Rhodococcus equi Disease Guidelines

Definition

Rhodococcus equi (*R. equi*) remains the most common cause of subacute or chronic granulomatous bronchopneumonia in foals less than 5 months of age. Extrapulmonary disease is not uncommon (see below). This gram-positive intracellular bacterial pathogen is normally present in the environment and in the manure of herbivores, making control and prevention extremely difficult.

Etiology

Rhodococcus equi is a soil-dwelling bacterium found worldwide. Pathogenic strains that infect foals possess a surface-expressed protein known as virulence-associated protein A (vapA). This protein is essential for bacterial survival within macrophages. Strains lacking the vapA gene are considered non-virulent. Both virulent and non-virulent strains are frequently present in the soil of equine farms. Therefore, identifying virulence factors, in conjunction with bacterial culture, is crucial for the definitive diagnosis of *R. equi*-related diseases.

Pathogenesis

It is now well established that foals are infected shortly after birth and that susceptibility to clinical disease decreases as horses reach adulthood. Adult horses are not susceptible unless immunocompromised. The physiologic reasons behind this age susceptibility remain undetermined.

Inhalation of virulent *R. equi* during the first few weeks of life is associated with the development of disease, with some farms being considered endemic for the organism. Once inhaled, virulent *R. equi* infects and replicates inside alveolar macrophages, leading to slow-forming abscesses. Foals also ingest virulent and avirulent *R. equi*, although the role that this enteral exposure plays in the development of disease or bacteremia, or in the development of resistance, requires additional evaluation.

Incubation Period

The incubation period following experimental intrabronchial challenge varies from approximately 9 days after administration of a heavy inoculum to approximately 2 to 4 weeks when a lower inoculum dose is administered. Field infections typically result in insidious, slow-developing disease, suggesting that most exposures are a low dose of the bacterium. The onset of clinical signs is variable and likely depends on several factors including environmental load of virulent bacteria, the age and immune competence of the foal, and the location of the infection.

Clinical Signs

The most common clinical manifestation of *R. equi* infections in foals is bronchopneumonia of variable severity, generally first noted at 2 to 6 months of age. Early clinical signs may include fever, lethargy, and/or anorexia, which are non-specific and can be easily missed. As the pulmonary infection progresses, clinical signs of pneumonia develop including tachypnea and increased respiratory effort (nostril flaring and abdominal effort). Nasal discharge (purulent) and cough are unreliable signs. Clinical signs may be more evident in hot and humid environments.

Extrapulmonary disease is not uncommon and the clinical signs vary with the location of the infection. Extrapulmonary disorders might occur concurrent with or independent of pneumonia. Infection of the abdominal cavity and/or viscera is the most common extrapulmonary manifestation, resulting in variable clinical signs ranging from fever, lethargy, anorexia, and diarrhea, but may be asymptomatic. Severe granulomatous enterocolitis or enterotyphlocolitis are not common, but occur. When present, foals fail to thrive and may develop leukopenia and hypoproteinemia. Abscessation of the abdominal lymph nodes is often found at necropsy but may be visible upon abdominal imaging.

Osteomyelitis and septic synovitis typically present with marked lameness (or neurologic signs if the vertebral bodies are affected) and require aggressive therapy. Immune-mediated polysynovitis is characterized by effusion in multiple joints without clinical signs of lameness. These cases typically respond positively to treatment with corticosteroids. Foals with immune-mediated synovitis can be distinguished from those with septic arthritis by degree of lameness (synovitis foals generally display minimal or no lameness), multiple affected joints (more likely in synovitis cases, although multiple septic joints are possible), and joint fluid cytology (septic arthritis cases tend to have higher joint fluid cell counts [>30,000 cells/uL] and higher total protein concentrations [>3 g/dL] when compared to immune-mediated synovitis cases).

Uveitis (aqueous flare, hypopyon, hyphema) may be unilateral or bilateral and can result from septic or immune-mediated processes. Other less common manifestations include immune-mediated hemolytic anemia, pericarditis, and meningitis.

Note: It is important to highlight that on endemic farms, a large percentage of foals may be infected but remain subclinical. The majority of these foals typically clear the disease without the need for treatment.

Diagnosis

As with any other cause of bacterial lower airway infection, definitive diagnosis of Rhodococcal pneumonia requires analysis of a sterile pulmonary fluid sample, typically collected via endoscopic or percutaneous tracheal wash. The fluid should be submitted for bacterial culture, identification of the vapA gene by PCR (when possible), and cytological analysis. Identification of vapA by PCR may be done in conjunction with, but should not replace, bacterial culture because PCR does not confirm live organisms and does not permit identification of other bacterial pathogens or *in vitro* antimicrobial susceptibility testing of *R. equi* isolates.

A presumptive diagnosis of *R. equi* pneumonia can be made using thoracic ultrasonography (or radiographs) on farms where *R. equi* is endemic. Treatment of foals lacking clinical signs solely based on the presence of lesions found upon thoracic ultrasonography is not recommended as it contributes to antimicrobial resistance (see Screening below).

The definitive diagnosis of extrapulmonary infections (e.g., abdominal abscess, osteomyelitis) caused by *R. equi* relies on bacteriologic culture or PCR amplification of vapA from the site of infection. The diagnosis of extrapulmonary disorders from sites at which *R. equi* cannot be detected (e.g., uveitis, internal abscessation, or polysynovitis) is challenging and sometimes relies upon response to treatment. The diagnosis of enterocolitis caused by *R. equi* is problematic because isolation of *R. equi* from feces cannot be taken as evidence of enterocolitis caused by *R. equi*.

Postmortem

The most common lesion noted on postmortem examination is pyogranulomatous bronchopneumonia with abscessation. Abdominal lesions such as ulcerative enterocolitis or typhlitis, suppurative inflammation of the mesenteric and/or colonic lymph nodes, or abdominal abscesses may be present. Polysynovitis and/or osteomyelitis might be present. Other rare extrapulmonary manifestations of *R. equi* infections in foals include guttural pouch empyema, sinusitis, pericarditis, and nephritis, as well as hepatic, renal, and intracranial abscessation.

Environmental Persistence

R. equi is ubiquitous in the soil and the manure of herbivores.

Treatment

Combination of a macrolide and rifampin is recommended for the treatment of *R. equi* infections, and drug selection should be based on culture and sensitivity testing of transtracheal wash samples, as resistance can be widespread on endemic farms. The combination of doxycycline and rifampin is occasionally used in foals with macrolide-resistant tracheal wash isolates, but it should be noted that this drug combination has been associated with fatal liver disease in some foals and should not be used as a first-line therapy. The duration of therapy typically ranges from 4 to 6 weeks but varies with the severity of the disease. Treatment of extrapulmonary lesions may require a more extended course of antibiotics. Antibiotic therapy is generally continued until clinical signs resolve. Thoracic ultrasound is useful for monitoring the resolution of pulmonary lesions, while changes in bloodwork—such as normalization of white blood cell counts, fibrinogen, and globulin levels—can also help guide treatment duration. These parameters are particularly valuable when managing extrapulmonary lesions. Non-steroidal anti-inflammatories, such as flunixin meglumine or meloxicam, may be needed to decrease inflammation and pain as well as to manage high fevers.

Foal Doses:

Rifampin: PO, 5 mg/kg q 12h or 10 mg/kg q 24h – should not be used as a sole agent

Azithromycin: PO, 10 mg/kg q 24h for 5 days, q 48h thereafter if foals are not severe.
Clarithromycin: PO, 7.5 mg/kg q 12h.

Tulathromycin: IM, 2.5 mg/kg once a week. This drug should not be used without rifampin.
Gamithromycin is not recommended due to its side effects (severe pain after administration).

Potential Side Effects of Macrolides:

Diarrhea: A common side effect of antibiotic therapy. The diarrhea is typically self-limiting, but some foals require supportive treatment. Care should be taken to avoid mares/adults coming into contact with macrolides to decrease the chances of them developing potentially fatal colitis.

Hyperthermia: Macrolides can inhibit a foal's ability to sweat (anhidrosis), a condition that may persist for up to a month after treatment cessation. This can lead to potentially fatal hyperthermia. To mitigate this risk, foals should be kept in a cool, well-ventilated environment during treatment.

Injection Site Reactions: Intramuscular administration of macrolides may cause localized swelling and pain.

Specific Control Measures

In the absence of an effective vaccine, control and prevention of the disease at farms endemic for infections caused by *R. equi* have relied on passive immunization and screening to promote earlier recognition of the disease. Absolute prevention of *R. equi* is unlikely; thus, the primary objective of a prophylactic program should be to reduce the incidence of clinical pneumonia. This, in turn, will help minimize the use of antibiotics in foals and decrease the risk of developing antimicrobial-resistant strains.

Administration of Hyperimmune Plasma (HIP)

Intravenous administration of commercially available, licensed *Rhodococcus equi*-specific hyperimmune plasma (Re-HIP), is recommended as an aid to prevent clinical pneumonia in foals on endemic farms. While early research yielded mixed results, recent studies highlight its clinical benefits. However, expectations should remain realistic as Re-HIP does not fully prevent infection, and lesions may still develop.

Experimental data suggests Re-HIP is most effective when administered before infection, making transfusions shortly after birth ideal. Traditionally, a 1L transfusion has been used in the US, but recent findings indicate that 2L may offer greater benefits. Further research is needed before a recommendation can be made to increase the volume of Re-HIP administered.

Screening

On farms where *Rhodococcus equi* is endemic, thoracic ultrasound is commonly used to diagnose and treat infected foals. While this approach was initially regarded as beneficial, recent evidence has revealed a temporal link between the widespread treatment of subclinical foals and the emergence of macrolide- and rifampin-resistant *R. equi* strains. Moreover, studies indicate that treating clinically normal foals with small pulmonary lesions is unnecessary, as it does not accelerate lesion resolution. Further, foals with small and low numbers of abscesses often resolve their disease spontaneously without treatment. These findings present an opportunity to reassess and refine treatment practices on endemic farms. Because it is hard to extrapolate data from one farm to another, each farm should develop a gradual plan to decrease the number of foals treated. The decision to treat (or not to) is complicated by the lack of specific biomarkers to identify foals at risk of developing pneumonia. Physical exam parameters, white blood cell counts, acute phase proteins (such as fibrinogen and serum amyloid A), and fecal shedding of pathogenic *R. equi* are not useful individually to identify foals in need of treatment.

Biosecurity Management

Foals with pneumonia caused by *R. equi* shed higher numbers of *R. equi* in their feces than healthy foals or foals with subclinical lesions. Therefore, pneumonic foals might be an important source of environmental contamination. However, there is no evidence that *R. equi* infection is contagious among foals and exposure to virulent *R. equi* is widespread in the environment of foals. Currently there are no isolation requirements for foals with this disease.

Zoonotic Potential

Rhodococcus equi can occasionally cause severe pulmonary or systemic infections in immunosuppressed people. Infections in immunocompetent individuals with *R. equi* are extremely rare and typically less severe.

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