

Management of *Rhodococcus equi* pneumonia in foals

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Abstract: *Rhodococcus equi*, a gram-positive facultative intracellular bacterial pathogen, is the most important cause of pneumonia in foals aged 3 weeks to 5 months. The disease occurs worldwide, resulting in significant morbidity and mortality on endemically affected farms. Foals appear to become infected early in life, but clinical signs are typically delayed until 1–3 months of age because of the insidious nature of the disease. Although pneumonia is the most common clinical manifestation, up to 74% of foals may concurrently have extrapulmonary disorders, including both extrapulmonary infections (abdominal abscessation, colitis, osteomyelitis) and immune-mediated disorders (nonseptic synovitis, uveitis). Diagnosis is based on the combination of clinical signs and abnormalities on hematologic screening and thoracic imaging in an appropriately aged foal and is confirmed by bacteriologic culture of the organism. Management of *R. equi* infections, in particular on farms with endemic disease, combines appropriate treatment of affected foals with preventative measures targeted at preventing infection and identifying foals before the development of severe disease. The combination of rifampin and a macrolide antimicrobial is recommended for treatment, as the combination is synergistic, reaches high intracellular concentrations, and should minimize the development of antimicrobial resistance. The prognosis for survival for foals with *R. equi* pneumonia is good, especially in foals mildly or subclinically affected, as is the prognosis for future athletic performance. Screening for early identification before the development of clinical signs has been advocated on endemically affected farms, although the most appropriate method, the timing of screening, and the selection of foals requiring treatment have yet to be determined. Recent evidence suggests that a high proportion of foals identified via screening methods such as ultrasonographic evaluation of the thorax can recover without treatment, questioning the “trigger” required for treatment of identified cases.

Keywords: extrapulmonary disorder, infection, rifampin, antimicrobial, immunity, inhalation, virulence

Introduction

Rhodococcus equi, a gram-positive facultative intracellular bacterial pathogen, is the most important cause of pneumonia in foals aged 3 weeks to 5 months.^{1,2} The disease occurs worldwide, resulting in significant morbidity and mortality on endemically affected farms.^{1–7} During the last several decades, our understanding of the pathogenesis, virulence, immunity, and treatment of *R. equi* pneumonia has advanced significantly, resulting in improved survival rates and preventative strategies. Despite these advancements, an effective vaccine has yet to be developed, and newer challenges, including the emergence of antimicrobial-resistant *R. equi* and effective management of subclinically affected foals, have been identified.^{3,4,8–10}

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Pathogenesis and virulence

The primary route of pulmonary infection is via inhalation, with ingestion of the organism as a secondary route of exposure. Although the age at which clinical signs develop in foals varies between studies, from 36–97 days, infection is believed to occur very early in life, as early as the first day or two.^{3,4,11–14} After inhalation, the bacteria fix complement on their surface, and on interaction with macrophages, stimulate phagocytosis via a receptor-mediated process.¹⁵ The virulence of *R. equi* relies on the ability of the organism to replicate in macrophages, which is dependent on its capacity to interfere with endosomal maturation after phagocytosis and to prevent acidification of the vacuole in which it resides.^{16–19} Eventually, intracellular proliferation of the pathogen leads to the necrotic death of the macrophage, with massive damage to lung tissue, resulting in the classic abscess formation. Not all strains of *R. equi* can cause disease, and those that are avirulent lack the capacity to effectively multiply within macrophages.²⁰ Virulent strains consistently contain a 15–17-kDa protein, called VapA, which is encoded by the virulence plasmid. This plasmid enables intracellular replication in macrophages by preventing maturation of the phagosome to the stage of vacuoles containing *R. equi* with lysosomes.²¹ Other virulence-associated proteins have been identified; however, they do not appear to be critical in the development of disease.²²

Immune response

In contrast to foals, immunocompetent adult horses are immune to infection and are thus used as a model for the “immune” phenotype for *R. equi* infection.

Cell-mediated immunity

Immunity to *R. equi* appears to rely on the presence of both specific antibodies and an efficient cell-mediated response, although the nature of this response, and why some foals are unable to clear the organism effectively, remains to be determined.^{23–26} Clearance of the organism after experimental bronchial inoculation in adult horses relies on the induction of a type 1, T helper (Th)1 response, which involves production of antigen specific Th1 lymphocytes to clear intracellular *R. equi* via production of interferon gamma (IFN γ) and macrophage activation, as well as production of antigenic specific cytotoxic T lymphocytes, which function to recognize and kill *R. equi*-infected cells.¹ A lymphoproliferative response, characterized by increased numbers of CD4+ and CD8+ T lymphocytes as well as *R. equi* cytotoxic T lymphocytes (CTL) subsets, is seen in bronchoalveolar lavage fluid collected from

horses after challenge.^{27,28} In mice, pulmonary clearance of *R. equi* requires functional T lymphocytes.^{24–26} Both CD4+ and CD8+ T lymphocytes contribute to host defence against *R. equi*, but CD4+ lymphocytes play the major role and are absolutely required for complete pulmonary clearance of the bacteria. CD4+ and CD8+ cells secrete IFN γ , which activates macrophages, the host cells of *R. equi*.²⁹ A cytokine profile dominated by IFN γ production results, as well as production of *R. equi*-specific immunoglobulin (Ig)G α and IgG β .^{29,30} Macrophages that have been activated by IFN γ produce both reactive oxygen and reactive nitrogen intermediates, combining to form peroxynitrate, which efficiently kills *R. equi*.¹⁸

Although CD4+ T lymphocytes are essential for clearance of the organism, the role of CD8+ CTL has recently been highlighted.^{27,31} Patton et al determined that adult horses have *R. equi*-specific CTL in both peripheral blood and within the lung, which function to recognize and kill *R. equi*-infected cells.²⁷

Antibody-mediated immunity

Although the cell-mediated immune response is dominant in clearance of *R. equi*, humoral immunity is also involved. Adult horses challenged with the organism have a significantly increased IgG, but not IgM, response, which is consistent with a protective recall response.³² Opsonization with *R. equi*-specific antibody increases the level of phagosome–lysosome fusion and significantly enhances the killing of *R. equi* by alveolar macrophages in foals.³³

Immune response in foals

An inability to mount an effective Th1 immune response has been suggested as the reason for foals' susceptibility to *R. equi*.³⁴ Evidence to support this has included studies showing that newborn foals exhibit a marked inability to express the *IFN γ* gene and produce IFN γ protein,³⁴ although a subsequent study indicated that in fact, foals are capable of producing IFN γ , but *R. equi*-infected foals have significantly reduced proliferative responses to *R. equi* antigens compared with adult horses.³⁵ An age-associated deficiency in *R. equi*-specific CTL has also been identified, with 3-week-old foals having a significantly lower activity of CTL in both peripheral blood and bronchoalveolar lavage fluid.²⁷ However, more recently, accelerated development of *R. equi*-specific CTL was demonstrated in foals after oral inoculation with virulent *R. equi*.³⁶ Thus, although an ability to mount an effective and protective Th1-type response was believed to explain the unique susceptibility of young foals to infection with *R. equi*, recent studies have shown that

with an appropriate challenge, foals can produce IFN γ and a specific antibody and can develop *R. equi*-specific cytotoxic T lymphocytes.^{35,36} This evidence, along with the apparent high rate of spontaneous resolution in foals with subclinical disease, suggests there is unlikely to be a “blanket” explanation based on a deficient immune response present in all foals, and a more cohesive explanation is likely to be multifactorial and multifaceted.^{3,4,10}

Clinical signs

The most frequently recognized clinical manifestation of infection caused by *R. equi* is pyogranulomatous bronchopneumonia and pulmonary abscessation in foals aged 3 weeks to 5 months.^{1,2,37} In most cases, the development of clinical signs of pneumonia is chronic and insidious, with initial signs including a cough, fever, and lethargy. As the pulmonary pathology progresses, increased respiratory rate and effort, tachycardia, and anorexia with loss of condition can occur.³⁸ In a small proportion of foals, severe clinical signs of respiratory distress develop rapidly, in some cases with minimal preexisting respiratory signs. This form is thought to be a manifestation of acute lung injury/acute respiratory distress syndrome and has been associated with a relatively poor prognosis, despite intensive therapy.^{39,40}

Extrapulmonary disorders

A proportion of foals with *R. equi* pneumonia will concurrently develop extrapulmonary disorders (EPD).^{41,42} Extrapulmonary manifestations of *R. equi* infection appear to occur commonly, with 74% of foals affected in one study.⁴¹ These disorders can develop as either infection in sites distant to the lungs, such as septic arthritis and osteomyelitis, abdominal abscessation, or colitis, or as a consequence of an immune-mediated reaction. Uveitis, nonseptic synovitis (typically of multiple joints), and hemolytic anemia are reported immune-mediated infections. The clinical signs of the EPD will depend on the body system affected, as will the treatment protocol. In cases of infectious EPD, antimicrobials targeted at the pulmonary infection will tend to be appropriate, although local therapy, such as synovial lavage, should be considered in cases with septic synovitis. Foals with nonseptic synovitis, characterized by nonpainful effusion of multiple joints, typically do not require specific treatment, with effusion resolving as the pulmonary infection resolves. In contrast, foals with uveitis and immune-mediated hemolytic anemia (IMHA) will typically require specific treatment of these disorders. Topical corticosteroids and atropine, as well as systemic

nonsteroidal anti-inflammatory drugs, are appropriate for the treatment of foals with uveitis. Although corticosteroids are the mainstay of treatment of horses with IMHA, their use in horses with severe bacterial infections may interfere with the immune response to clear the infection, as steroid treatment diminishes the lysosomal enzyme and oxygen radical release from polymorphonuclear leukocytes and depresses intracellular killing of bacteria.^{43,44} However, the IMHA in foals with *R. equi* may be sufficiently severe that systemic corticosteroids are indicated, in addition to packed red cell/whole blood transfusions.⁴²

Although the presence of EPD appears to be a relatively common occurrence in foals with *R. equi* infections, their presence can complicate and prolong treatment and is associated with a poorer prognosis, with 43% survival in one study of foals with EPD compared with 82% survival in foals without EPD.^{41,42}

Diagnostics

Identification of the organism

Although identification of clinical signs consistent with pneumonia in an appropriately aged foal housed on a farm with a history of *R. equi* infections is commonly used to make a diagnosis of *R. equi* pneumonia, definitive diagnosis requires identification of the organism from an infected site (tracheobronchial aspirate in foals with pneumonia, or other site in foals with EPD) in conjunction with evidence of septic inflammation and consistent clinical signs.¹ Bacteriologic culture allows for identification of possible concurrent bacterial infection, as well as permitting antimicrobial sensitivity testing. Mixed infections with a wide variety of gram-positive and gram-negative bacteria have been reported in foals with *R. equi* pneumonia, highlighting the importance of sensitivity testing, especially in foals with concurrent gram-negative infections resulting from the relatively limited action of routinely used antimicrobials against gram-negative pathogens.^{38,45,46} The need for sensitivity testing of *R. equi* isolates has become increasingly important, with increased rates of resistance to both rifampin and macrolides reported in recent years, in particular when antimicrobial prophylaxis has been used.^{8,9} Amplification of the *vapA* gene via polymerase chain reaction has been shown in several studies to be more sensitive than bacterial culture, but has the disadvantages of allowing neither for culture of concurrent pathogens nor for sensitivity testing of isolates.⁴⁷ In addition, small numbers of bacteria can be detected, which may result in a higher incidence of false-positive results secondary to environmental contamination. As such, polymerase chain

reaction is not recommended as the sole method by which to identify *R. equi*.¹

Imaging

Both radiography and ultrasound can be used to image pulmonary lesions and can be useful tools in assessing the severity of disease and the response to therapy. Ultrasound tends to be used more routinely, in particular in nonhospitalized foals, because of its ease of use and wide availability. Although ultrasound will only detect lesions on the peripheral lung surface, and will thus fail to identify lesions within the pulmonary parenchyma that are deep to normally aerated lung, the method appears to perform adequately when compared with radiography. In some instances, such as when identifying pleural effusion and small pleural lesions, it may be more sensitive.^{2,48} In one study of foals with *R. equi* pneumonia in which both radiographic and ultrasonographic evaluations were performed, radiographic lesions were visible ultrasonographically in 16 of 17 foals.⁴⁸ Radiographic abnormalities most commonly identified in foals with *R. equi* pneumonia include single or multiple nodular or cavitory lesions (abscesses), an alveolar or interstitial pattern, and tracheobronchial lymphadenopathy.^{12,49} Although *R. equi* is not the only cause of pulmonary abscesses in foals, their presence had a specificity of 85% in one study of 113 foals with bacterial pneumonia.³⁸

Pulmonary abscesses can be similarly identified via ultrasound, characterized as well-defined, hypoechoic nodules without evidence of normal pulmonary architecture such as small airways or vessels within the central region. Consolidated lung tends to have a less well-defined margin and also will be hypoechoic relative to the surrounding lung parenchyma, but in contrast to an abscess, it will retain elements of the normal lung architecture such as bronchi (linear hyperechoic foci) and vessels. Pleural effusion is rarely identified in foals with *R. equi* pneumonia, but even small amounts of fluid can be readily identified as an accumulation of anechoic material between the visceral and parietal pleura.⁴⁸

Hematology and acute phase proteins

Although a neutrophilic leukocytosis, hyperfibrinogenemia, and hyperglobulinemia are commonly seen in foals with *R. equi* infections, they are specific neither for the bacterial species nor for the body system affected.^{1,14,38} Used with other diagnostic abnormalities such as the presence of clinical signs of pneumonia and pulmonary abscessation, an increased white cell count and fibrinogen concentration may increase the index of suspicion for *R. equi* pneumonia, which may

prompt appropriate treatment while awaiting confirmatory diagnostic tests results, such as bacterial culture and polymerase chain reaction.³⁸

Serology

Although several serological assays have been developed to detect the presence of anti-*R. equi* antibodies, none can be recommended for use in the diagnosis of the disease. A positive result on a serologic assay cannot be used to differentiate among active infection, subclinical infection, exposure without infection, or maternal transfer of antibodies, and as such, use of these tests as either a diagnostic tool or as a screening tool (see following) is not justified.^{1,13,50}

Treatment

Treatment with a macrolide antimicrobial in combination with rifampin is the recommended therapy for infection caused by *R. equi*¹ (Table 1). Duration of treatment is dependent on the severity of the disease at the time of diagnosis but is typically weeks to months.^{12,37,42,51} Although a wide range of antimicrobials is reported to have in vitro efficacy against *R. equi*, their in vivo efficacy is limited, likely because of their limited ability to establish effective intracellular concentrations.^{12,45} The introduction of a combination of erythromycin and rifampin for *R. equi* treatment was first reported in the 1980s and was associated with an improvement in outcome based on historical survival data.^{12,51} Newer macrolides such as clarithromycin and azithromycin have more recently been used, primarily in an attempt to minimize the adverse effects reported after erythromycin use, and also to potentially improve treatment outcome.^{52,53} Adverse effects reported after erythromycin treatment include diarrhea (usually mild and self-limiting) and hyperthermia, and tachypnea in foals treated during hot weather. In one study, 26 (36%) of 73 foals treated with erythromycin developed diarrhea, 18 developed hyperthermia (25%), and 11 (17%) developed respiratory distress.⁵² No difference in complication rates was reported in a retrospective study comparing combinations of rifampin with erythromycin, clarithromycin, or azithromycin, although a significantly better short- and long-term outcome was

Table 1 Recommended antimicrobial regimes for the treatment of *Rhodococcus equi* in foals

Drug	Dose (mg/kg)	Frequency
Rifampin	5	q12h
Erythromycin	25	q6–8h
Clarithromycin	7.5	q12h
Azithromycin	10	q24–48h

Abbreviation: h, hours.

reported for clarithromycin and rifampin treatment.⁵³ The requirement for less frequent dosing with either azithromycin (once a day) or clarithromycin (twice a day) when compared with erythromycin has also led to these drugs now being more commonly administered in cases of *R. equi* infection.¹ Tularithromycin is a long-acting macrolide antimicrobial that has been investigated for treatment of *R. equi* infections, as its ability to provide sustained therapeutic concentrations could result in less-frequent treatment of affected foals.^{3,4} No significant differences among standard treatment, placebo, or treatment with tularithromycin was observed in two studies comparing treatment regimes in foals with ultrasonographically identified abscesses.^{3,4}

The combination of rifampin and a macrolide is synergistic both in vitro and in vivo, and the use of the 2 drug classes as a combination decreases the chances of *R. equi* resistance to either drug.^{54–56} When used as monotherapy, resistance to rifampin develops quickly, as chromosomal mutation develops rapidly in most bacteria exposed to rifampin.^{56,57} Isolates resistant to rifampin have tended to exhibit high-level resistance, which suggests that this resistance develops in a single-step event and supports the use of rifampin in combination with other antimicrobials. Despite this, rifampin-resistant isolates have been isolated from foals treated with combination therapy.^{8,42,56} A recent study suggested that when both clarithromycin and rifampin are administered at the same time, the bioavailability of clarithromycin decreases significantly.⁵⁸ This effect was believed to be associated with induction of intestinal efflux transporters and liver-metabolizing enzymes, resulting in less systemic absorption of clarithromycin. Despite this, the concentrations in epithelial lining fluid and bronchoalveolar lavage cells remained above the minimum inhibitory concentration (MIC) for the *R. equi*, and the clinical relevance of this effect remains to be determined. Although this treatment regime remains the mainstay of therapy for many clinicians, some have questioned whether, with this newer information, sole therapy with clarithromycin should be considered.

Prevention

Preventative measures aimed both at decreasing the risk of infection in foals, and at identifying foals early in the disease course, are widely used on farms with endemic infections in an attempt to decrease mortality and minimize the need for often long-term and expensive treatment.

Hyperimmune plasma

Administration of hyperimmune plasma (HIP) for prevention against *R. equi* pneumonia is a common practice on

farms with endemic disease.^{1,59,60} Hyperimmune plasma is thought to confer protection primarily through the provision of *R. equi*-specific antibodies, but other constituents in plasma, such as fibronectin, complement components, collectins, cytokines, and acute-phase proteins, may also be involved. Intravenous administration of HIP has consistently proved effective in significantly reducing the severity of *R. equi* pneumonia in foals after experimental challenge.^{61–63} However, results of studies evaluating the efficacy of various HIP preparations under field conditions have given contradictory results.^{5,59,60,64} This suggests that various factors such as the method of immunizing plasma donors, the amount of HIP used, the timing of plasma administration, and management conditions, as well as the number of virulent bacteria in the environment, may influence the effectiveness of a particular HIP product.

In the recent American College of Veterinary Internal Medicine Consensus Statement, administration of plasma containing antibodies against *R. equi* was recommended as an aid in the prevention of infection on endemic farms, although the optimal dose and timing of administration remain unclear.¹ Foals are believed to become infected within the first few days of life,¹¹ and thus early administration of plasma, commonly no later than 2 days of age, is recommended. This passively acquired immunity is, however, likely to have waned to a nonprotective level within the period that foals are still susceptible to infection, and thus a second dose, administered at 2–4 weeks of age, is also commonly administered.¹¹

Vaccination

Although there has been much interest in developing a vaccine capable of protecting foals against *R. equi* infection, to date, no effective vaccination strategy has been identified. Vaccination of mares during pregnancy with a vaccine containing proteins from a VapA containing *R. equi* strain has been shown to result in anti-*R. equi* antibody production in mares, transfer of antibody in colostrum to foals, and an increased opsonic antibody activity in foals.⁶⁵ Significantly fewer foals in the vaccinated group (0/32) compared with in the control group (4/15; $P=0.02$) developed *R. equi* pneumonia. As with HIP, vaccination of mares and subsequent passive transfer of antibodies is unlikely to provide full protection against *R. equi* infection because of the importance of cell-mediated immunity in protection against the disease. As such, vaccination of foals to stimulate this type of immunity is more likely to be a successful preventative strategy. However, the vaccine would need to be administered very

early in life and be effective rapidly to be protective at the time when foals are believed to become infected. Vaccination at this time is complicated by the interference of maternal antibodies and the relative immaturity of the foal's immune system. Oral immunization with a live virulent *R. equi* was shown to be protective in foals after experimental challenge in one study.⁶⁶ Foals were immunized at 2 days, 1 week, and 3 weeks of age via nasogastric administration of either *R. equi* or a placebo, and were then challenged by intrabronchial administration of bacteria at 3 weeks of age. Foals in the control group (n=4) developed clinical signs of pneumonia by 9 days postchallenge, whereas those in the immunized group did not. Postmortem examinations performed 2 weeks after challenge also supported the production of a protective response in immunized foals, with control foals all developing extensive pyogranulomatous pulmonary consolidation, whereas the lungs of immunized foals were free of lesions. Although the results of this study appear promising, the efficacy of this protocol under field conditions has not been tested, and the effect of oral administration of virulent bacteria on environmental bacterial load should be considered.

Environmental management

R. equi is a saprophyte that persists and replicates in soil. It is ingested by grazing horses, survives passage through the gastrointestinal tract, and is then excreted in feces. Its ubiquitous nature on equine breeding farms can be explained by its enhanced growth in horse feces and its use of the volatile fatty acids present in the feces.^{67,68} Mares excrete bacteria within the feces, which can then be ingested by foals. In one study, *R. equi* could be isolated from the feces of 100% of foals by 4 weeks of age.⁶⁹ Bacterial replication in the soil is enhanced in particular types of soils (pH 7.0–8.5) and at higher environmental temperatures.⁶⁷ Aerosolization of virulent soil *R. equi*, favored by high soil concentrations and dry, dusty conditions, is considered to be the major mechanism of pulmonary infection.³⁷ Preventative strategies targeted at minimizing environmental bacterial load, and thus aerosolization and inhalation, have been investigated. Increased stocking density, an increased number of mares and foals on a premises, and increased numbers of transient mares and foals have been identified as risk factors for the development of *R. equi* pneumonia in foals.^{6,7,70} Strong evidence for a decrease in the number of cases of pneumonia after modification of risk factors is lacking, although minimizing housing foals in bare, dusty paddocks, lanes, or holding pens and reducing stocking rates would seem to be a logical method of minimizing foal exposure to the organism.⁷ In a

recent study, concentrations of virulent *R. equi* in air samples from stalls housing foals that developed *R. equi* pneumonia were significantly higher than those in samples from stalls housing foals that did not develop pneumonia, suggesting that attempts to minimize concentrations of airborne virulent *R. equi* may be beneficial.⁷¹

Isolation of clinically affected foals in an attempt to minimize environmental contamination and thus exposure of noninfected foals to virulent *R. equi* has been advocated as a preventative measure.⁷² Concentrations of virulent *R. equi* in the breathing zone of foals with *R. equi* pneumonia have not, however, been shown to be significantly higher than foals without disease, suggesting that affected foals do not pose an increased risk for direct aerosol transmission.^{73,74} Foals are known to have increased concentrations of virulent *R. equi* in their feces compared to adult horses,⁷⁵ and in one small study, infected foals had higher concentrations of *R. equi* in fecal samples compared with nonaffected foals.⁷⁶ Environmental contamination may be thus be diminished if affected foals are prevented from being housed in paddocks where nonaffected mares and foals may be grazed.

Chemoprophylaxis

Gallium

Gallium is a trivalent semimetal that is chemically similar to ferric iron and has been used as an aid in the management of infections caused by iron-dependent bacteria.⁷⁷ Although sequestration of ferric iron by host proteins such as transferrin, lactoferrin, and ferritin is an innate defense mechanism aimed at minimizing bacterial survival by limiting access to iron, *R. equi* has the ability to acquire and use iron bound to both transferrin and lactoferrin, thus neutralizing this defence mechanism.⁷⁸ When gallium is present, bacteria acquire it instead of iron from the host iron-binding proteins, and it is then incorporated into the bacterial metabolic pathways and enzymes that require iron. Because many of these enzymes are critical for cell functions such as DNA synthesis, the incorporation of gallium, which cannot be reduced from its trivalent form to the divalent form (as would occur with iron), results in cell death resulting from the inhibition of DNA synthesis and bacterial replication.^{77,79} Use of gallium for chemoprophylaxis has been reported to be an effective strategy in the management of a variety of bacterial diseases, and has been shown to have antimicrobial activity against *R. equi* in vitro.^{79,80} Gallium, as gallium maltolate, can be administered safely to foals via the oral route and has been shown to reach concentrations sufficient to suppress growth or kill *R. equi* in macrophages at a dose of 20–30 mg/kg.^{80–83}

However, a controlled, randomized, double-blinded clinical trial performed on breeding farms with a history of endemic *R. equi* infection showed no significant difference in the rate of clinically apparent *R. equi* pneumonia between foals treated with gallium maltolate (30 mg/kg by mouth every 24 hours for the first 2 weeks of life) compared with foals treated with a placebo.¹³ A recent study investigated the utility of peripartum treatment of mares with gallium on decreasing fecal and airborne concentrations of virulent *R. equi*, which would thereby decrease environmental contamination.⁸⁴ Fecal shedding of *R. equi* was significantly lower in mares treated with gallium, but this was not reflected in lower airborne concentrations.

Antimicrobials

Mass antimicrobial prophylaxis of all foals on endemically affected farms has been suggested as a method of preventing the development of pneumonia. Although in one study a significantly lower proportion of foals treated with azithromycin (every other day for the first 2 weeks of life) developed pneumonia compared with those not treated (5.3% versus 20.8%), this method of prophylaxis is not recommended because of the high chance of the development of antimicrobial resistance.^{1,85} Although resistant isolates were not reported in this study, a subsequent report from a farm using treatment of foals who were subclinically affected identified widespread macrolide and rifampin resistance in *R. equi* isolates, which increased from a rate of 25% before treatment to 62% after treatment.⁹ Two recent studies have also questioned the efficacy and need for mass antimicrobial prophylaxis in subclinically affected foals on farms with endemic *R. equi*.^{3,4} In these studies, foals were screened on a weekly basis using clinical examinations and white cell counts, and abnormalities detected on these, including a rectal temperature of greater than 39.5°C, respiratory rate greater than 80/minute, abnormal thoracic auscultation, or an abnormally high white cell count, prompted thoracic ultrasonographic evaluation. Foals with an abscess score between 1–10 cm in one study, or between 5–10 cm in the second study, were randomly assigned to either treatment groups (various antimicrobial regimes including tularithromycin, rifampin and azithromycin, azithromycin alone, doxycycline, and doxycycline with rifampin) or a placebo on a blinded basis. Foals were subsequently monitored weekly until lesion resolution. Deterioration in clinical or ultrasonographic findings prompted a change in treatment to azithromycin and rifampin. There was no significant difference between groups in the proportion of foals that responded to the initial

treatment, the duration of treatment, the proportion of foals that required a change of treatment, or the number of days until this treatment change was required. These results suggest that a high proportion (up to 88%) of foals with subclinical *R. equi* infections can recover without antimicrobial treatment, and that treatment with antimicrobials does not appear to alter the proportion of those that resolve.^{3,4}

Screening

Because of the potentially devastating outcome in foals infected with *R. equi*, and because in many cases the disease is well advanced by the time clinical signs become apparent, identification of foals with subclinical infections has become standard practice on many farms with endemic infections. Although screening for early identification of *R. equi* pneumonia is recommended, the best method to achieve this has yet to be identified.¹ Because most *R. equi* infections are believed to occur within the first week or two of life, screening beginning at 3–4 weeks of age tends to be implemented, regardless of the method used. Screening methods evaluated have included visual inspection of foals, clinical examinations by farm personnel/veterinarians, hematologic parameters, serology, and thoracic imaging with either radiography or ultrasonography. Evaluation of serum antibody levels, fibrinogen, and serum amyloid A concentrations are considered ineffective screening tools, whereas clinical examinations, white cell count, and thoracic imaging (ultrasound) may allow for early identification of subclinically infected foals.^{10,14,86}

In a population of 162 foals on a farm with a history of *R. equi* infections, measurement of fibrinogen concentration, white blood cell concentration, and anti-*R. equi* antibodies via an agar gel immunodiffusion assay (AGID) at 4-weekly intervals was investigated as a means of early identification of foals with *R. equi* pneumonia.¹⁴ Although both fibrinogen concentration and positive serology had poor sensitivity and specificity, the authors suggest that monitoring white cell concentration may be a useful approach for the early detection of *R. equi* pneumonia. In this study, a white cell count greater than 15,000/μL had a relatively good sensitivity (78.6%) and specificity (90.8%). In contrast, a more recent study¹⁰ in which white cell count, neutrophil count, and fibrinogen concentrations were evaluated in foals at 2-weekly intervals, hematologic screening had limited ability to predict foals that subsequently developed clinical signs of pneumonia.

In recent years, ultrasonographic screening of all foals on endemic farms at regular intervals has been employed in an attempt to detect evidence of pneumonia before clinical

signs develop. Ultrasonographic abnormalities have been identified in 80%–93% of foals in recent studies performed on endemic farms^{3,4,10} although the percentage of foals with lesions that go on to develop clinical signs of pneumonia is considerably lower. Chaffin reported that only 21% (46/216) of foals that had ultrasonographically detectable lesions went on to develop pneumonia.¹⁰ A similarly high rate of apparent spontaneous resolution has been reported in Europe, suggesting that although ultrasound is a useful tool in detecting foals that may be subclinically infected with *R. equi*, the majority of these foals appear to be able to resolve the infection without treatment, and that identification of lesions should not be used as the sole reason to initiate therapy.^{3,4} Indeed, in a controlled study, there was no difference in the rate of recovery of foals with ultrasonographically identified pulmonary lesions between those that were administered a placebo and those that were treated with antimicrobials.³ Several grading systems have been developed in an attempt to quantify the severity of ultrasonographically visible lesions, and thus determine which foals may need to be treated and which ones will be able to resolve the infection without treatment.^{3,4,87} Despite these grading systems, it remains unclear which foals require treatment. It could be argued that because of the morbidity and mortality associated with clinical *R. equi* infections, treatment of foals subclinically affected should be implemented. However, the effect of mass antimicrobial therapy on rates of antimicrobial resistance, the cost associated with treatment, the risk of adverse reactions to the antimicrobials administered, and the evidence that many foals with subclinical pulmonary lesions recover without treatment should be considered before treatment protocols for these foals are implemented. It is likely that screening programs and the response to detection of a “positive” case will need to be adapted to individual farms and will vary depending on the historic morbidity and mortality, the finances and resources available, and the ability to alter practices depending on the results of the screening program.

Prognosis

The prognosis for foals with *R. equi* pneumonia varies depending on the origin of the foals (referral hospital versus farm study). Survival rates of 48%–82% in foals with pneumonia treated at a referral hospital have been reported.^{12,41,46,53,88} Foals in which an EPD is present were reported to have a poorer prognosis (43% survival) compared with those without (82% survival).⁴¹ Survival rates of foals subclinically affected with *R. equi* (as assessed by thoracic

ultrasonographic abnormalities) are very high, with close to 100% of foals recovering even without treatment.^{3,4}

The prognosis for athletic function in foals that recover from pneumonia is also excellent. In one study, although only 54% (45/83) of foals that survived *R. equi* pneumonia went on to race compared with 65% of unaffected foals born in the same year, their performance was not different from that of the US racing population.⁸⁸ Pulmonary function also appears to be normal in foals that recover from *R. equi* pneumonia. In a small study of seven 3-year-old horses with a history of *R. equi* pneumonia as foals, gas exchange during intense treadmill exercise was not compromised.⁸⁹

Summary

Management of *Rhodococcus equi* infections in foals remains challenging, both for treatment of individual foals and for implementing effective and evidence-based preventative strategies. New evidence suggests that although many foals on endemically affected farms become infected, the majority appear to resolve the infection without treatment, highlighting the challenge of identifying effective preventative measures.

Disclosure

The author reports no conflicts of interest in this work.

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