Consultant’s Corner

Treating Foals with *Rhodococcus equi* Infection: What Do You Recommend?*

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This column reviews my current treatment recommendations for foals infected with *Rhodococcus equi*. The most common clinical manifestation of *R. equi* infection is pneumonia. In addition to pulmonary disease, extrapulmonary disorders may result from infection. Although there is an overlap in treating pulmonary and extrapulmonary disorders, these two topics are considered separately in this column.

TREATING *RHODOCCUS EQUI* PNEUMONIA

A wide variety of antimicrobials are effective in vitro against *R. equi*. However, because of the intracellular location of *R. equi* and its development within pyogranulomatous lesions, drugs that are effective in vitro may not be effective in vivo. Controlled clinical trials to establish the efficacy of any antimicrobial in treating foals with *R. equi* pneumonia are lacking. Some retrospective data indicate that the combination of penicillin and gentamicin is ineffective; however, in some countries, this combination is still used with apparent success to treat affected foals.

Erythromycin in combination with rifampin has been the standard treatment of *R. equi* pneumonia. This combination is synergistic in vitro and in vivo, and the combination reduces the likelihood of resistance to either drug. Doses of rifampin range from 5 to 10 mg/kg. The drug is available in capsules for human use (e.g., Rifadin gel capsules, Sanofi-Aventis, Bridgewater, NJ). Bulk powder forms are marketed, but clinical use of bulk products is illegal. Doses for oral administration of erythromycin range from 15 to 25 mg/kg q6h to 25 to 37.5 mg/kg q12h; intravenous use is not recommended because of adverse gastrointestinal effects.

As previously described in *Compendium*, there are several different formulations of erythromycin for oral use. Erythromycin ethylsuccinate is not well absorbed in foals and should be avoided. Erythromycin estolate is available as a cherry-flavored liquid suspension that is generally well absorbed by foals. Erythromycin phosphate comes as a powder for use in poultry. It is relatively cheap, easy to administer, and appears to be as bioavailable as erythromycin estolate. Erythromycin base is available as enteric-coated tablets for use in humans, and the microencapsulated base in gelatin granules reportedly has excellent bioavailability. Use of this product requires opening the gelatin capsules to administer the drug to foals as a suspension; the volume of the suspension can be large, and this formulation is expensive. Erythromycin stearate appears to be well absorbed in adult horses and is less expensive than the estolate formulation.

Adverse effects associated with erythromycin include environmentally modulated hyperthermia and diarrhea in foals as well as diarrhea in dams; the latter is generally severe and can be fatal. Diarrhea is likely the result of disrupted intestinal flora by the drug, and clostridial organisms are often implicated. The effectiveness of concurrent probiotic treatment to prevent diarrhea is unknown, but I have occasionally adminis-

*A related article appears on p. 47.*
tered *Saccharomyces boulardii* (1.5 to 3 billion colony-forming units PO q12h) to older foals being treated with macrolides. Although fungemia has recently been reported in three humans receiving *S. boulardii* in the management of antimicrobial-associated diarrhea,7 risk of developing fungemia is likely trivial relative to the risk of developing diarrhea in foals receiving macrolides. A number of other rare adverse effects of erythromycin (and other macrolides) have been reported in humans, including the syndrome of inappropriate diuresis and sudden death from cardiac causes.

Resistance to rifampin has been reported for isolates of *R. equi* from foals,8 and the Texas Veterinary Medical Diagnostic Laboratory and others have identified erythromycin-resistant isolates from foals. When resistance to one macrolide is identified, the organism is usually resistant to other macrolides.9 Although many practitioners eschew performing tracheobronchial aspiration to obtain isolates of *R. equi* from foals with pneumonia at endemic farms (because the probability that foals with signs of pneumonia have *R. equi* is considered high in these circumstances), it may be valuable to occasionally obtain isolates from foals at these farms to monitor for emergence of resistance to macrolides and other antimicrobials used to treat *R. equi* infections.

The use of azithromycin (10 mg/kg PO q24h for 5 to 7 days, then q48h) in treating affected foals has greatly increased.10,11 Advantages of the drug include once-daily or every-other-day dosing (versus multiple daily dosing for erythromycin) and persistently high intracellular concentrations of the drug. Azithromycin is often used in combination with rifampin. If it proves clinically to be more effective than erythromycin, it is conceivable that the duration of treatment might be reduced. Azithromycin is available as a human product and is expensive. Adverse reactions include diarrhea, increased activity of liver enzymes in serum, and hyperthermia; the prevalence of hyperthermia with this drug relative to erythromycin is unknown. Less-expensive formulations using bulk drug have been marketed, but clinical use of these products is illegal. However, compounding Zithromax (Pfizer, Inc) for use in foals (e.g., preparing syringes with Zithromax powder to which water may be added to create a suspension) is legal.

Like azithromycin, clarithromycin is available for use in humans. Current recommendations for oral dosing are 7.5 mg/kg q12h.12 A recent retrospective study indicated that this drug was more effective than erythromycin or azithromycin13 and may be combined with rifampin. Adverse effects include diarrhea, which may occur more frequently with this drug than with other macrolides used to treat *R. equi* infection. It is unclear whether increased activity of liver enzymes in serum or hyperthermia should be expected with use of this product, but these adverse effects should be considered possibilities.

Very little information is available about alternatives to the use of macrolides in combination with rifampin. Some veterinarians use chloramphenicol (with or without rifampin) and doxycycline (generally in combination with rifampin) as alternatives to macrolides in treating foals with *R. equi* infection. The organism has been demonstrated to be somewhat susceptible to these drugs in vitro (more so to doxycycline than chloramphenicol).14,15 Pharmacokinetic studies of doxycycline in foals are lacking, and it is unclear whether serum concentrations exceed the minimum inhibitory concentration for *R. equi* infection; some recent data from adult horses suggest that the dose of doxycycline in treating susceptible intracellular bacteria should be 20 mg/kg q24h.16 Because doxycycline attains high concentrations intracellularly, it might be more effective than predicted based on in vitro data; I lack clinical experience with the use of chloramphenicol or doxycycline in treating *R. equi* pneumonia. New classes of antimicrobials (e.g., the oxazolidinones) and antimicrobial peptides (e.g., citropin 1.1) have efficacy against *R. equi* in vitro.17,18 Pharmacokinetics for these drugs are lacking in horses or foals. Linezolid, an oxazolidinone, has been used to treat *R. equi* and other gram-positive bacterial infections in humans, including methicillin-resistant *Staphylococcus aureus* infection. Because of use of this drug in treating the latter infection, linezolid use in veterinary medicine may be restricted or discouraged. With the specter of the emer-
gence of macrolide resistance among isolates of *R. equi*, consideration of alternative drugs may be necessary.

The duration of treatment is generally prolonged. Foals with radiographically apparent lesions should be treated for a minimum of 3 weeks. Monitoring cases with radiography or ultrasonography can be helpful. In general, treatment should be extended at least a few days beyond resolution of ultrasonographic lesions or until radiographic lesions are no longer visible. However, some foals may never have complete resolution of radiographic abnormalities. The leukocyte count or fibrinogen concentration can be monitored, but these tests are known to be imprecise. If the leukocyte or fibrinogen concentrations are increased and used for monitoring, I recommend treating the patient at least 2 weeks beyond reduction of either parameter to a value within the reference range, along with evidence that the foal is clinically healthy. Evidence exists that serologic testing is not accurate in the diagnosis or early detection of infection; therefore, it has no value for monitoring. It was recently suggested that serum amyloid A might be valuable for monitoring foals with *R. equi* pneumonia. However, another report indicated that serum amyloid A was of no value in the diagnosis or early detection of *R. equi* pneumonia. Because changes in serum amyloid A can occur rapidly and are inconsistent among infected foals, I do not believe this test will adequately monitor affected foals.

Ancillary treatments can also be administered to affected foals. The benefits of administering hyperimmune plasma (which can be used to reduce the incidence of *R. equi* pneumonia when administered prophylactically) as adjunctive therapy are unknown, but hyperimmune plasma might be valuable for immunomodulation. The use of NSAIDs to reduce fever and pulmonary inflammation may be beneficial in some foals. Intranasal administration of oxygen may help foals in severe respiratory distress. The benefit of bronchodilators in treating foals with this disease is unknown. Nebulization of antimicrobials, bronchodilators, and mucolytic agents may be beneficial in some foals. Avoidance of exposure to high heat and humidity (if possible) may help foals avoid macrolide-associated hyperthermia and may make pneumatic foals more comfortable. Combinations of some medications (e.g., aminophylline and erythromycin) can have interactions that result in adverse effects.

**Extraluminal Disorders**

There are a number of extraluminal manifestations of *R. equi* infection (see box on this page). In my experience, the two most common extraluminal disorders are intraabdominal abscesses or pyogranulomas and polysynovitis. Treatment with erythromycin or another macrolide in combination with rifampin is indi-

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### Extraluminal Disorders Associated with *R. equi* Infection

**More Common Disorders**
- Abdominal lymphadenitis
- Granulomatous enterocolitis or typhlitis (with or without diarrhea)
- Peritonitis

**Less Common Disorders**
- Diskospondylitis
- Guttural pouch empyema
- Granulomatous laryngitis
- Hepatic pyogranuloma
- Immune-mediated hemolytic anemia
- Immune-mediated thrombocytopenia
- Mediastinal lymphadenitis
- Osteomyelitis
- Paravertebral abscessation
- Pericarditis
- Pleuritis
- Pyelonephritis
- Pyogranulomatous dermatitis
- Septic arthritis
- Septic sinusitis
- Telogen effluvium
- Uveitis, keratouveitis, panophthalmitis, intracranial abscessation

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Clarithromycin may be the most effective macrolide available for treating foals with *R. equi* pneumonia.
accompanying *R. equi* pneumonia. I occasionally use corticosteroids as adjunctive therapy. Although intraarticular administration may be beneficial, I prefer to use oral dexamethasone (0.05 to 0.1 mg/kg q24h for no more than 7 to 10 days). Limiting but not eliminating exercise may be beneficial in helping minimize the extent of joint distention and possibly inflammation. In general, appropriate adjunctive therapy for septic conditions (e.g., drainage of abscesses, curettage for osteomyelitis) may be needed. Some manifestations may be immune mediated or nonresponsive to antimicrobials (e.g., uveitis); such conditions may resolve with successful treatment of accompanying *R. equi* pneumonia.

**REFERENCES**

15. Prescott JF: The susceptibility of isolates of *Corynebacterium equi* to antimi-

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