere with the thermoregulatory mechanisms causing respiratory distress in foals kept in hot climates. Treated foals should be maintained in cool, shaded environments and if necessary treated with antipyretics (flunixin meglumine) or alcohol baths. The rifampin/macrolide therapy is administered for 4-8 weeks but resolution of clinical signs and pulmonary abscesses (or other sites of infections), along with normalization of the CBC and fibrinogen count, should serve as a guide for cessation of therapy.

Other antimicrobials that have been evaluated for the treatment of R. equi in foals include intramuscular tulathromycin and tilmicosin—a special formulation, not Micotil used in cattle and swine. However, based on the few studies, these two drugs do not offer an advantage over the conventional rifampin/macrolide approach. A new long-acting macrolide, gamithromycin, demonstrates in vitro activity against R. equi and maintains bronchoalveolar cell concentrations above the MIC₉₀ for R. equi for approximately one week following IM administration (6 mg/kg). Once clinical safety and efficacy trials have been conducted, this drug may provide an alternative therapeutic approach.

Prognosis for survival is 70-80% with many foals able to achieve successful athletic careers as adults as racehorses. Poor prognosticators for survival include multiple sites of extrapulmonary infections, including those that induce lameness (osteomyelitis, arthritis), the development of respiratory distress and tachycardia or abdominal abscesses. In preventing R. equi infections, a multifaceted approach is taken: Reduce exposure to organism by reducing inhalation of the organism from the environment. On 3 endemic farms in a temperate climate (Ireland), investigators found that the concentrations of virulent R. equi were greater in stables than in dusty paddocks. A more recent US study conducted on farms in central Kentucky found that airborne concentrations of R. equi correlated with the location of horses at the time of sampling. When horses were predominantly in the stalls, airborne virulent R. equi concentrations were significantly lower in paddocks compared to stalls. When horses were not in the barn, concentrations of virulent R. equi were significantly higher in the paddocks. These findings suggested that the physical activity of the mares and foals enhances aerosolization of the bacteria suggesting that foals should be maintained on grassy, dust-free areas and manure should be removed from stalls and paddocks and composted. Stocking density of mares and foals, which increases environmental R. equi concentrations, should be as low as possible. Dust in congregating areas should be minimized by sprinkler systems. Enhance passive immunity of the foal by hyperimmune plasma containing anti-R. equi antibodies that enhance opsonization and macrophage clearance of the organisms. Some trials demonstrate a reduction in foal morbidity and mortality while others fail to show a statistically significant beneficial effect. Differences in the outcome might reflect the antigen used to generate the hyperimmune plasma; the type of immunoglobulin isotype generated during the immunization process (complement fixing or not); and the timing and dose of hyperimmune plasma administered relative to the foal’s exposure to R.
equi. Nevertheless, intravenous administration of 1 liter of hyperimmune plasma within 48 hours of birth followed by a second administration at 25 days of age is still recommended for farms with high morbidity rates and may actually help to reduce the prevalence of disease by 30%.35

Screen foals for evidence of infection on endemic farms: monitor rectal temperatures daily; evaluate WBC and serum fibrinogen concentrations weekly (?monthly) and perform thoracic ultrasound exams (weekly, ?monthly) to detect hypoechoic lesions suggestive of abscesses. Prophylactic administration of azithromycin to foals on endemic farms has also been tried. In one study conducted by Chaffin et al. (2008), neonatal foals received 10 mg/kg PO q 48 h for the first 2 weeks of life with the next result of reducing the prevalence of R. equi infections to 5% compared to 21% prevalence in non-treated controls.37 Venner (2009) reported different results following prophylactic administration of azithromycin to neonatal foals (10 mg/kg PO q 24 h) for the first 28 days of their life. Although not one treated foal developed evidence of pulmonary abscesses while receiving the drug, it merely increased the age at which abscesses developed. In that study, 60% of the azithromycin-treated group versus 68% and 70% in the two non-treated control groups had detectable abscesses at 83 days versus 47-54 days, respectively. One potential worry is that prophylactic use of this macrolide will increase the development of antimicrobial resistance although this was not evident in the Texas study.37

VERMINOUS PNEUMONIA

Pulmonary migrations of either Dictyocaulus arnfieldi or Parascaris equorum cause respiratory disease. Of the two parasites, roundworm infections are more prevalent in weanling and yearling foals.

Etiopathogenesis. The adult round worms reside in the small intestine where females may lay up to 200,000 eggs per day.39 Eggs passed into the environment larvate into the infective stage (L3) in approximately 10 days at environmental temperatures of 25-35 °C.39 Embryonated eggs are extremely resistant to environmental degradation and survive for years on the pastures or in the stall.30 (Conventional disinfectants such as bleach, iodine, cresol, quaternary ammonium compounds are not very useful against ascarid eggs. Even steam cleaning of concrete block stalls has not been completely effective.) Following ingestion of infective larvae, parasites migrate through the liver (within 2 days of ingestion) and then into the lungs (days 7-14 post ingestion). After they emerge from the pulmonary capillaries into the alveoli, the larvae are expectorated, swallowed and returned to the small intestine where they mature into adults (30 days). The presence of migrating larvae in the lung activates both the humoral and cellular immune systems resulting in an inflammatory process involving mast cells, basophils and eosinophils.41 Secondary bacterial infections may ensue and contribute to the clinical signs. Historically, transient improvements in clinical signs may be noted with antimicrobial therapy.

The clinical signs of verminous pneumonia include fever, chronic cough, bilateral mucoid or mucopurulent nasal discharge and decreased exercise performance. In foals with established small intestinal infections, unthriftiness and reduced weight gain are noted. Inflammatory changes in the CBC (mature neutrophilia, hyperfibrinogenemia) can be found with secondary bacterial infections however systemic eosinophilia is not a prominent feature of the leukogram. Thoracic auscultation may demonstrate crackles or wheezes however clinical signs are non-specific for verminous pneumonia. Cytological analysis of TBA demonstrates an abundance of eosinophils, mucus and potentially degenerative neutrophils if a secondary bacterial infection exists. In healthy foals, eosinophil percentages in the tracheal aspirates should not exceed 2% but in those with verminous pneumonia, eosinophil percentages can exceed 75%.41 Tracheal aspirates should be cultured to detect the presence of secondary bacterial infections. Because the
Prepatent period is 10-12 weeks fecal egg counts may be negative in foals experiencing respiratory signs.

**Treatment.** Foals should be treated with appropriate anthelmintics and broad spectrum antimicrobials as needed. In one study of foals (median age 5 months) requiring surgery due to ascarid impactions of the small intestine, administration of pyrantel pamoate or ivermectin had preceded the development of colic by 24 hours. Thus some clinicians initially treat foals with fenbendazole (5 mg/kg PO) followed by a second treatment at 10 mg/kg one week later. Recall that moxidectin is not approved for use in foals < 6 months of age. In very young foals, any macrocyclic lactones can cause neurotoxicity.

**Prevention.** In North America, as well as in Europe, reports of round worm resistance to ivermectin as well as to fenbendazole have emerged emphasizing the importance of evaluating ascarid fecal egg reduction counts. Minimizing exposure of young stock to infective eggs is essential in reducing verminous pneumonia. Manure should be picked up and disposed of by composting. For eggs to be killed, a minimum temperature of 40°C for at least five days is required and during that 5 day period, the temperature must rise above 55°C for at least 4 hours. Additional measures include (1) elevating feed and water bins to minimize fecal contamination; (2) using gravel as a base for dry lots to decrease transmission and (3) separating yearlings from weanlings.

**BRONCHOINTERSTITIAL PNEUMONIA**

Foals 1-6 months of age may present with acute or chronic onset of respiratory distress, tachypnea, pyrexia, and hypoxemia.

- In the acute onset syndrome reported by Lakritz and colleagues seven of the 23 foals had been normal prior to the onset of respiratory distress, 3 were simply found dead and 13 had been treated for respiratory tract infections. Microbiological culture of TBA from 9 of the foals yielded positive growth but no one bacterial agent was consistently isolated (E.coli, Enterobacter, Proteus, Klebsiella, R. equi, Strep zooe). Viral isolation was negative with the exception of one foal that had EHV-2 (a virus of questionable pathogenicity). These cases are respiratory emergencies with symptomatic therapies: Nine of the 13 foals (69%) that received treatment (oxygen, antimicrobials, bronchodilators, nonsteroidal anti-inflammatory drugs, thermoregulatory control survived and were discharged from the hospital. Additional therapies that are used in our hospital include nebulization therapy (Table 1), judicious use of dexamethasone (0.1 mg/kg IV) and nutritional support. If the affected foal is receiving a macrolide, a different antimicrobial should be substituted (e.g. chloramphenicol).

- A chronic syndrome of respiratory disease characterized by a prominent interstitial radiographic pattern was reported by Nout et al (2002) in foals 3-9 months of age. In contrast to the acute syndrome, these foals had had a history of respiratory disease for at least one month. On evaluation they tended to be bright, afebrile, tachypneic and exhibit a cough and nasal discharge. Again, no consistent bacterial agent was identified (foals with R. equi were excluded from the study). Foals responded well to a combination of broad spectrum antimicrobials and corticosteroids, with all foals surviving.

**FUNGAL PNEUMONIA**

Fortunately, this rarely occurs in foals 1 month or older but opportunistic infections from Aspergilla spp have been reported. As occurs with adult infections, pulmonary aspergillosis in foals can accompany enterocolitis, especially in foals that are neutropenic, immunosuppressed and/or have a compromised enteric mucosal barrier. The latter enables fungal elements from the intestinal tract to gain access to the blood stream. The typical clinical scenario is one in which the ente-
Crocolitis may be resolving but then suddenly the foal develops a fever and tachypnea which is unresponsive to antibiotics. Thoracic radiographs demonstrate evidence of an interstitial pneumonia and tracheal aspirates yield fungal hyphae. These cases are associated with a poor prognosis.

REFERENCES

10. Topino S, Galati V, Gulli E et al. Rhodococcus equi infection in HIV-infected individuals: case reports and review of the literature. AIDS Patient Care Std

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dosing interval</th>
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<td>Ceftiofur</td>
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*Natal colitis reported in the dams of foals receiving erythromycin.

Nebulization therapy: albuterol sulfate (0.025 mg/kg q 6 h), acetylcysteine (4 mg/kg q 6 h), ceftiofur (1 mg/kg q 6 h) and saline qs to 30 mL volume.


