Review Article

Current Understanding of *Rhodococcus equi* Infection and its Zoonotic Implications

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Abstract | *Rhodococcus equi* is a soil actinomycete responsible for severe respiratory disease in young foals leading to high mortality. The organism is also emerging as an important pathogen in immune-compromised humans. Intracellular localization of *R. equi* makes therapeutic management very difficult and prolonged lasting up to three months. Presently no suitable vaccine and effective serological test for early diagnosis is available. High mortality rate, non-availability of suitable diagnostic methods during early phase of infection and high cost of prolonged treatments makes it a disease of high economic importance and thus is considered among the top most disease problems affecting equine industry globally.

Keywords | *Rhodococcus equi,* Foals, Diagnosis, Treatment

Editor | Kuldeep Dhama, Indian Veterinary Research Institute, Uttar Pradesh, India.
Received | October 18, 2014; **Revised** | December 05, 2014; **Accepted** | December 07, 2014; **Published** | December 11, 2014
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Citation | Khurana SK (2015). Current understanding of *Rhodococcus equi* infection and its zoonotic implications. Adv. Anim. Vet. Sci. 3(1): 1-10.
DOI | http://dx.doi.org/10.14737/journal.aavs/2015/3.1.1.10
ISSN (Online) | 2307-8316; **ISSN (Print)** | 2309-3331

INTRODUCTION

Rhodococcus equi is a gram-positive, aerobic, non-motile, pleomorphic coccobacillus having simple nutritional requirements and forms irregular, smooth, mucoid colonies which acquire salmon pink colour in 4 to 5 days. The organism has circular chromosome of about 5 Mb, G+C content is 68.8% and may possess different plasmids (Sanger Institute, 2008). A 15-17 kDa cell surface lipoprotein known as virulence associated protein A (Vap A) is essential for virulence in foals, another cell surface lipoprotein of 20 kDa size, Vap B which is analogous to Vap A is often associated with disease in pigs and humans.

This organism is causative agent of zoonotic infections in horses, foals and some other herbivorous animals (Giguère et al., 2011a, b). *R. equi* mostly affects foals aged between one to four months (Tkachuksaad and Prescott, 1991; Yager et al., 1991; von Bargen and Haas, 2009). Disease occurs in adult horses rarely and in horses with severe immunodeficiency. The extra-pulmonary complications due to *R. equi* include enteritis often with necrosis, bone and joint infections, lymphadenopathy, diarrhoea, and abscesses in abdomen and uveitis (Giguère and Prescott, 1997). *R. equi* was first recovered from lung of a foal with respiratory illness as *Corynebacterium equi* in Sweden (Magnusson, 1923). Later, it was classified as *R. equi* (Goodfellow and Alderson, 1977).

R. equi is also an important emerging pathogen in immunocompromised human beings. Immunocompetent persons also rarely get infected. This infection was first recorded in human beings in a case of hepatitis in 1967. There are reports of *R. equi* as opportunistic pathogen in AIDS patients (Weinstock and Brown, 2002), drug therapy (Mizuno et al., 2005) and other immunosuppressive conditions (Napoleão et al., 2005).

Treatment requires prolonged combination antibiotic

therapy, primarily due to intracellular localization of this pathogen. It is reported by von Bargen and Hass (2009) that this organism arrests the phagosome maturation and resultantly forms a special niche inside the host cells. Surgical intervention also becomes essential in some instances.

The disease is direct anthropozoonosis since the animals are primary reservoirs of the etiological agent (Khurana, 2014). Comparative analysis of whole cell proteins of *R. equi* isolates from different geographical locations in India revealed varied protein banding patterns, thus varied on molecular epidemiological basis (Khurana et al., 2014), however comparable reports are not available from other countries.

The knowledge about pathogenesis, immunity, diagnostic methods, preventive and therapeutic management approaches regarding *R. equi* has increased gradually, but still no effective vaccine is available apart from newer managemental challenges including appearance of multidrug resistant virulent strains of *R. equi* (Giguère et al., 2010; Venner et al., 2012, 2013; Burton et al., 2013; Chaffin et al., 2013). Muscatello (2012) has reviewed the details regarding management, diagnosis, treatment, immunity, pathogenesis and epidemiology of *R. equi i*nfections. Vazquez-Boland et al. (2013) have described the biology, immunological and clinical aspects of the organism in great details. The present review provides an insight into current status of equine-centric *R. equi* infections as well as anthropozoonotic aspects.

ETIOLOGY OF INFECTION

R. equi is a gram-positive, pleomorphic coccobacillus and an intracellular pathogen of macrophages. It is catalase positive, oxidase negative and usually urease positive. The organism is known as *Rhodococcus* because it forms salmon pink-coloured colonies on solid media due to pigmentation. *Rhodococcus* species include symbionts as well as animal, human and plant pathogens (Bell et al., 1998). The organism is mainly soil bacteria having simple nutritional requirements and grows well in animal manure.

HOST RANGE AMONG ANIMALS AND HUMANS

R. equi primarily affects equines especially foals aged between one to four months (Prescott, 1991; Takai, 1997). Cattle (Soedarmanto et al., 1997), pigs (Mutimer and Woolcock, 1980; Soedarmanto et al., 1997), goats (Jeckel et al., 2011), camels (Kinne et al., 2011), dogs (Takai et al., 2003a), cats (Takai et al., 2003a) and human beings (Weinstock and Brown, 2002) are also affected. This organism has been isolated from a number of terrestrial and aquatic animals like crocodiles, several avian species and arthropods (Prescott, 1991). *R. equi* in human beings is reported as opportunistic pathogen in AIDS patients (Weinstock and Brown, 2002), drug therapy (Mizuno et al., 2005) and other immunosuppressive conditions (Napoleão et al., 2005).

GEOGRAPHICAL DISTRIBUTION

The disease is present worldwide with highly variable pattern (Hughes and Sulaiman, 1987). There are many endemic areas and endemic equine farms as animal manure especially horse manure is suitable for growth of this organism in soil and environment (Prescott, 1991). Disease was reported in India (Garg et al., 1985; Khurana et al., 2009; Saxena and Narwal, 2009). The prevalence of *R. equi* has been reported from several countries including Argentina, Australia, Canada, France, Hungary, Japan, Ireland and others (Ocampo-Sosa et al., 2007). *R. equi* infections have been also reported from Thailand (Asoh et al., 2003), Korea (Kim et al., 2008), USA (Weinstock and Brown, 2002; Burton et al., 2013), Denmark (Gudeta et al., 2014), Brazil (Gressler et al., 2014) and China (Liu et al., 2014).

TRANSMISSION OF DISEASE

The main route of exposure is by inhalation or ingestion (Martens et al., 1982; Johnson et al., 1983a, 1983b). The organism is present in soil and enters the respiratory tract of foal through inhalation of dust having airborne bacteria. Ingestion of soil is another common mode of transmission. Naturally occurring *R. equi* infections are mostly chronic with varying incubation period. However, incubation period ranging from 6 to 18 days has been reported in foals with an experimental dose of 10^4 cfu of virulent *R. equi* (Barten and Embury, 1987; Wada et al., 1997).

R. equi bacteria are present in the soil of most farms in large numbers, but disease pattern varies from farm to

farm. The incidence of the disease at a farm depends on the density of foals and horses at farm, climate, contamination level of organisms and virulence of the *R. equi* (Weinstock and Brown, 2002). Airborne *R. equi* bacteria are the major source of disease transmission at farms, but has direct correlation with age and immunological status of foals (Muscatello, 2009). The most susceptible age is one to four months and immunologically deficient foals are more vulnerable.

Human beings acquire infection by inhalation of airborne bacteria from dust or soil, wound or mucous membrane inoculation and from domestic animals harbouring *R. equi* (Weinstock and Brown, 2002). Horizontal transmission among human beings is rarely understood (Weinstock and Brown, 2002).

SYMPTOMS AND DISEASE MANIFESTATIONS IN FOALS/EQUINE

The disease usually occurs in one to four month old foals (Tkachuksaad and Prescott, 1991; Yager et al., 1991; von Bargen and Haas, 2009). The highest incidence of the disease is witnessed between one and a half to three months of age. This is the period when maternal antibodies decline and antibodies produced by the foal have not developed. Infectious occur rarely in adult horses and they are more common and severe in foals due to compromised immunity (Hondalus and Mosser, 1994). Protective immunity develops in adult horses and in some foals which clears the infection (Lopez et al., 2002). The disease is insidious in nature, so requires considerable experience to detect the disease in early phases. In the beginning there are diffuse bronchial sounds, later rattling sounds develop. Pyrexia along with high respiratory rate occurs within two days. Symptoms in foals include pyrexia and respiratory distress. Chronic pus filled lung abscesses in untreated foals lead to death due to asphyxiation (Wichtel et al., 1991; Lavoie et al., 1994). The disease may spread from lungs to other organs and joints (Prescott, 1991). Ulcerative enteritis, mucosal invasion of the bacteria along with diarrhoea is usual feature in chronic cases (Bell et al., 1998; Vazquez-boland et al., 2009). Development of uveitis, anaemia and thrombocytopenia, occasionally arthritis and osteomyelitis are also seen (Giguère et al., 1999). Osteomyelitis due to *R.equi* infection has been described in a mature immunocompetent horse (Watts, 2014; Kilcoyne et al., 2014). Concurrent extra-pulmonary disorders are reported in about 74% foals, though pneumonia is primary clinical manifestation (Johns, 2013).

Morbidity and mortality rates were reported to be 5-17% and 40-80% respectively in foals due to *R.equi* (Elissalde et al., 1980).

SYMPTOMS AND DISEASE MANIFESTATIONS IN HUMAN BEINGS

The most common manifestation of *R. equi* infection is pneumonia. Other manifestations include pyrexia, diarrhoea, abscessation of thyroid gland, brain, meninges and peritoneum, lymphadenitis, pericarditis, bone and joint inflammation.

Colonic polyps associated with disseminated *R. equi* infection were reported in a male patient with homosexual orientation (Talanin et al., 1998). Donisi et al. (1996) reported this organism from patients suffering from HIV. Kedlaya et al. (2001) reported that in *R. equi* infected patients, mortality rate was highest among HIV infected patients, intermediate among non-HIV infected immunocompromised patients and lowest among the immunocompetent patients. Nath et al. (2013) reported granulomatous mastitis in an immunocompetent woman due to this organism. Ferretti et al. (2011) reported dissemination of this bacterial infection in HIV patients even after application of highly active antiretroviral therapy. Brain abscess due to *R. equi* was reported in an immunocompetent patient who recovered after a prolonged antibiotic therapy (Corne et al., 2002). A case of endophthalmitis was reported in a 9 year old patient (Ebersole and Paturzo, 1988). *R. equi* infection was reported in a kidney transplant recipient who ultimately died after several relapses within a year (Menon et al., 2012). Speck et al. (2008) reported a mass in lungs due to *R. equi* infection in a kidney transplant recipient. Guyssens et al. (2010) reported invasive infections with this organism, a pulmonary form and another with brain abscess, both in immunocompromised patients.

Chronic *R. equi* infection has been reported in 47% of patients with HIV, whereas in patients with non-HIV associated immunocompromised conditions it was reported to be 17% (Verville et al., 1994). Discontinuation of antibiotics may commonly lead to relapse of *R. equi* infection. Most common site of extra pulmonary relapse is the central nervous system.

An overall mortality rate of about 25% has been reported in these infections (Cornish et al., 1999; Harvey and Sunstrum.1991). Long-term subsidence of disease manifestations have been reported especially in HIV patients (Vladusic et al., 2006).

Capdevila et al. (1997) reported that in HIV patients with *R. equi* pneumonia, the mortality rate only attributable to *R. equi* was limited to 15% only.

Prevalence of *R.equi* infections has been reported three times in men as compared to women with no racial difference (Kedlaya et al., 2001). The high mortality rate in these infections is attributed to lack of early diagnosis, misdiagnosis, insidious nature of disease and r*equi*rement of specific and prolonged antibiotic therapy.

DIAGNOSTIC PROCEDURES

Diagnosis in Foals

Firstly diagnosis at most farms is practically made on the basis of clinical symptoms. Confirmation of the disease is dependent on history of occurrence of disease on a farm or endemicity at the farm.

These infections are routinely diagnosed by cultural examination, colonial characteristics, staining characteristics and biochemical tests. *R.equi* grows well on simple solid bacteriological media. Mucoid, tear drop like colonies appear in about two days which coalesce. The salmon pink coloured pigment appears later which deepens in colour over a period of time.

Nakazawa et al. (1987) developed an agar gel diffusion test for screening of *R.equi* in foals at farms. Giguère et al. (2003) evaluated performance of various ELISAs for detection of antibodies to *R.equi*. However there was poor performance of these assays.

In India, only a few reports are available in the literature which include diagnosis of this infection by post mortem examination (Garg et al., 1985; Saxena and Narwal, 2009) and isolation of organism from clinical samples collected from infected foals (Khurana et al., 2009).

Since conventional cultural methods cumbersome and time consuming, molecular techniques are desired for early diagnosis to save the foals.

PCR assays are employed for detection *R. equi* infection, which are rapid, sensitive and specific (Sellon et al., 2001; Arriaga et al., 2002; Ladro´n et al., 2003; Pusterla et al., 2007; Letek et al., 2008). The virulence of *R. equi* is associated with plasmids encoding virulence-associated proteins predominantly protein A (VapA) or protein B (VapB) (Letek et al., 2008; Takai et al., 1991b). Avirulent *R. equi* have no virulence associated plasmids and are widely distributed in horse premises (Wada et al., 1997). Careful standardization and meticulous optimization is essential for detection of plasmids in *R. equi* isolates (Takai et al., 1991a; Makrai et al., 2002). A PCR-based assay that differentiates between strains of *R. equi* with or without plasmid and also discriminates between *vap*A and *vap*B plasmid is very valuable (Oldfield et al., 2004; Ocampo-Sosa et al., 2007; Monego et al., 2009).

Pathogenesis of *R. equi* infections is different in humans than from horses. Makrai et al. (2002) showed that 88% of the isolates of *R. equi* in foals have VapA, which is also reported about 20-25% human isolates. Pig *R. equi* isolates demonstrate VapB. The isolates of VapA origin are highly virulent, whereas that of VapB origin are of intermediate virulence. About 75% of human isolates expressed VapB (Takai et al., 2003b). IcgA is a factor identified in *R. equi t*hat negatively affects its intracellular replication and is another pathogenicity island-encoded protein which has a role in intracellular growth of this organism (Wang et al., 2014). Mc Queen et al. (2014) have identified a region on chromosome 26 associated with *R. equi* pneumonia in foals based on single nucleotide polymorphism (SNP) and copy number variant (CNV) genome-wide association studies as an evidence that genetic factors might be contributing towards occurrence of *R. equi* pneumonia in foals.

Another PCR assay of *R. equi* based on C*hoE* gene which encodes for cholesterol oxidase, is a rapid, sensitive, specific and reliable identification method (Ladro´n et al., 2003).

A combination of cultural examination along with PCR based assay is considered valuable for its diagnosis.

Differential Diagnosis

The pneumonic form should be differentiated from viral respiratory infections due to rhinovirus, herpes-

virus and influenza virus, *Streptococcus zooepidemicus*, parasitic pneumonia by migrating stages of *Parascaris equorum* and *Pneumocystis carinii*a.

Diarrhoea should be differentiated from infection due to *Salmonella* sp., parasitism due to cyathostomes and antibiotic induced diarrhoea. Joint infection should be differentiated from septic arthritis due to *Streptococcus zooepidemicus*, *Salmonella* sp. and some other bacteria.

PREVENTION AND CONTROL STRATEGIES

Prevention in Equines and Foals

Regular and proper cleaning of foal sheds, proper and frequent disposal of manure along with dust control results in reducing the levels of bacteria effectively, and hence the incidence of *R. equi* infection. Quaternary ammonium compounds (QACs), hypochlorites, chlorhexidine, iodophors and phenolic compounds are effective for control of *R. equi* on farms (Dwyer, 1995). Till date, no suitable vaccination is available due to several complicated immunological reasons including occurrence of diseases at a very early stage of life, poor humoral response and intracellular localization of this organism. If foals are administered antibiotics during the first 15 days of life, infection may be reduced to some extent as this is most probable period of infection.

Some recent studies are exploring suitable vaccine against this organism. Administration of hyperimmune plasma to foals during the first few days and then again at 3 weeks of age is reported to reduce the incidence and severity of the disease. A recent study has shown that the immunization of pregnant mares with *R. equi* vaccine candidate having aqueous medium based nanoparticle mineral oil adjuvinated inactive bacterin and VapA along with administration of anti- *R. equi* hyperimmune plasma in foals may be effective in protection of foals from *R. equi* infection (Erganis et al. 2014). Bordin et al. (2014) have studied the immunogenicity of an electron beam inactivated *R. equi* vaccine in foals. They could demonstrate that electron beam inactivates *R. equi* without affecting cell wall integrity and it was found to be immunogenic in foals when administered enterally. However, till date no effective vaccine is commercially available.

Another method of preventing the disease is simply its early detection.

Treatment in Foals/Equines

The prognosis of *R. equi* pneumonia is poor even after prolonged treatment. Erythromycin along with rifampin are antibiotics of choice (Hilldge, 1987; Sweeney, 1987). Rifampin is paired with some macrolides for treatment of foals (Giguère et al., 2004). These drug combinations are effective, but have side effects of serious nature. Treatment durations vary from two to eight week. Therapeutic management of the pathogen is complicated due to its intracellular localization making it necessary to administer prolonged treatments, sometimes even more than three months with no guaranteed outcome of successful treatment (Muscatello et al., 2007; Prescott et al., 2010).

Treatment in Human beings

Use of combination antibiotics is recommended. Rifampin-erythromycin, rifampin-minocycline, erythromycin-minocycline, imipenem-amikacin have been reported as effective combinations under *in vitro* conditions (Nordmann et al., 1992). In a case report by Scotton et al., (2000), a meningitis patient was successfully treated with levofloxacin. Munoz et al. (2008) reported successful treatment with linezolid in pulmonary *R.equi* infection. However use of single antibiotic is not recommended for treatment of systemic *R. equi* infections.

Pulmonary infections r*equi*re a prolonged course of treatment lasting more than two months. A shorter course of treatment is suggested in immunocompetent patients. Some local *R. equi* infections also require a shorter course. Early and accurate diagnosis along with proper antibiotic therapy is a key to prevent the relapses in *R. equi* infections. Local *R. equi* infections and infections in immunocompetent children have fair chances of successful treatment.

Emergence of Antibiotic Resistance

Anderson et al. (1997) demonstrated a highly significant resistance to rifampicin in *R. equi* attributable to monooxygenase like sequence. Mutations in rpoB gene leading to rifampicin resistance have been reported (Asoh et al., 2013; Liu et al., 2014). Rifampicin resistance has also been reported by other authors (Burton et al., 2013; Goldstein, 2014). Macrolide resistance in *R. equi* has also been reported (Burton et al., 2013; Liu et al., 2014). A glycopeptides resistance

operon vanO having potential implications in *R. equi* therapy has been described (Gudeta et al., 2014). Cohen (2014) has warned about the challenges of emergence of resistance to macrolide due to non-availability of effective alternative for *R. equi* therapeutics.

Rifampicin along with macrolide is drug of choice for effective treatment of *R. equi* infections. Therefore emergence of resistance against these antibiotics poses a serious challenge in therapeutic management and there is an urgent need for judicious use of antibiotics.

FUTURE OUTLOOK

There are no suitable serological tests for early and accurate mass screening diagnosis due to complex immunological status of the infection. Suitable vaccination is also not there due to of similar reasons. This organism is very versatile and goes across species. Since the organism resides intracellularly, treatment with conventional antibiotics is not successful. Emergence of multi drug resistant strains is also an upcoming challenge which needs to be researched and tackled suitably. There seems to be a need for early and accurate diagnostic tests so that both foals and human patients may be saved. At present molecular diagnostic tools are available but these are required at grass root level for human patients and in field for foals and other animals. There is a need for development of suitable vaccines especially for foals, but age at which the disease occurs coupled with its complex immunological nature makes the proposition very difficult. Preventing disease by proper management and sanitation at farms is very important. Special care and hygiene for immunocompromised humans is also very essential.

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