Rhodococcus equi: An Emerging Pathogen

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More than 100 cases of *Rhodococcus equi* infection have been reported since the first description of human disease caused by this organism. The vast majority of patients infected with *R. equi* are immunocompromised, and two-thirds have human immunodeficiency virus infection. The clinical manifestations of *R. equi* infection are diverse, although 80% of patients have some pulmonary involvement. The organism is easily cultured from specimens of infected tissue or body fluid, but it may be misdiagnosed as a contaminant. Treatment is often prolonged, and relapses at distant sites are common. This article summarizes the history, diagnosis, clinical features, and treatment of infection with this emerging pathogen.

Rhodococcus equi (formerly *Corynebacterium equi*) was first isolated in 1923 from the lungs of foals in Sweden [1]. Since then, researchers have identified *R. equi* in a variety of land and water animals, including cattle, goats, swine, buffalo, sheep, crocodiles, wild birds, deer, seals, marmosets, and koala bears [2]. The organism is present in soil in all continents except Antarctica, thrives in freshwater and marine habitats, and can live in the intestines of bloodsucking arthropods [3].

The first *R. equi* infection in a human was not reported until 1967 [4]. The details of that case illustrate many salient features of *R. equi* infection. The patient was a 29-year-old man with autoimmune hepatitis who was undergoing treatment with prednisone and 6-mercaptopurine. He presented with fever and cavitary pneumonia. Cultures of samples from the lung abscess yielded pleomorphic, gram-positive coccobacilli that were identified as *R. equi.* The patient worked in a stockyard, cleaning animal pens. All symptoms resolved after 8 weeks of treatment with erythromycin. Six weeks later, he developed a subcutaneous abscess, specimens of which grew *R. equi* in culture. He received treatment with erythromycin for 6 additional weeks and had no further recurrences of infection [4].

Only 12 more cases of *R. equi* infection in humans were reported during the next 15 years (through 1983) [5]. The incidence of *R. equi* infection has subsequently increased markedly, coincident with the era of HIV infection and advances in organ transplantation and cancer treatment. In the past 15 years, at least 100 cases have been reported and a score of literature reviews of *R. equi* infection have been published [6–24]. Improvements in laboratory techniques and better recognition of *R. equi* as a pathogen also may explain much of the increase in the incidence and reporting of *R. equi* disease.

POSSIBLE MECHANISMS OF ACQUISITION

R. equi is thought to be acquired either by inhalation from the soil, inoculation into a wound or mucous membrane, or ingestion and passage through the alimentary tract. Exposure to domesticated animals, such as horses and pigs, may play a role in some cases of infection [3, 4, 8, 25, 26]. *R. equi* is found in the soil of 50%–95% of farms, and concentrations are high in horse feces [27]. In Oklahoma, which Verville et al. [8] claim has the highest numbers of horses per acre and horses per capita in the United States, 12 cases of *R. equi* infection were treated during a 6-year period at a single institution. However, only one-third of all patients with *R. equi* infection have a history of exposure to horses or pigs.

Other routes of *R. equi* acquisition, including human colonization and person-to-person transmission, are poorly understood. Rhodococci with biochemical properties identical to those of *R. equi* are among the species that dominate the nasal microbiota of healthy adults [28], raising the intriguing possibility that nasal colonization plays a role in the acquisition of disease. It is believed that *R. equi* does not colonize the large intestine [18]. At least 3 nosocomial cases of *R. equi* have been reported [29], including 1 that occurred in a patient who developed sepsis and hydrocephalus from an infected ventricular

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shunt 2 weeks after hospitalization. Patient-to-patient transmission was implicated in 2 HIV-infected patients who developed *R. equi* infections after sharing a room with another HIV-infected patient who had *R. equi* pneumonia [11]. A single report [30] suggested occupational acquisition of *R. equi* by an immunocompetent laboratory worker who developed *R. equi* pneumonia.

PATHOGENESIS

Much of the information on *R. equi* pathogenesis comes from studies that used isolates recovered from foals and pigs. In nearly all infected foals, the virulence of *R. equi* is mediated by a surface antigen, VapA, that is associated with an 85–90-kbp plasmid [31, 32]. Foals infected with VapA-positive isolates develop severe bronchopneumonia, whereas plasmid-cured derivatives are innocuous. In pigs, nearly all isolates are of intermediate virulence and express a 20-kDa antigen associated with 5 large plasmids [33].

There are clear differences between *R. equi* infection in animals and in humans. Only 20%–25% of isolates recovered from humans express VapA [34–36]. Expression of the 20-kDa antigen is highly variable and may differ between *R. equi* strains from different geographical areas. The pathogenesis of infection with intermediately virulent strains and avirulent strains appears to involve different mechanisms than those of VapA-positive isolates. For example, pathogenesis may involve cell wall mycolic acids that play a role in intracellular survival, the production of IL-4, and granuloma formation [34].

The majority of laboratory studies that have investigated the virulence and immunity associated with *R. equi* infection have used VapA-positive isolates, which tempers any conclusions about the pathogenesis of *R. equi* in humans. In animals, both humoral and cell-mediated immunity play a role in the control of *R. equi* infection. Transfer of plasma from immunized horses to infected foals increases opsonization and clearance of *R. equi* [37]. Although normal mice and $CD8^+$ T cell–deficient mice can clear *R. equi* infection [38], SCID (severe combined immunodeficiency) mice remain persistently infected but do not develop granulomas [39]. Nude mice that are given a $CD4^+$ Th1 cell line transferred from immune mice are able to express IFN-γ and clear *R. equi* from their lungs. On the other hand, mice that receive $CD4^+$ Th2 cells but do not receive Th1 cells express IL-4 but not IFN-γ, fail to clear the infection, and develop large granulomas with eosinophils in the lung [40, 41]. Thus, the Th1 response, acting through IFN-γ, appears sufficient to effect pulmonary clearance of *R. equi* while the Th2 response is nonprotective.

MICROBIOLOGY AND DIAGNOSIS

In 1889, Zopf coined the name "Rhodochrous complex" to describe the aerobic actinomycetes with properties of both *Nocardia* and *Mycobacterium*. Rhodococci belong to the family Nocardioform, order Actinomycetes, which includes *Corynebacterium, Mycobacterium, Nocardia,* and *Gordonia* species. *R. equi* is an asporogenous, nonmotile, gram-positive, obligate aerobe capable of metabolizing a wide variety of organic compounds. *R. equi* has been isolated from diagnostic specimens of tissue or fluid from almost every body site.

R. equi grows optimally at 30°C but can grow at temperatures from 10°C to 40°C [2]. Colonies form on solid media in ⩽48 h and appear irregularly round, smooth, semitransparent, glistening, and mucoid. The characteristic salmon-pink color may not appear until days 4–7. The organism varies from distinctly coccoid to bacillary, depending on growth conditions and the phase of the growth cycle. *R. equi* appears coccoid on solid media or in purulent tissue but can form long rods or short filaments with rudimentary branching in liquid media. *R. equi* are characterized by the presence of catalase, urease, lipase, and phosphatase and by the absence of oxidase, DNAse, elastase, lecithinase, and protease. The *R. equi* cell wall includes mycolic acids of carbon length 34–52, and at least 27 capsular serotypes have been identified [3]. Results of acid-fast staining are highly variable. On the basis of its morphologic characteristics, *R. equi* can easily be mistaken for a diphtheroid contaminant, or for *Bacillus* or *Micrococcus* organisms; on the basis of acid-fast staining results, it can be mistaken for *Mycobacterium* organisms [3, 4, 11]. Communication between the primary clinician who suspects *R. equi* infection, the surgeon who obtains specimens for culture and the microbiology laboratory is essential to ensure accurate diagnosis.

Two unique features of *R. equi* help distinguish it from other organisms. First, synergistic hemolysis occurs when *R. equi* cultured on sheep blood agar are cross-streaked with other bacteria, including *Staphylococcus aureus, Listeria monocytogenes,* and *Corynebacterium pseudotuberculosis* [3]. Second, antagonism between imipenem and other β-lactam antibiotics has been documented in vitro. This antagonism is widespread among *R. equi* isolates and is novel among gram-positive bacteria [42]. Serologic assays have not been clinically validated and are not commercially available.

Pathologic findings in patients with *R. equi* infection are relatively consistent, despite the broad range of tissues involved. Specimens are typically necrotic and contain a dense, histiocytic infiltrate with an eosinophilic, granular cytoplasm and intrahistiocytic coccobacilli. Multiple microabscesses that contain abundant neutrophils may be present. In some cases, concentrically layered basophilic inclusions, called "Michaelis-Guttman bodies," are prominent. The inclusions are

thought to result from impaired macrophage lysosomal function that leads to failure of lysophagosomal fusion and ineffective killing of ingested organisms [43]. This characteristic pathologic finding, together with Michaelis-Guttman bodies, is termed "malakoplakia" and has been described in other bacterial infections [9, 13]. In rare cases, a dense proliferation of spindle cells can mimic either Kaposi's sarcoma or lymphosarcoma [9, 44].

CLINICAL MANIFESTATIONS

Prospective studies to better describe rates of *R. equi* infection are lacking, and the published literature is subject to reporting bias. On the basis of available reports of cases, approximately 10%–15% of infections occur in seemingly immunocompetent hosts [45], with the remainder divided between patients with HIV infection and patients who are otherwise immunocompromised (either from disease, immunosuppressive medications, or both) [15]. Concurrent infection with other opportunistic organisms is common in immunocompromised patients [6, 46–48].

The manifestations of *R. equi* infection are protean (table 1), although pulmonary infection is present in ~80% of cases. Bacteremia occurs in >80% of immunocompromised patients and 30% of immunocompetent patients [6, 10, 45]. Patients may present with infection at a single site or at multiple sites, and they may develop additional sites of disease during antibiotic therapy. Relapses are common and can occur at the initial site of disease or at distant locations [7, 8, 15]. Pulmonary infection may present as either a nodular infiltrate or a pneumonic consolidation. Pleural effusion or empyema may also be present. Pulmonary cavitation frequently occurs, even in patients infected with HIV, among whom cavitation caused by organisms such as *M. tuberculosis* is less common [4, 14, 25]. *R. equi* infection should be considered along with *M. tuberculosis* and *Nocardia* infections in the differential diagnosis of cavitary or nodular pneumonia. Although the data are limited, there do appear to be some differences in the natural history of *R. equi* infection between patient groups.

Immunocompetent hosts. An extensive review of *R. equi* infections in immunocompetent hosts was recently published [45]. Of the 19 reported cases, localized infections accounted for nearly 50%, including all infections in children. Pulmonary infection was present in >40% of infected patients, and disseminated infection did occur [45, 49, 50]. Two immunocompetent patients (11%) died of *R. equi* infection, although one had multiple medical comorbidities and the other was treated with inadequate antibiotics and died before *R. equi* infection was identified.

R. equi *infection after transplantation.* Approximately 10% of *R. equi* infections occur in transplant recipients, primarily as a late complication in patients receiving immunosuppressive therapy [14, 51, 52]. The prognosis for such patients is intermediate, compared with that for immunocompetent hosts and patients with HIV infection. A review of *R. equi* infections in transplant recipients [14] found that infection occurred at a mean of 49 months (range, 1–180 months) after transplantation. Eleven of the 12 patients were solid-organ-transplant recipients and 1 patient had received an allogeneic bone marrow transplant. Eleven patients were receiving immunosuppressive therapy. The lung was the primary site of infection in 10 patients. Pulmonary involvement was evenly divided between nodular and consolidative infiltrates and was often cavitary. In 50% of patients, extrapulmonary infection was present, including femur osteomyelitis, subcutaneous nodules, multiple brain abscesses, paravertebral abscess, and purulent pericarditis. Two patients died of *R. equi* infection; the

Table 1. Previously reported clinical manifestations of *Rhodococcus equi* infection.

Pulmonary nodules
Lung abscess
Pneumonia, with or without cavitation
Spontaneous pneumothorax
Wound infection
Traumatic keratitis and endophthalmitis
Bacteremia, isolated and catheter related
Fever of unknown origin and infected bone marrow
Peritonitis, spontaneous and peritoneal dialysis associated
Mesenteric adenitis, isolated or with peritonitis
Cervical adenitis
Osteomyelitis, by direct extension from pneumonia or due to disseminated infection
Septic arthritis
Brain abscess, spontaneous or postneurosurgical
Hepatic abscess, by direct extension from pneumonia or due to disseminated infection
Renal abscess
Urinary tract infection
Subcutaneous or deep-tissue abscess
Sternal-wound infection following coronary bypass grafting
Ventricular shunt infection
Bronchobiliary fistula by direct extension from pneumonia
Pedunculated and sessile colonic polyps
Otomastoiditis
Thyroid abscess
Colitis mimicking Whipple's disease
Spleen abscess
Prostate abscess

other 10 patients cleared the infection, although 1 had a relapse after 2 years.

Patients with HIV infection. HIV-infected patients account for approximately two-thirds of cases of *R. equi* infection in humans. Most studies of *R. equi* infection in patients with HIV infection were performed before the era of highly active antiretroviral therapy (HAART). In these studies, infection occurred primarily in patients with CD4 counts of <100 cells/μL, and the mortality rate was high [6, 8, 10]. Patients with HIV infection were more likely to have *R. equi* bacteremia, extrapulmonary sites of *R. equi* infection, and simultaneous opportunistic infections than were patients without HIV infection. Five of 11 HIV-infected patients described by Harvey et al. [6] had concurrent infections, including infections with species of *Pneumocystis, Cryptococcus, Candida, Histoplasma,* and nontuberculous *Mycobacterium*. The mortality rate due to *R. equi* infection was also higher among HIV-infected patients (54.5%) than among patients without HIV infection (20%). Donisi et al. [10] described 12 HIV-infected patients with *R. equi* infection and a mean CD4 count of 47 cells/μL (range, 2–164 cells/μL). Eighty-three percent of the patients had blood cultures positive for *R. equi,* and 58% of the patients died. Interestingly, *R. equi* infection was the AIDS-defining illness for 7 of the 12 patients. By inducing immune reconstitution, HAART has probably reduced the incidence of *R. equi* infection among HIV-infected patients in developed countries.

R. equi infection may be significantly underdiagnosed in developing countries with limited laboratory facilities. In a study performed in Uganda from 1995 through 1998 [25], the rate of *R. equi* infection was 1.4 cases per 1000 person-years, compared with a rate of 50.1 cases per 1000 person-years for tuberculosis (ratio, 1:36). Misdiagnosis may prompt treatment for tuberculosis with regimens that include rifampin, which promote the emergence of resistance [25]. In areas of the world where HIV infection is epidemic and laboratory facilities are lacking, *R. equi* infection should be considered in the differential diagnosis of a "*Mycobacterium*-like" illness with negative smear results.

TREATMENT

Considering the limited number of reported cases, the varying degree of host immune competence, the vast geographic distribution of disease, and the diverse clinical manifestations, it comes as no surprise that standard treatments for *R. equi* infection have not been established. Combination antibiotic therapy is the mainstay of treatment, although surgical drainage of large cavities and abscesses in sites of poor antibiotic penetration (e.g., the CNS) is probably beneficial. Surgical intervention in other cases is controversial but may reduce the microbial burden and improve the control of disease in some patients [6, 30].

Susceptibility testing should be performed for all *R. equi* isolates, to avoid the use of antibiotics to which the isolate has in vitro resistance. *R. equi* is usually susceptible in vitro to erythromycin, rifampin, flouroquinolones, aminoglycosides, glycopeptides, and imipenem. Susceptibility to cotrimoxazole, tetracycline, chloramphenicol, clindamycin, and cephalosporins is variable. Isolates are typically resistant to penicillins, and the use of penicillins is not recommended, even for susceptible isolates, because rapid acquisition of resistance can occur [8, 24, 28, 45]. In one study, linezolid was effective in vitro against all 102 strains of *R. equi* tested (MIC, $\leq$2 μg/mL) [53], but no reports of in vivo activity have been published. In a nude-mouse model of *R. equi* infection, the agents most effective for monotherapy were vancomycin, imipenem, and rifampin [54]. Despite the intrahistiocytic survival of *R. equi,* the importance of intracellular antibiotic activity is unclear. Some authors have used combinations of antimicrobials that contain $\geq$1 agent with intracellular activity. Others have argued that bactericidal activity is more important, especially during the initial phase of treatment, when both extracellular and intracellular organisms are numerous [55].

A proposed approach for the treatment of patients with *R. equi* infection, based on in vitro susceptibility data and published case reports [6–24], is outlined in figure 1. Localized infections in immunocompetent hosts can often be treated with oral antibiotics [45]. Empiric 2-drug regimens that include erythromycin, rifampin, and/or ciprofloxacin are appropriate and should be adjusted once the results of susceptibility tests are available. Newer flouroquinolones and linezolid are also likely to be effective, but fewer data are available on their effectiveness in vivo. For immunocompromised patients and patients with serious infections, intravenous therapy with 2-drug or 3-drug regimens that include vancomycin, imipenem, aminoglycosides, ciprofloxacin, rifampin, and/or erythromycin are appropriate. Regimens that include >2 drugs have been successful for some patients, but no data are available to indicate that they are superior. Most patients will require intravenous antibiotics for a minimum of 2 weeks, at which point clinical improvement should be evident. Oral antibiotics can then be substituted and continued until all culture results are negative and the patient's symptoms and radiologic abnormalities have resolved [2, 5, 7, 8, 14, 15, 52]. The duration of therapy depends on the site(s) and extent of infection, underlying immunocompetence of the host, and the clinical response to therapy. A minimum of 6 months of antibiotic therapy is typically required for immunocompromised patients with pulmonary, bone and joint, or CNS infections.

When selecting an antibiotic regimen, several important points should be considered. Acquired resistance among *R. equi*

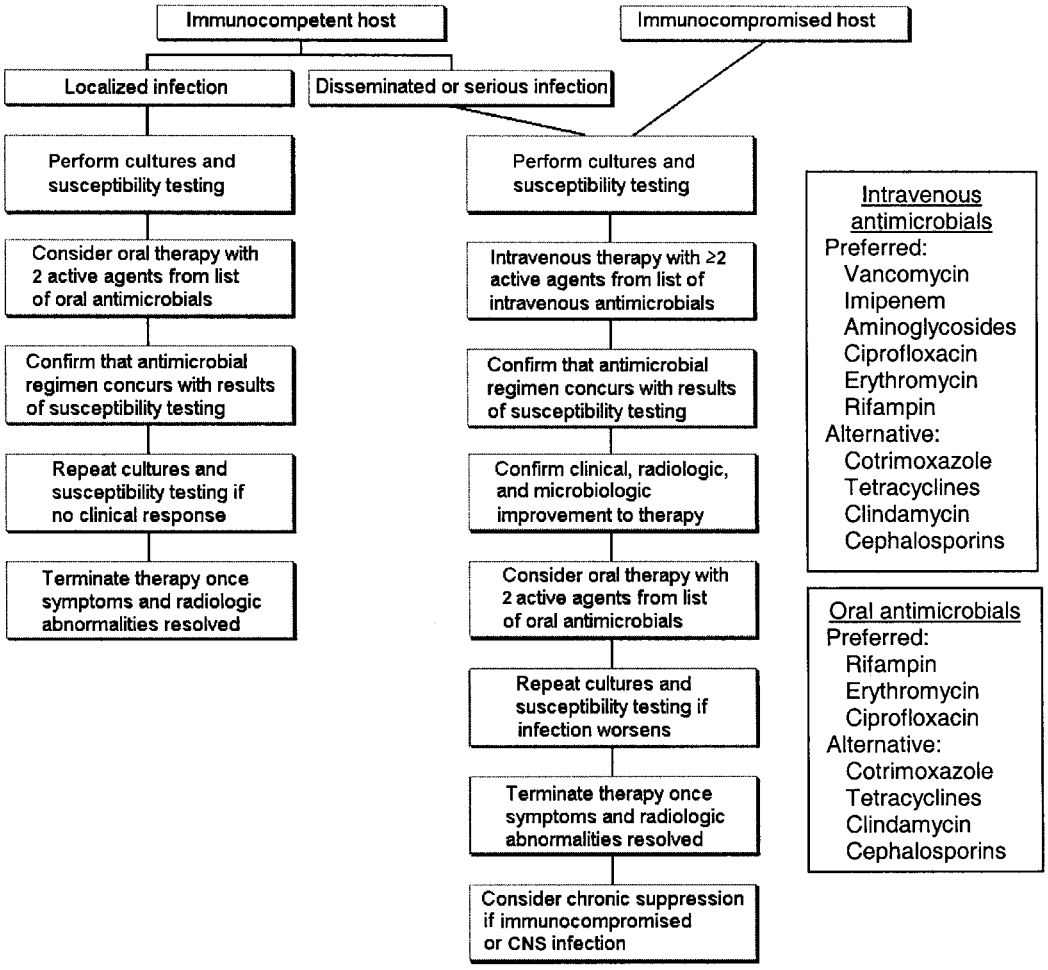

Figure 1. Proposed approach for the treatment of *Rhodococcus equi* infection. Intravenous antibiotics are typically required for initial treatment, except in the case of localized infection in an immunocompetent host. Antimicrobial agents are rated as "preferred" or "alternative" on the basis of their in vitro activity, the results of animal studies, clinical experience, and published case reports [6–24].

isolates has been reported after treatment with multiple antibiotics, including doxycycline, penicillin, erythromycin, vancomycin, cotrimoxazole, and rifampin [8, 21, 46]. Therefore, combination therapy that includes multiple agents with in vitro activity should be used. Patients must be observed closely during treatment; serial cultures and antibiotic susceptibility testing should be performed, if possible. Drug interactions in patients receiving HAART or immunosuppressants, such as cyclosporine, should also be considered. Patients who are currently receiving or recently received antibiotic therapy, including antimycobacterials and cotrimoxazole, may be more likely to harbor *R. equi* isolates that are resistant to antibiotic therapy. Patients with CNS infection should receive agents with good penetration of the blood-brain barrier. Poor enteric absorption and a history of noncompliance are relative contraindications for oral therapy. Geographic variations in *R. equi* susceptibility patterns have also been described and should be considered when selecting antibiotics for empiric therapy. For example, all 12 isolates of *R. equi* discussed in a report from Italy [10] were susceptible to vancomycin, whereas 3 of 7 isolates from Taiwan [12] were resistant to vancomycin (MIC, >4 μg/mL). After the treatment course is completed, suppressive therapy with a single agent that has in vitro activity (e.g., erythromycin or ciprofloxacin) should be strongly considered for patients with ongoing immunosuppression, immunodeficiency (e.g., patients with AIDS who fail to achieve sustained CD4 cell repletion while receiving HAART), or a treated CNS infection.

PREVENTION

Primary prophylaxis against *R. equi* is not routinely recommended, because no data are available to support its efficacy and because the infection is rare. Macrolide prophylaxis against *Mycobacterium avium* complex infection may offer some protection against *R. equi* infection for patients with AIDS. Immunocompromised patients with significant exposure to domesticated an-

imals should be cautioned regarding the possible risk of *R. equi* infection. Some investigators have advocated isolation of hospitalized patients with *R. equi* pneumonia, to prevent nosocomial spread, and this practice may be reasonable, especially considering our poor understanding of *R. equi* transmission and the previous reports of nosocomial spread [11, 29].

CONCLUSIONS

R. equi is a rare but recognized pathogen in humans and has emerged as an important cause of morbidity and mortality among immunocompromised patients. Increasing awareness of *R. equi* infection improves the likelihood of its accurate and timely diagnosis. Further clinical and laboratory research is needed to better define the routes of acquisition and the mechanisms of pathogenesis of *R. equi* infection and the appropriate treatments for it.

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