Neonatal sepsis due to *Rhodococcus equi* in two preterm infants

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We present two cases of *Rhodococcus equi* bacteremia as a cause of sepsis in premature infants who had increasing respiratory distress with multiple episodes of apnea. When we investigated these infants for apnea etiology, blood cultures were taken, and *R. equi* was confirmed based on the colony characteristics on nutrient agar; extended antibiotherapy was started. *R. equi* has been identified frequently as an opportunistic pathogen in immunocompromised patients. Infection in immunocompetent patients is rare. *R. equi* infection in the neonatal period is also rare, and to our knowledge, these are the first cases of *R. equi* as a sepsis agent in preterm infants.

**Key words:** *Rhodococcus equi*, bacteremia, neonatal sepsis, preterm infant, prematurity, apnea.

*Rhodococcus equi* (*R. equi*) is an intracellular, aerobic, gram-positive, weakly acid-fast coccobacillus. It has been recognized as an animal pathogen since its original isolation from foals with pneumonia in Sweden in 19231. The organism is commonly found in dry and dusty soil and can be important for diseases in domesticated animals (horses and goats). The route of infection is via inhalation of contaminated dust particles2. *R. equi* has been identified frequently as an opportunistic pathogen in immunocompromised patients such as human immunodeficiency virus (HIV)-infected patients or transplant recipients with or without history of animal exposure3. It causes granulomatous inflammation and eventual cavitary formation especially in the lungs. *R. equi* can also cause disseminated infection, in the brain, skin, subcutaneous tissue, pericardium, and joints4.

*R. equi* infection in the neonatal period is very rare in the literature12,13. Bearing in mind that premature infants tend to have an immature immune system, *R. equi* could be an expected potential pathogen in premature infants. Herein, we present *R. equi* bacteremia as a cause of sepsis in two premature infants.

**Case Reports**

**Case 1**

The child was born to a 31-year-old gravida 1, para 3 preeclamptic mother with intracytoplasmic sperm injection at 31 weeks of gestation by cesarean section in Hacettepe University İhsan Doğramacı Children’s Hospital. He weighed 1340 g at birth. The Apgar scores were 6 and 8 at first and fifth minutes, respectively. The mother was positive for HbsAg. The baby received 200 IU (SI units) hepatitis B immunoglobulins and hepatitis B vaccine (HB vaccine, 10 µg) intramuscularly within 1 hour after birth. On admission to the Neonatal Intensive Care Unit (NICU), the infant was intubated and developed respiratory distress syndrome requiring three doses of surfactant. Initial sepsis work-up (hemogram, peripheral blood smear, C-reactive protein, blood culture) was performed to rule out congenital pneumonia, and empiric ampicillin and gentamicin treatments were started according to our NICU policy. Sepsis work-up and blood culture were negative. On day four, the infant was extubated and placed on nasal continuous positive airway pressure for one day. On the same day, the infant received three doses of intravenous ibuprofen for patent ductus arteriosus confirmed by echocardiography. Follow-up echocardiographic examination showed closure of the patent ductus arteriosus after the ibuprofen treatment. On day eight, he had increasing respiratory distress with multiple
episodes of apnea, bradycardia and arterial desaturation. Hypothermia, poor peripheral perfusion, and reduced movements and sucking were noted on the physical examination. Cranial ultrasonography was normal. He was subsequently replaced on continuous positive airway pressure, and a complete sepsis work-up was performed. The white blood cell count was 6000/mm$^3$ with an increased percentage of immature polymorphonuclear cells (Immature/total neutrophil ratio: 0.30), and platelet count was 70000/mm$^3$. Elevated C-reactive protein was found as 4.3 mg/dl. Serum electrolytes were normal. Blood culture was performed for the second time. Meropenem, vancomycin and amikacin were started considering late-onset neonatal sepsis. The therapy regimen was intravenous meropenem 20 mg/kg/dose twice daily, amikacin 15 mg/kg/dose once daily, and vancomycin 10 mg/kg/dose twice daily. After the Bactec automated blood culture system 9120 was reported as Streptococcus spp., R. equi was confirmed based on the colony characteristics on nutrient agar and 5% sheep blood agar with typical salmon pink color four days after the extended antibiotherapy was started. The characteristics of colonies were catalase-positive, oxidase-negative, nitrate reduction-positive, alkaline phosphatase-positive, and urease-negative. Antimicrobial sensitivity test was done, and it was found to be sensitive to vancomycin and teicoplanin. Clinical improvement was seen on the fourth day of antibiotherapy. The infant responded well to antibiotic treatment, which was maintained for 10 days. It was noted that the mother was a nurse and the father was an officer living in an urban area with no history of animal or soil/dust exposure. There was no travel history to rural areas during pregnancy.

Case 2

A premature infant of 29 weeks gestation and a birth weight of 1200 g was delivered to a 29-year-old mother by cesarean section because of placenta previa. On admission to the NICU, sepsis work-up was performed, and the blood culture was negative. On day seven, the need for additional oxygen increased with multiple episodes of apnea. Echocardiography and cranial ultrasonography were normal. A complete sepsis work-up was performed. Immature/total neutrophil ratio was 0.21, elevated C-reactive protein was 5.87 mg/dl, and elevated procalcitonin was 2.63 ng/ml. R. equi was cultured in the blood sample taken on day seven as a cause of sepsis. Our therapy regimen was intravenous ceftazidime 30 mg/kg/dose twice daily, amikacin 15 mg/kg/dose once daily, and vancomycin 10 mg/kg/dose twice daily. Antibiotic treatment was maintained for 10 days with clinical improvement of the infant. The infant was discharged in a healthy condition weighing above 1700 g.

Discussion

The first human case with R. equi infection was reported in 1967 in a patient with autoimmune hepatitis who was undergoing an immunosuppressive treatment. Since then, there have been numerous reports described in immunocompromised patients. Pulmonary involvement with necrotizing pneumonia is the most frequent clinical presentation of R. equi in this population. The majority of immunocompromised cases are HIV-infected and renal transplant recipients. Extrapulmonary infection may include wound infection, subcutaneous abscesses, brain abscess, meningitis, pericarditis, osteomyelitis, cervical adenopathy, endophthalmitis, lymphangitis, and mastoiditis.

Although most of the cases are seen in immunocompromised patients, R. equi is also a cause of infection in immunocompetent hosts, at rates of 10-15%, and about one-third of infections involve children. Infection with R. equi in humans is likely through inhalation, inoculation or ingestion. Other routes of acquisition, including nosocomial and person-to-person transmission, have been reported as well. However, a review of R. equi disease in immunocompetent individuals showed no suggestive epidemiological exposures in 10 of the 19 patients in the case series. Yamshchikov et al. suggested that epidemiological exposures might be more readily evident when the patient is immunocompromised, such as in infection with HIV. In our cases, acquisition of R. equi was possibly nosocomial. Blood cultures, which were obtained initially after arrival to the NICU, were negative, and there was no history of soil or dust contamination for either mother. Second blood cultures were positive.
for *R. equi*, suggesting nosocomial acquisition. *Rhodococcus* spp. have been isolated from resident bacterial flora of healthy adults, which may be a potential route of nosocomial transmission⁹.

There is no consensus on the optimal duration and regimen of the antibiotic treatment. Combined antibiotic treatment is suggested to decrease the risk of developing resistance during therapy¹¹. The organism is usually resistant to penicillin G, oxacillin, ampicillin, and carbenicillin, and cefazolin, carbapenem and a glycopeptide, such as meropenem and vancomycin, are the preferred choices⁷,¹⁰. Some authors recommend inclusion of antibiotics with intracellular activity, such as rifampicin and azithromycin, because intrahistiocytic survival remains a major virulence determinant for *R. equi* pathogenesis¹.

The duration of total antibiotic treatment is prolonged in immunocompromised patients, up to six months⁸. Treatment duration depends on the site and degree of tissue involvement and duration of immunosuppression. Short-course antibiotic therapy is effective in immunocompetent children and adults. Devi et al.,¹² reported seven days of combined parenteral antibiotic treatment, which was sufficient in a newborn infant with localized infection. In that case, combined antibiotic treatment was given according to antibiotic susceptibility, and the treatment was stopped when the septic condition improved and follow-up negative blood culture was obtained. A combination of antibiotics according to antibiotic susceptibility is the rational way of adjusting the appropriate agents.

There are very limited reports about *R. equi* infection in the neonatal period¹²,¹³, and to our knowledge, our two cases are the first descriptions of *R. equi* as a sepsis agent in preterm infants. There is no doubt that premature neonates are more susceptible to nosocomial infections. A high index of suspicion for the diagnosis is very important because of the mortality risk of *R. equi* infection, even in immunocompetent patients, and the risk of misidentification of more common organisms, such as mycobacteria and nonpathogenic coryneform organisms.

### REFERENCES