Therapy of *Rhodococcus equi* Infections in Foals

Steeve Giguère, DVM, PhD, Diplomate ACVIM

The combination of a macrolide (erythromycin, azithromycin, or clarithromycin) with rifampin remains the mainstay of therapy. Although the vast majority of *Rhodococcus equi* isolates are still susceptible to these antimicrobials, the frequency of macrolide-rifampin–resistant isolates seems to be increasing. Author’s address: College of Veterinary Medicine, University of Georgia, Athens, Georgia 30602; e-mail: giguere@uga.edu. © 2010 AAEP.

1. Introduction
A wide variety of antimicrobial agents are active against *Rhodococcus equi* in vitro. However, because *R. equi* is a facultative intracellular pathogen surviving and replicating in macrophages, many of these drugs are ineffective in vivo. For example, in one study, all 17 foals with *R. equi* pneumonia treated with the combination of penicillin and gentamicin died despite the fact that all isolates were sensitive to gentamicin.1 The combination of rifampin and erythromycin became the treatment of choice in the 1980s and has dramatically reduced foal mortality at least compared with historical data since its introduction.1,2 In recent years, clarithromycin or azithromycin, both newer-generation macrolides, often replaces erythromycin in combination with rifampin.3

2. Macrolides and Rifampin
Macrolides and rifampin are highly active against *R. equi* in vitro but only exert bacteriostatic activity.4 As a result, macrolides exert time-dependent activity against *R. equi* in vitro. Of the three macrolides listed above, clarithromycin is the most active against *R. equi* in vitro. The minimum inhibitory concentration at which 90% of *R. equi* isolates are inhibited (MIC₉₀) is 0.12, 0.25, and 1.0 µg/ml for clarithromycin, erythromycin, and azithromycin, respectively.5 The combination of a macrolide and rifampin is synergistic both in vitro and in vivo, and the use of the two classes of drugs in combination reduces the likelihood of *R. equi* resistance to either drug.4,6 Rifampin and macrolides are lipid soluble, allowing them to penetrate cell membranes and caseous material.

The recommended doses are listed in Table 1. Several formulations of erythromycin are commercially available. Although they all show slight differences in bioavailability and elimination, they all result in therapeutic concentrations at recommended doses. Advantages of azithromycin and clarithromycin over erythromycin in foals include enhanced oral bioavailability, prolonged half-lives, and much higher concentrations in bronchoalveolar cells and pulmonary epithelial lining fluid (Table 1).7–10 These properties of the newer-generation macrolides contribute to their lower doses and longer dosing intervals. Concentrations of clarithromycin in pulmonary epithelial lining fluid and bronchoalveolar cells of foals at steady state are considerably higher than concentrations reported after daily administration of azithromycin to foals.5,9 However,
clarithromycin concentrations at these sites decrease rapidly, whereas the release of azithromycin from cells is much slower, resulting in sustained concentrations of azithromycin in tissues for days after discontinuation of therapy.\(^7\)\(^-\)\(^10\) In a retrospective study, the combination clarithromycin-rifampin was significantly more effective than erythromycin-rifampin or azithromycin-rifampin, especially in foals with severe radiographic lesions.\(^3\)

Tulathromycin, a semi-synthetic macrolide recently approved for use in swine and cattle, was recently compared with azithromycin-rifampin for the treatment of foals with subclinical pneumonia as identified by ultrasonographic screening on a farm with a high incidence of \(R.\) \(equi\) infections. Pulmonary lesions 1 wk after initiation of treatment with tulathromycin were significantly larger and duration of therapy was significantly longer, indicating that tulathromycin is not as effective as standard therapy with azithromycin-rifampin.\(^11\) Tulathromycin is currently not recommended for use in foals, at least until the drug is proven effective in foals with clinical pneumonia caused by \(R.\) \(equi.\) Tilmicosin, another macrolide approved for use in swine and cattle, is not active against \(R.\) \(equi,\) and administration to foals sometimes result in swelling at the site of injection.\(^9\)

Resolution of clinical signs, normalization of plasma fibrinogen concentrations, and radiographic or ultrasonographic resolution of lung lesions are commonly used to guide the duration of therapy, which generally ranges between 2 and 12 wk, depending on the severity of the initial lesions and response to therapy.

Although well tolerated by most foals, macrolides commonly cause diarrhea. Most of the time, the diarrhea is self-limiting and does not necessitate cessation of therapy. Affected foals should be monitored carefully because some may develop severe diarrhea, leading to dehydration and electrolyte loss that necessitate intensive fluid therapy and cessation of oral macrolides. The incidence of diarrhea in foals treated with erythromycin-rifampin has ranged between 17% and 36%.\(^3\)\(^,\)\(^12\) During surges of very hot weather, an idiosyncratic reaction characterized by severe hyperthermia and tachypnea has been described in foals treated with erythromycin.\(^12\) Anecdotal reports suggest that these reactions may occasionally occur with newer macrolides as well. Administration of antipyretic drugs and placing the foal in a cool environment will treat this problem. Severe enterocolitis has also been reported in mares whose foals are being treated with erythromycin, presumably because of disruption of the mare’s normal colonic microflora after ingestion of small amounts of active drug during coprophagia or from contamination of feeders or water buckets with drug present on the foal’s muzzle.\(^13\)

### 3. Bacterial Resistance to Commonly Used Antimicrobial Agents

Although the vast majority of \(R.\) \(equi\) isolates from foals are highly susceptible to macrolides and rifampin, resistant strains to either drug class have been encountered. The percentage of \(R.\) \(equi\) isolates resistant to either macrolides or rifampin has ranged between 0% and 4% depending on the study.\(^5\)\(^,\)\(^14\) Rifampin should not be used in monotherapy because this increases the chance of resistance development.\(^4\)\(^,\)\(^15\) Rifampin resistance is conferred by mutations in the RNA polymerase \(\beta\) subunit encoded by the \(rpoB\) gene.\(^16\)\(^,\)\(^17\) Progressive development of resistance to both erythromycin and rifampin during treatment is extremely rare, but it has been reported.\(^18\) In a recent study, the overall prevalence of resistant isolates in Texas and Florida over a 10-yr period was 4%.\(^19\) In the same study, the survival proportion of foals infected with resistant \(R.\) \(equi\) isolates was significantly lower than that of foals receiving the same treatment from which susceptible isolates were cultured. The odds of non-survival were seven times higher in foals infected with resistant isolates.\(^19\) In addition, the study showed that isolates of \(R.\) \(equi\) susceptible to macrolides are sometimes misclassified as resistant; therefore, it is reasonable to request re-testing/
validation of resistance by the testing laboratory. The molecular mechanisms of macrolide resistance in R. equi isolates have not been determined, but R. equi isolates resistant to one of the three macrolides listed above are typically resistant to the other two as well.

4. Alternative Antimicrobial Agents

Therapy of foals developing severe diarrhea during macrolide therapy or therapy of foals infected with resistant isolates is problematic because of the limited range of alternative effective drugs. Oral doxycycline in combination with rifampin has been used successfully for the treatment of foals with pneumonia caused by R. equi. Recommended dosage for doxycycline in foals is 10 mg/kg, PO, q 12 h.20 This dosage results in serum, pulmonary epithelial lining fluid, and bronchoalveolar cell concentrations above the MIC90 of R. equi isolates (1.0 μg/ml) for the entire dosing interval. Doxycycline is bacteriostatic against R. equi, but the drug is highly synergistic with rifampin and with macrolides in vitro. Therefore, doxycycline could also be combined with a macrolide for the treatment of rifampin-resistant isolates. Chloramphenicol can be administered orally and achieves high concentrations within phagocytic cells in other species. The recommended dosage regimen is 50 mg/kg, PO, q 6 h. However, the fact that only 70% of R. equi isolates are susceptible to this drug and the potential human health risk make this drug a less attractive alternative. High doses of a trimethoprim-sulfonamide (TMS) combination (30 mg/kg of combination, PO, q 8 or 12 h) have been used alone or in combination with rifampin in foals with mild or early R. equi pneumonia or for continued therapy in foals responding well to other antimicrobials.1 However, TMS is not subjectively as effective as the combination macrolide-rifampin.

In an experimental model of R. equi infection in immunosuppressed mice, the most effective drugs in monotherapy were found to be, in order of effectiveness, vancomycin, imipenem, and rifampin.21 Amikacin, erythromycin, ciprofloxacin, or minocycline in monotherapy did not lead to a significant decrease in bacterial counts. The most active drugs in combination were those including vancomycin or rifampin, but these combinations were not significantly different from vancomycin monotherapy.21 Vancomycin and imipenem in foals should only be used for the treatment of life-threatening R. equi infections caused by isolates confirmed to be resistant to all other possible alternatives.

5. Ancillary Therapies

Nursing care, provision of adequate nutrition and hydration, and maintaining the foal in a cool and well-ventilated environment are important. Oxygen therapy using humidified oxygen by pharyngeal insufflation in moderately hypoxicemic foals, or by percutaneous transtracheal oxygenation in severely hypoxicemic animals, is indicated.22 Judicious use of non-steroidal anti-inflammatory drugs is of value in reducing fever and improving attitude and appetite in febrile, depressed, anorectic foals. Nebulization may be helpful in selected cases with tenacious secretions and non-productive cough. However, most cases of R. equi pneumonia do not benefit from nebulization, and the procedure is stressful to some foals. Similarly, bronchodilators are rarely helpful clinically in foals with pneumonia caused by R. equi. In addition to appropriate systemic antimicrobial therapy, foals with R. equi septic arthritis or osteomyelitis often require aggressive local therapy such as joint lavage, surgical debridement, and IV or intraosseous regional limb perfusion with antimicrobial agents. The prognosis of foals with abdominal abscesses is poor, although rare cases will respond to long-term antimicrobial therapy.23,24 Surgical removal or marsupialization has been attempted in some foals, but abdominal adhesions usually result in the inability to resect the lesion and in chronic intermittent episodes of colic.

6. Prognosis

Before the introduction of the combination of erythromycin and rifampin as the treatment of choice in the early 1980s, the prognosis of R. equi–infected foals was poor, with reported survival rates as low as 20%.25 Using erythromycin and rifampin, Hillidge2 reported a successful outcome (as assessed by survival) in 50 (88%) of 57 foals with confirmed R. equi pneumonia. Studies in referral centers, more likely to see the most severely affected cases, have shown survival rates ranging between 59% and 72%.3,26,27

References


