**Rhodococcus equi**

By Erica Larson and Stacey Oke, DVM, MSC

*Rhodococcus equi* is a dangerous pathogen that causes pneumonia in foals that are generally between the ages of 3 weeks and 5 months. In cases caught early on, the foal can make a full recovery with proper treatment. However, in more serious cases the mortality rate is quite high, noted Steeve Giguère, DVM, PhD, Dipl. ACVIM, professor and Marguerite Thomas Hodgson Research Chair in Equine Studies at the University of Georgia’s College of Veterinary Medicine. He discussed the importance of understanding the pathogenesis of the bacterium *R. equi* (how it’s acquired and how it causes disease), the associated clinical signs, and the diagnostic methods used to detect infection.

“The most common manifestation of *R. equi* infections in foals is a chronic suppurative (pus-producing) bronchopneumonia with extensive abscessation,” Giguère said. “The slow spread of the lung infection combined with the remarkable ability of foals to compensate for the progressive loss of functional lung makes early clinical diagnosis difficult.”

**Clinical Manifestations** Giguère closely analyzed the different clinical manifestations of *R. equi* pneumonia that the foals presented.

He noted that many foals with *R. equi* pneumonia also have extrapulmonary (outside the lungs) disorders, such as immune-mediated polyarthritis (arthritis of multiple joints), ulcerative enteritis (small erosions and abscesses in the wall of the small or large intestines), intra-abdominal abscessation, abdominal lymphadenitis (inflammation in one or more lymph nodes), uveitis (moon blindness), and pyogranulomatous hepatitis (microscopic abscesses in the liver).

Intestinal lesions were one of the most common extrapulmonary disorders, evident in about 50% of foals with *R. equi* pneumonia that were presented for necropsy, Giguère noted. However he added that most foals that contract *R. equi* pneumonia do not show signs of intestinal disease while undergoing treatment for the pneumonia. “Foals with abdominal abscesses typically have a high fatality rate,” Giguère said.

Giguère also found that polyarthritis (a condition in which multiple joint surfaces are inflamed) was present in about 25%-30% of live foals undergoing treatment for *R. equi* pneumonia. He added that in many of these cases, lameness was mild, if present at all.

Giguère added that immune-mediated processes might aid in the development of other extrapulmonary conditions seen in these cases, such as uveitis, anemia, and thrombocytopenia (low platelet counts) in some foals.

**Pathogenesis** According to Giguère, little was known about the virulence of *R. equi* before scientists identified a virulent plasmid in 1991 that is essential to the bacterium’s ability to cause disease.

“With the presence of the plasmid, *Rhodococcus* can replicate in macrophages (white blood cells) and cause disease,” Giguère said. “Without it, it loses its ability to cause disease in foals. Without the plasmids, the foals cleared the *Rhodococcus* within two weeks.”

Researchers sequenced the plasmid’s nucleotide and “the genes for a family of eight closely related virulence-associated proteins,” targeting one that they designated as VapA. After further research, Giguère said, scientists discovered that while VapA aided reproduction of the bacteria in the foal, it wasn’t able to produce an *R. equi* infection on its own. Other proteins were evaluated as well, although the role that each plays in the pathogenesis of *R. equi* is unknown, Giguère concluded.

Giguère also relayed that inhaling *R. equi* bacteria is one avenue by which a foal can contract pneumonia. He added that *R. equi* pneumonia could be detected as little as three days after a foal inhaled a large concentration of bacteria.

**Diagnosis** Giguère said that several tests are available for diagnosing foal pneumonia. He added that *R. equi* pneumonia could be detected as little as three days after a foal inhaled a large concentration of bacteria.

There are several tests that are able to detect *R. equi*, including complete blood counts, measurement of fibrinogen.
concentrations, and ultrasonographic and radiographic exams. But Giguère cautions that veterinarians should use a bacteriology culture or a polymerase chain reaction (PCR) test for the VapA protein, along with a cytological exam of the tracheobronchial aspirate, to definitively diagnose pneumonia caused by *R. equi* bacteria.

“A PCR test is slightly more sensitive than the other tests; however, the culture offers the advantage of detecting other bacterial pathogens present and permits *in vitro* susceptibility testing of the recovered pathogens,” Giguère said. “As a result, PCR amplification of the VapA gene may be done in association with, but should not replace, bacterial culture.”

Giguère added that foals should be tested for *R. equi* infections at the first sign that they might be ill: “Early diagnosis is of paramount importance for successful therapy of infected foals.”

**Epidemiology**

Noah Cohen, VMD, MPH, PhD, Dipl. ACVIM, professor of Large Animal Clinical Sciences at Texas A&M University’s College of Veterinary Medicine & Biomedical Sciences, presented a study on the epidemiology (“scientific discipline concerned with quantifying the distribution of disease and determinants of disease and health in populations”) of *R. equi*.

In his presentation he reviewed published research about why some foals contract *R. equi* pneumonia in the same environment where other foals do not, and why *R. equi* is prevalent at some farms but virtually nonexistent at others.

According to Cohen, virulent (disease-causing) *R. equi* has been isolated from several sources on breeding farms including feces (from both foals and their dams), horse feed, the soil, and the air. Especially at farms with high concentrations of foals, Cohen says it’s likely that all foals are exposed to the disease-causing bacterium, but only a small portion of foals actually contract pneumonia.

He noted in the study that the concentration of virulent (disease-causing) *R. equi* in the dams’ feces was not related to the risk of a foal developing pneumonia caused by the bacterium; in other words, mares shedding more *R. equi* in their feces did not appear to explain the disease. However, that study also observed that nearly all mares shed virulent *R. equi* in their feces during the period shortly after birth of foals.

There might be genetic factors that influence a foal’s susceptibility to *R. equi*, he said, as veterinarians in the field report that some mares have had multiple foals that have contracted the disease. Moreover, variations in the DNA sequence (known as polymorphisms) for several genes have been associated with somewhat greater risk of disease. He also suggested that some foals could just be particularly immunologically susceptible to the disease.

No matter the cause, he stressed that more research is needed to obtain more accurate information about what predisposes some foals to contract *R. equi*.

Cohen also examined why some breeding farms seem to have a higher prevalence of *R. equi* than other farms. Again, combing through the available data provided few definitive answers.

“The density of mares and foals per acre seems to be positively correlated with incidence of *R. equi* pneumonia,” he noted. Foaling at pasture also may reduce risk of this disease, but more work is needed to confirm existing observations.

Cohen also explained that in the studies he examined, *R. equi* seemed to occur at “well-managed farms that use practices generally deemed to be desirable for preventing infectious diseases of foals.”

“This association is not likely causal,” Cohen wrote. “But it does indicate that practices effective for preventing other infectious diseases of neonates are of limited benefit against *R. equi*.”

The take-home message, Cohen said, is that researchers don’t yet understand why some foals contract the disease while others in the same environment do not. Some farm-level interventions such as reducing density of mares and foals and foaling at pasture need to be systematically evaluated.

**Control/Prevention**

For years foal owners have struggled with controlling *R. equi* and the infections it causes—some farms manage cases annually, despite following strict farm management strategies to reduce the risk of infection. Resulting pneumonia and diarrhea can be deadly for foals, and treating survivors is costly and labor-intensive.

Cohen said preventing and controlling *R. equi* infections might be the ideal way to deal with some farms’ recurrent *R. equi* problems. However, finding the means to prevent and control *R. equi* infections is still a challenge that researchers face.

Cohen explained that two options for controlling and preventing *R. equi* infections were recently the subjects of several peer-reviewed studies: chemoprophylaxis and immunoprophylaxis.

Chemoprophylaxis (the use of antimicrobial agents to prevent foal pneumonia), was considered as an option for preventing *R. equi* infections, Cohen said. He cited two studies in which researchers used azithromycin in an attempt to prevent infections, one of which showed a 76% reduction in the risk of contracting an infection. The other study, however, showed little difference between the infection risk of foals treated with azithromycin and those untreated. Cohen said the reason for the discrepancies in the results is unknown. But the reason for the discrepancy is moot; using azithromycin for preventing *R. equi* infections should not become common practice because it could create microbial-resistant bacteria in the foal and its environment. If the foal subsequently contracts an *R. equi* infection, the prognosis would be worse due to the resistant bacteria (which can be shed by carriers and picked up by other foals, resulting in them contracting a resistant form of infection).

Cohen also discussed the option of immunoprophylaxis (immune system modifiers) to prevent *R. equi* infections. He said that despite extensive research into developing a vaccine, no such product has been effective against *R. equi* infections.

The only clinically acceptable prevention

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**DR. NOAH COHEN**
method, Cohen said, is the administration of hyperimmune plasma (which contains high levels of antibodies against *R. equi*) to young foals via transfusion shortly after birth and possibly again at 3 to 4 weeks of age. Hyperimmune plasma is thought to provide passive immunity to treated foals against *R. equi* and reduce the incidence of pneumonia caused by this bacterium.

Cohen adds that although observational studies haven’t produced uniform evidence of effectiveness, the cumulative interpretation of published studies indicates that plasma transfusion has reduced the risk of foals contracting *R. equi* infections.

“There is tremendous need for the development of a highly effective preventative strategy,” Cohen said in his study. “In the absence of a preventative strategy, further application, evaluation, and development of screening tests are greatly needed to address this important health problem of foals.”

### Antimicrobial Combo Targets *R. equi*

The ideal treatment for *R. equi* infection remains debatable because of the lack of research comparing the efficacy of each possible treatment in foals. However, according to Giguère, current evidence suggests that the most successful treatments include a combination of the drug rifampin and a macrolide (a class of antimicrobial drugs). He reviewed treatments for *R. equi* pneumonia.

Giguère said that veterinarians have used the combination of rifampin and erythromycin (a macrolide) since the 1980s, and with this strategy they have drastically reduced the number of fatalities resulting from *R. equi* pneumonia, at least compared to historical data.

“The combination of a macrolide and rifampin is synergistic both *in vitro* (in the laboratory) and *in vivo* (in a live animal), and the use of the two classes of drugs reduces the likelihood of *R. equi* resistance to either drug,” he said. Giguère added that rifampin and macrolides are liquid-soluble, a trait that “allows the drugs to penetrate cell membranes.”

In addition to erythromycin, veterinarians have begun using two more recently developed macrolides to treat *R. equi* infections. Both azithromycin and clarithromycin have more modern chemical properties, meaning a smaller amount of drug is required to be effective, and the drug can be administered less frequently. Both characteristics result in fewer doses for the horse.

Giguère mentioned that there is a need for newer antimicrobial agents that are long-acting and require less frequent administration. However, the two long-acting macrolides currently available in the United States (tulathromycin and tilmicosin) are poorly active against *R. equi*. As a result, their use for treating *R. equi* infections is not recommended.

In addition to the macrolide antimicrobial agents, Giguère mentioned a few alternative classes of drugs that can be used for foals with *R. equi* pneumonia. One treatment option that might be successful for foals is an oral dose of doxycycline in combination with rifampin. Finally, he said the antibiotic drug chloramphenicol has some activity against many *R. equi* strains, but it carries with it a health risk to the humans administering it.

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### *R. equi* Immunity and the Foal

Why is it that only foals are affected by *R. equi* pneumonia? According to M. Julia B. Felippe, DVM, MS, PhD, Dipl. ACVIM, of Cornell University’s College of Veterinary Medicine, one of the contributing factors is that some aspects of the foal’s immune system take time to develop and, thus, contribute to susceptibility to disease. Felippe summarized research findings on the topic at the convention.

“The unique susceptibility of young foals to *R. equi* disease is still puzzling, despite many studies investigating their innate and acquired immune systems,” Felippe said. Part of the puzzling aspect is why only certain foals contract the disease, while other foals remain healthy.

Despite the fact that many foals with naive immune systems (they haven’t been exposed to the pathogen in question before) are exposed to *R. equi*, only some of them develop disease in the face of that exposure. According to Felippe, this points towards some foals having individual risk factors that make them more susceptible to the *R. equi* bacterium.

Felippe explained that the foal must have both innate and acquired immunity for complete protection from *R. equi* bacteria. The innate immune system recognizes the presence of organisms without the need of previous exposure. Some cells of the innate immune system of the foal are very effective in killing extracellular (outside cells) pathogens, including *R. equi*. But the interaction of the innate with the acquired immune system seems necessary for protection against disease.

She added that acquired immune responses develop after *R. equi* exposure, and are carried out by a variety of “T-helper” cells, which scientists call “Th cells.” Each Th cell plays a different role in fighting diseases. For example, in the horse Th-1 cells support an immune response to fight intracellular (within cells) infections, while Th-2 cells promote antibody production for protection against extracellular organisms.

According to Felippe, recent studies have indicated that foals can develop Th1 immunity as a defense against *R. equi*. She said this is the type of immune response that adult horses produce when challenged with experimental infection in scientific studies; such a response indicates that some foals can defend against *R. equi*. The question remains if, for some foals, this type of response takes longer to become effective, creating the window of susceptibility to the organism.

Additionally, she examined the possibility of antibodies providing immunity for the foal against *R. equi*. Although a protective effect of antibodies on the bacterium has been shown *in vitro* (in the laboratory, not in the live horse), studies evaluating the use of plasma products enriched with antibodies against *R. equi* have contrasting results in the field. Nevertheless, colostrum and plasma products supply at birth essential antibodies for the optimal function of the cells of the innate immune system, until the foal can produce its own antibodies through the acquired immune system.

Felippe concluded that while scientists have made strides in understanding how *R. equi* affects foals, further studies are required to uncover how—and why—it only affects certain foals.
“Many current studies (are investigating) the pathogenic mechanisms in the early stages of infection,” she said, adding that the goal is to develop better preventive methods, including immunomodulators (drugs that alter the immune system), vaccines, and herd management techniques.

**The Hunt for Effective New Antibiotics Continues**

It isn’t for lack of effort that the equine industry still doesn’t have new options for treating *R. equi* pneumonia in foals. According to Cohen, he and his colleagues are well aware that veterinarians are in dire need of better antibiotic alternatives. “Treatment of foals with *R. equi* pneumonia is generally prolonged, making treatment both expensive and labor-intensive,” said Cohen. “Currently, the treatments of choice are a combination of the drug rifampin with azithromycin, clarithromycin, or erythromycin.”

The latter three drugs are members of a family known as macrolides. Cohen explained the significance of macrolides, noting, “To date, alternatives to macrolides for effective treatment of *R. equi* pneumonia in foals have not been identified. Thus, when new macrolide treatments are developed, there is considerable interest among equine practitioners and farm managers about the prospects of using these new macrolides to treat foals with pneumonia.”

One of the disadvantages of azithromycin, clarithromycin, or erythromycin is that these must be administered at least every 24 hours. Because treatment is generally prolonged, availability of a macrolide that could be administered less frequently to foals is desirable.

Tulathromycin is a long-acting injectable macrolide antibiotic, and data from Germany has suggested tulathromycin was useful for managing abscessing pneumonia in foals at a large breeding farm. Cohen et al. therefore tested tulathromycin and 14 other antimicrobials on 98 different types of *R. equi* bacteria grown in laboratory culture dishes (they tested these drugs *in vitro*, or in the laboratory, rather than the live horse). They wanted to determine if any of these drugs might be potentially beneficial in live foals with *R. equi* infections.

“Unfortunately, we found tulathromycin had poor activity against *R. equi*,” Cohen said. “It appeared that it would be impossible to achieve therapeutic concentrations of tulathromycin in blood or tissues.”

Giguère is also well aware of the need for new drugs for treating *R. equi* infections. “There are other long-acting macrolides with good *in vitro* activity against *R. equi* that are currently available for use in cattle in other countries,” he said. “These agents are currently being studied in foals here in the U.S. Some viable options do seem to be upcoming.”

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