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Review Articles

A REVIEW ON *Rhodococcus Equi*: HORSE, CAT AND HUMAN

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SUMMARY

In recent years, *Rhodococcus equi* has emerged as pathogen of importance in respiratory and non-respiratory infectious diseases of animals and humans. Its distribution is worldwide and incidence of disease is increasing in non-equine species like cats and humans. Sporadic infection in human and cat is hypothesized to infect immunocompromised cases largely. While predominantly in foals, infection is quite endemic/epidemic in nature depending on virulence of strain, and incidence is 10 – 20% since birth till weaning. Mode of acquisition is quite variable in humans, cats and foals and depends on the route of exposure. Pathogenesis is well understood in natural host but in cats and humans it is still in its infancy because of the manifestation of unusual cases with low to no exposure to contaminated elements. Clinical signs depend on the site of infection but respiratory manifestations are quite common in foals and human cases. In cats extra-pulmonary disorders are hypothesized as more common presentation. Definitive diagnosis is based on the microbiological culture and cytology from tracheobronchial aspirate for respiratory cases and site of sample for non-respiratory lesions. White blood cells and fibrinogen have some correlation in degree of diagnosis in foals but not in cats and humans. Macrolides especially clarithromycin along with rifampin are considered best combination at the moment and recently resistance is being reported against erythromycin and rifampin. In foals, consensus statements by ACVIM published detailed control and preventions but in humans and cats so far hygiene and isolation of infected patients are for the time being the methods to control nosocomial spread.

Keywords: infection, respiratory, epidemiology, transmission

INTRODUCTION

The word "*Rhodococcus"* was firstly described by a German botanist "Wilhelm Friedrich Zopf" in 1891 during classification of pigment producing bacterial and fungal organisms (Zopf, 1891). Later on, the members (organisms similar to *nocardiaform* and *mycobacterial* species) of inappropriately named *rhodochrous complex* were also included in genus *Rhodococcus,* redefined in 1977 (Goodfellow & Alderson, 1977).

The organism was formerly known as *Corynebacterium equi* and *Mycobacterium equi* (Finnerty, 1992; Shinji Takai, 1997). Currently, *Rhodococcus equi (R. equi)* is classified in family *Nocardiaceae* and order *Actinomycetales* but a proposal had been made in 2013 to reclassify this organism as *Prescottia equi* (Jones *et al*., 2013). *R. equi* is ubiquitous, facultative, intracellular, non-motile, telluric, gram-positive coccobacillus bacterium that is capable of infecting macrophages by interfering phagolysosomal fusion and has zoonotic potential as well (Muscatello *et al*., 2007; Passamonti *et al*., 2011; Trevejo *et al*., 2005). *R. equi* might appear as coccoid or rod depending on the growth environment and the life cycle's phase (Hines, 2014).

EPIDEMIOLOGY OF *Rhodococcus Equi*

R. equi is distributed worldwide including Asia, Europe, Australia, South and North America continents with highly variable pattern (Khurana, 2015). This bacterium can be cultured from the soil, faeces of herbivores especially horses and horse farm and around equine breeding area because of its widespread nature. Also, its presentation is virtually considered in all equine related areas (Barton & Hughes, 1984; Shinji Takai, 1997; Shinji Takai *et al*., 1986). Optimal conditions for bacterial growth are 30 degree celsius temperature, aerobic environment with pH between 7.5 – 8.0 (best 7.3) and faecal enriched soil as compare to soil alone. Organic acids present in horse dung are supportive elements for the bacterial survival and growth (Hughes & Sulaiman, 1987).

Very first clinical case of *Corynebacterium equi* (classified later in 1977 as *R. equi*) related respiratory illness in a foal was reported in Sweden (Magnusson, 1923). Recently, *R. equi* has been isolated as resident aerobic microbiota of a healthy nasal cavity in human which can become opportunistic pathogen in immunocompromised patients (Rasmussen *et al*., 2000). Furthermore, It has been isolated abundantly from contaminated soil surface (Shinji Takai *et al*., 1986), infected or exposed foals (actual colonization in intestine) and adult horse faeces as passive intestinal carriage from contaminated soil (Shinji Takai, 1997). Also, this pathogen has been isolated from contaminated wounds, abscess and pyogranulomatous lesions of muscles, bones, body organs like liver, spleen, lymph nodes, eyes, trachea, vagina, joints and lungs of infected foals, cats, dogs, goats, cattle including immunocompromised humans and many more wild animal species like monkeys and wild boars too (Aslam *et al*., 2019; Bryan *et al*., 2017; Fairley & Fairley, 1999; Gunew, 2002; Khurana, 2015; Passamonti *et al*., 2011; Stranahan *et al*., 2018; Shinji Takai *et al*., 2001; Shinji Takai *et al*., 2003).

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Incidence and host range among animals

The disease is quite sporadic in nature in non-equine hosts like cats, dogs, goats, cattle, monkeys and wild boars and very few cases have been reported so far, but it can be endemic or epidemic in nature in equine host. Generally, the incidence of disease is considered to be 10 – 20% in foals since birth till weaning, although higher cumulative incidence has also been calculated in some studies (Cohen, 2014). Pneumonia associated with *R. equi* tends to be confined to younger animal in equines and typically seen between the age of 1 to 6 months (Gary Muscatello, 2012a). Horses that are more than 1 year are rarely affected by this infection but if there is any report, most of the time accompanying immunodeficiency factor (Cohen, 2014). A previously reported comprehensive case study in a 10-years old horse diagnosed with *R. equi* related pleuropneumonia, suggested that perhaps this type of infection is being overlooked in adult horses and also negated immunodeficiency factor, as it was not proven in this particular case (Vengust, *et al*., 2002).

R. equi has been considered an emerging pathogen causing disease in immunocompromised patients like HIV, renal transplant and AIDS patients, although immunocompetent people also get infected in rare cases (Khurana, 2015).

The disease has been diagnosed in cat population at minimum age of 2 months kitten (suppurative bronchopneumonia) until 15 years (extrapulmonary lesion) in reported cases till date. Also, extrapulmonary form was considered predominant in cat population, and inefficient immune system was hypothesized as predisposing cause in most of these studies which still remained unproven (Aslam *et al*., 2019; Fairley & Fairley, 1999; Gunew, 2002; Passamonti *et al*., 2011; Shinji Takai *et al*., 2003). In cats, this disease is important because < 20% cases of the feline pyothorax occur because of non-oropharyngeal infectious agents and *R. equi* is one of them (Barrs & Beatty, 2009). In documented cases of a dog population, minimum age reported was between 3 to 12 years where pulmonary and extra-pulmonary pathologies were found, and also immunodeficiency factor was hypothesized as predisposing cause (Bryan *et al*., 2017; Shinji Takai *et al*., 2003). In goats, age distribution was between 1 – 4 years with pulmonary and extrapulmonary lesions, while in a monkey, infection was diagnosed at the age of 6 months presented with interstitial pneumonitis (Stranahan *et al*., 2018; S. Takai *et al*., 2001).

Epidemiological factors of disease characterisation

Factors characterising epidemiology of the infectious diseases can be related to environment, host and infectious agent itself (Lilienfeld *et al*., 1994). Virulence levels of *R. equi* have been described as: avirulent, intermediate and virulent. The type of virulence associated proteins (Vaps) and virulence plasmid DNA is the determinant of severity of disease in different species (Passamonti *et al*., 2011). In this aspect, three host-associated virulence plasmid types have been described in recent scientific studies, viz. the pVAPA (equine specific), pVAPB (porcine specific) and pVAPN found in ruminant (bovine) isolates (Witkowski *et al*., 2016).

There are emerging reports on isolation of one host associated virulence plasmid type from other species like pVAPN and pVAPB isolated from human cases which are actually bovine and porcine specific, respectively (MacArthur *et al*., 2017). About 20 – 25% cases of immunocompromised humans were reported to be infected by VapA virulent strain (Shinji Takai *et al*., 1995). In dogs and cats only avirulent and VapA positive isolates have been reported so far (Shinji Takai *et al*., 2003). Because of the close association and high degree of similarity of the plasmid profiles of VapA isolates from dogs and cats with horses, there are highly likely chances that they carried infection from equine-loaded premises or perhaps from their environment contaminated with *R. equi* (Passamonti *et al*., 2011).

About 50 - 95% of horse farm's soil have been reported to be concentrated by *R. equi* (Yamshchikov *et al*., 2010). The cumulative incidence of *R. equi* pneumonia is not dependent of soil concentration of virulent strain but air-borne concentrations have been positively correlated with disease (G Muscatello *et al*., 2006). Exposure of the newborn by virulent strain and further raring and management was considered a major risk factor for disease development. Those foals, born in a foaling stall which was exposed heavily to a virulent strain were more prone to disease as compared to the foals born in pastures and paddocks (Cohen *et al*., 2005).

Host factors such as less than 6 months of age (Gary Muscatello, 2012a), immune response (naïve or deficient) and immune function such as expression of interferon gamma are remarkably less in foals as compared to adults (Breathnach *et al*., 2006), and changes in the gene expression of leukocytes with ageing in response to *R. equi* can also play a key role in disease development (Kachroo *et al*., 2013). Although there are some studies which found that immune function of newborn foals were quite conflicting in response to infection or vaccine-based immunity development. For example, in one vaccination study (live intracellular bacterial or killed or attenuated viral), response of newborn foals was not the same as that of adults (Ryan & Giguere, 2010; Sturgill *et al*., 2014). On the other hand, in another study, response of stimulated interferon gamma was the same by an adult horse and a ten-days-old foal (Jacks *et al*., 2007). Some reported predisposing factors of human infection are AIDS, HIV, hemolymphatic tumor (usage of steroids), renal transplant, corticosteroid therapy, excessive alcohol usage, penetrating eye injury, raw carrots ingestion and hepatic fistula (Prescott, 1991).

Conclusively, further work is needed in this area for host factor to be considered as the key player in disease development. An anecdotal evidence of genetic susceptibility to *R. equi* infection has also been reported in a previous study where in some affected stallions and mares did not produce same form of disease as with other groups, under similar exposure (Halbert *et al*., 2006).

Mode of transmission

Possible routes of transmission of *R. equi* are: inhalation, inoculation of wound and mucous membranes

or transcutaneous infection or contamination of wound, ingestion or food-borne transmission, and dissemination to distant sites by hematogenous route. In foals, the predominant route of bacterial transmission is inhalation followed by ingestion (Gary Muscatello, 2012a). Contamination of the wound is also rarely reported in this specie (Hondalus, 1997).

In humans, possible routes of *R. equi* transmission are exposure to contaminated manure of domestic animals especially foals and soil, inhalation, and inoculation into a wound or mucous membrane (Doig *et al*., 1991; Khurana, 2015; Weinstock & Brown, 2002; Yamshchikov *et al*., 2010). Nosocomial route of infection was also reported in the past (Scotton *et al*., 2000). In a previous study, pet animals like cats and dogs infected with *R. equi* can possess some risk of infection to just immunocompromised human patients, they are otherwise not suggested as source of infection for humans (Shinji Takai *et al*., 2003). Food-borne transmission (like pigs) can contribute to the probability of disease development in human patients (Makrai *et al*., 2008).

Contrary to foals and humans, in cats and dogs; the most common route of transmission is transcutaneous infection of wounds followed by aerogenous route which can finally disseminate to body cavities and organs through hematogenous route (Fairley & Fairley, 1999; Passamonti *et al*., 2011; Shinji Takai *et al*., 2003). A recent report on goats documented respiratory-acquired *R. equi* and its further dissemination by hematogenous route and some cases of wound contamination also, which may hypothesize similar mode of transmissions in domestic animals just like the occurrence in in foals, dogs and cats (Stranahan *et al*., 2018).

PATHOGENESIS OF *R. Equi*

The pathogenesis of *R. equi* in its natural host foal is well understood and well documented by Gary Muscatello (2012a), whereas, it is considered an emerging pathogen in other accidental or opportunistic hosts like dogs, cats, humans, domestic and wild animals like goats, cattle, wild boars, and monkeys. It is hypothesized that it may act differently in terms of pathogenesis in non-equine hosts. Also, it is hypothesized that other host's immune system responds differently when infected by *R. equi* (Aslam *et al*., 2019; Hondalus, 1997; Khurana, 2015; Passamonti *et al*., 2011).

The infectivity of *R. equi* is limited to monocyte or macrophage lineage where replication also takes place (Hondalus & Mosser, 1994) and eventually leads to the death of infected cells by inhibition of phagosome-lysosome fusion. On the other hand, neutrophils are considered completely bactericidal in foals (Meijer & Prescott, 2004). Consequence of infection is migration of large number of inflammatory or protective cells of the body which finally lead to granuloma formation (Hines, 2014). In human, there is little known about the immune response to *R. equi* because of their infectivity with avirulent strains of *R. equi* and inefficient cell-mediated immunity (mandatory to control *R. equi* infection) in immunocompromised patients. Hence, they can possess a different pathogenesis in future experimental studies (Kanaly *et al.,* 1993; Shinji Takai *et al*., 1994).

Further work was suggested by previous studies in other species like humans, cats, and pigs infected with *R. equi*, because of their unclear pathogenesis and predisposing factors, although the same might be true for a large range of other non-equine species also like dogs, goats, cattle and camels (Aslam *et al*., 2019; Hondalus, 1997; Kinne *et al*., 2011; Makrai *et al*., 2008; Passamonti *et al*., 2011).

CLINICAL SIGNS OF *R. Equi Infection*

Because the major route of transmission of infection is inhalation and ingestion & principle pathogenicity is regarded in equine specie, so lungs and intestines have been described as predilection sites in foals by manifesting pyogranulomatous bronchopneumonia and ulcerative enterotyphlocolitis, respectively (Gary Muscatello, 2012a). Although, extrapulmonary disorders (EPDs) such as ulcerative lymphangitis, pyogranulomatous lymphadenopathies, pyogranulomatous hepatitis, peritonitis, pericarditis, granulomatous meningitis, subcutaneous abscess, immune mediated polysynovitis and haemolytic anaemia, osteomyelitis and arthritis type consequences have also been reported in foals (Reuss *et al.,* 2009). Manifestation of EPDs with primary predilection site's infection has been correlated with poor survival rate of 43% by 82% without EPDs (S Giguère *et al*., 2011).

In a recent review on *R. equi*, Khurana (2015) documented pneumonia as the most common manifestation in humans. Although, extrapulmonary disorders like fever, diarrhea, abscess of brain (Corne *et al*., 2002), meninges, peritoneum and thyroid glands, lymphadenitis, pericarditis, polysynovitis, osteoarthritis, osteomyelitis, colonic polyps (Talanin *et al*., 1998), lung mass (Speck *et al*., 2008), granulomatous mastitis (Nath *et al*., 2013) and endophthalmitis (Ebersole & Paturzo, 1988) were also seen especially in immunocompromised human patients. Highest mortality rate has been reported among HIV patients, intermediate rate among non-HIV immunocompromised patients and lowest rate was reported among the immunocompetent patients (Kedlaya *et al.,* 2001). They also reported overall mortality rate of 25% in human patients infected with *R. equi*. Tables 1, 2, and 3 elaborate the comparative clinical signs, affected organs and extra-pulmonary signs in human, horses and cats from previously documented reports and reviews

DIAGNOSIS OF *R. Equi* INFECTION

Just based on the major (pneumonia) or minor (extra-pulmonary lesions) clinical signs, it is not possible to diagnose disease associated with *R. equi*, unless patient belongs to an endemic area but still other infections possessing similar clinical signs can be overlooked (Barrs & Beatty, 2009; Prescott & Hoffman, 1993). A number of tests can be used in disease diagnosis like complete blood count, blood chemistry parameter like fibrinogen, radiological procedures like radiographs, and serological tests like enzyme-linked immunosorbent essay (ELISA).

Table 1: Clinical signs of *R. equi* infection in different species

Symptoms	Humans No. (%)	Horses No. (%)	Cats No. (%)
Fever	61 (91)	109 (68)	[5]5 (12.5)
Cough	59 (88.1)	115 (71)	[2]1 (16.7); [5]5 (12.5)
Pneumonia/ Bronchopneumonia	64 (95)/--	161 (100)/--	[5]36 (90); [3]Group of kittens
Abnormal lungs sound	--	75 (47)	[2]1 (16.7); [5]11 (27.5)
Expectoration	57 (85.1)	--	--
Chest Pain	30 (44.8)	--	--
Haemoptysis	21 (31.3)	--	--
Dyspnea/ Respiratory Failure	20 (29.8)/--	70 (43)/--	[5]35 (87.5); [1]1 (100)
Tachypnea	--	50 (31)	[5]19 (47.5)
Asthenia	17 (25.4)	--	--
Weight loss	16 (23.9)	--	[5]7 (17.5)
Anorexia	12 (17.9)	--	[5]26 (65)
Diarrhea/ Gastroenteric signs	04 (06)/--	--	[5]2 (5); [1]1 (100)
Headache	02 (03)	--	--
Tumor	02 (03)	--	[4]1 (09)
Dysarthria	01 (1.5)	--	--
Lethargy/ Depression	--	85 (53)/--	[5]8 (20) / [2]1 (16.7)
Nasal discharge	--	50 (31)	[5]2 (5)
Polysynovitis	--	1 (0.6)	--
Pyothorax	--	--	[5]32 (80); [3*]1 (100)
Musculoskeletal manifestations	--	--	[5]4 (10); [2]5 (83.3); [4]7 (63.6)
Total number of cases	**67**	**161**	[1]**1** [2]**6** [3]**Group of kittens**; [3*]**1** [4]**11** [5]**40**
References	(Torres-Tortosa *et al*., 2003)	(Chaffin *et al*., 2011)	[1](Passamonti *et al*., 2011), [2](Fairley & Fairley, 1999), [3](Gunew, 2002), [4](Shinji Takai *et a*l., 2003), [5](Aslam et *al*., 2019)

Table 2: Organ affected by *R. equi* in different species

Affected Organs	Humans No. (%)	Horses No. (%)	Cats No. (%)
Lung	64 (95.5)	[1]161 (100)	[5]36 (90); [1,2,3]3 (--) [3*]Group of kittens
Pleura	10 (14.9)	[2]5 (3)	[5]32 (80); [3*]1 (100)
Peritoneum	--	[2]11 (7)	--
CNS	03 (4.5)	[2]5 (3)	[2]1 (16.7)
Skin and soft tissue	03 (4.5)	[2]8 (5)	[2]5 (83.3) ; [4]7 (63.6) [5]4 (10)
Mediastinum	01 (1.5)	--	[5]36 (90); [3*]1 (100)
Thyroid	01 (1.5)	--	--
Liver	01 (1.5)	[2]16 (11)	[5]30 (75)
Heart	01 (1.5)	[2]6 (4)	--
Blood	40 (59.8)	[2]11 (7)	[3*]1 (100)
Kidney	--	[2]7 (5)	[5]3 (7.5)
Peripheral lymph node	--	[2]11 (7)	--
Intestines	--	[2]50 (33)	[1]1 (100); [5]2 (5)
Joints	--	[2]14 (9)	--
Bone/Bone marrow	--	8 (5)	--
Eye	--	[2]16 (11)	--
Total number of cases	**67**	[1]**161** [2]**150**	[1]**1** [2]**6** [3]**Group of kittens**; [3*]**1** [4]**11** [5]**40**
References	(Torres-Tortosa *et al*., 2003)	[1](Chaffin *et al.,* 2011) [2](Reuss *et al*., 2009)	[1](Passamonti *et al*., 2011), [2](Fairley & Fairley, 1999), [3](Gunew, 2002), [4](Shinji Takai *et al*., 2003), [5](Aslam et *al*., 2019)

Table 3: Extrapulmonary signs for *R. equi* in different species

Humans	Horses n=150 (%)	Cats
Pyrexia	Diarrhea 50 (33)	[1]Wound infection
Diarrhea	Immune mediated polysynovitis 37 (25)	[1]Subcutaneous abscess
Abscessation of thyroid gland	Ulcerative enterotyphlocolitis 31 (21)	[1,5]Soft tissue pyogranulomatous lesion
Abscessation brain, [2]kidney and [2]liver	Intra-abdominal abscesses 25 (17)	[1]Vaginitis
Abscessation of meninges	Abdominal lymphadenitis 25 (17)	[1,5]Hepatitis
Abscessation of peritoneum	Uveitis 16 (11)	[1]Osteomyelitis
Lymphadenitis (cervical, mesenteric)	Pyogranulomatous hepatitis 16 (11)	[1]Myositis
Pericarditis and [2]ventricular shunt	Septic synovitis 14 (9)	[1,5]Lymphadenitis mediastinal
Osteomyelitis	Mediastinal lymphadenitis 12 (8)	[1]Mesenteric lymphadenitis
Synovitis	Peritonitis 11 (7)	[3]Contaminated ulcerated tissue
Colonic polyp	Peripheral lymphadenopathy 11 (7)	[2]Depression
Granulomatous mastitis	Bacteraemia (*R. equi*) 11 (7)	[2]Lameness
Endophthalmitis	Subcutaneous abscesses 8 (5)	[2]Firm swelling of legs
Bacteraemia (*Rhodococcus equi*)	Pyogranulomatous nephritis 7 (5)	--
[2]Spontaneous pneumothorax	Hyperthermia 6 (4)	--
[2]Traumatic keratitis	Pericarditis 6 (4)	--
[2]Peritonitis (dialysis related)	Osteomyelitis 5 (3)	--
[2]Septic arthritis	Pleural effusion 5 (3)	--
[2]Urinary tract infection	Granulomatous meningitis 5 (3)	--
[2]Prostate abscess	Vertebral body osteomyelitis 3 (2)	--
[2]Spleen abscess	Paravertebral abscess 3 (2)	--
[2]Otomastoiditis	Cellulitis/lymphangitis 2 (1)	--
[2]Broncho-biliary fistula	Immune-mediated haemolytic anaemia 2 (1)	--
(Khurana, 2015) [2](Weinstock & Brown, 2002)	(Reuss *et al*., 2009)	[1](Passamonti *et al*., 2011), [2](Fairley & Fairley, 1999), [3](Shinji Takai *et al*., 2003), [4](Aslam et *al*., 2019)

to distinguish *R. equi* pneumonia from other aetiologies (Steeve *et al.,* 1997). Radiography and computed tomography scan (CT Scan) are also used in human cases as supportive diagnostic aids (Kedlaya *et al*., 2001; Stewart *et al*., 2019). Consensus statements of American College of Veterinary Internal Medicine (ACVIM), however, consider microbiological culture in conjunction with polymerase chain reaction (PCR) for amplification of VapA gene as the gold standard. Samples can be collected by tracheobronchial aspiration (TBA) or trans-tracheal wash (TTW) for bronchopneumonia and from the sites of extra-pulmonary lesions. For inclusion criteria, supportive clinical signs, cytological and radiological aids should be considered for bronchopneumonia cases of horses to run these diagnostics (S. Giguère *et al*., 2011; Heidmann *et al*., 2006).

Radiological findings in different species

In previous human studies containing radiological findings related to *R. equi* infection, there is a contradicting statement regarding upper lung lobe infection being the most common or preferred site. Previous studies (Muntaner *et al*., 1997; Yamshchikov e*t al*., 2010) documented cavitary lesion oriented upper lung lobes pneumonia as most common finding, but (Kedlaya *et al*., 2001) negated this statement because of almost-equal involvement of upper, middle and lower lung lobes in their study. Furthermore, in a previous retrospective study for evaluation of *R. equi* infection in 67 HIV-infected human patients, revealed more or less same results for all lung lobes without any preferred or most common predilection site. Chest radiographs were abnormal in 97% cases with 67% containing cavitary lesions. Involvement of multiple lobes, pleural effusion and mediastinal lymph nodes was noticed in 19%, 16%, and 3% cases, respectively (Torres-Tortosa *et al*., 2003).

Another study (Kedlaya *et al*., 2001) also reported 62% patients with pneumonia findings on radiographs but reasonably low (5%) pleural effusion findings as compared to that of Torres-Tortosa *et al*., (2003) where it was 16%, although sample size was smaller (19 cases) in this study. Broncho-biliary fistula was also noticed in 5% cases. Thick walls with air or fluid filled spaces are characteristics of cavities formed with *R. equi* infection (Cornish & Washington, 1999).

In another retrospective study of 48 human cases, abnormal radiographic findings were noticed in 100% of cases and cavitation was reported in 77% radiographs. This study concluded a criteria for strongly suspected immunocompromised (AIDS, HIV patients) candidates infected with *R. equi.* And included parameters were low

CD4 lymphocytes (<200 mm^3), cavitary lesion in chest radiographs especially in upper lobe region and subacute onset with poor response to conventional antibiotic therapy (Muntaner *et al*., 1997). CT scan and magnetic resonance imaging (MRI) is more sensitive to characterize lesions associated with *R. equi* infection (Marchiori *et al*., 2005; Nath *et al*., 2013).

Radiography is considered one of the most frequently used diagnostic technique for foals suspected to be infected with *R. equi* (Steeve Giguère & Prescott, 1997). A predominant alveolar pattern with regional consolidation and abscess/es characterized by discrete nodular or gas filled cavitary lesion are commonly seen in foals infected with this bacterium. Dorsal displacement of trachea was also reported because of tracheobronchial lymphadenopathy. Syndrome of sporadic bronchointerstitial pneumonia (severe dyspnea and radiographically bronchointerstitial pattern) can be a sequalae of *R. equi* related pneumonia (Lakritz *et al*., 1993). Thoracic abscess as a feature of radiological diagnosis of *R. equi* infection has sensitivity of 71% and specificity of 85% in foals (Leclere *et al*., 2011). A distinct reticulonodular lesion type miliary pattern was also reported in one of the previous study where *R. equi* was a concurrent infection with another bacteria (Ainsworth *et al*., 1993).

Ultrasonography is a useful technique for screening foals at earlier stage of disease (Gary Muscatello, 2012b) but the only drawback is it can demonstrate superficial lesions. Comet tail appearance of the lung fields and fluid or air-filled pockets raise index of suspicion for veterinarian to look for further radiological and diagnostic procedures for the diagnosis of pneumonia in foals at early stages (Ramirez *et al*., 2004; Slovis *et al.,* 2005). Manifestations on thoracic radiographs depend on the clinical progression of the disease. Initial stages of disease can show an interstitial pattern and/or consolidation but in advanced stages of infection nodular pattern of variable size is seen on chest radiographs (Heidmann *et al*., 2006). As some cases of *R. equi* pneumonia can display bronchointerstitial pattern only without any evidence of abscess on radiographs, in such cases CT scan and MRI can be the more sensitive and useful tools to characterize lesions. These advanced modalities are best in the diagnosis of extra-pulmonary lesions, for instance brain abscess caused by these bacteria. In a previous study, CT scan was used to diagnose a mediastinal abscess caused by *R. equi* in a foal (Wion *et al*., 2010).

Currently, there is only one study on radiological feature of this disease in cats where mixed alveolar-interstitial, pleural effusion, hepatomegaly, thoracic lymphadenopathy, atelectasis of any lung lobe, consolidation of any lung lobe, cavitary or mass opacity lesions and pneumothorax were predominant findings (Aslam *et al*., 2019). Also, it is hypothesized that this infection causes more extra-pulmonary disease in cat host instead of pulmonary infection (Passamonti *et al*., 2011). Barrs & Beatty (2009) reviewed new insights in the investigation of feline pyothorax and documented that less than twenty percent of cases occurred because of unusual bacteria like *R. equi*, *E. coli*, *Nocardia* spp., *Salmonella* spp., *Proteus, Pseudomonas* and *Klebsiella* spp. Pleural effusion with rounding of costophrenic angles and retraction of lung lobes from thoracic wall and prominent lobar edges and fissure are therefore characteristics of chest radiographs of cats with pyothorax. Abscess or cavitary lesions on lung tissues and pyothorax have been reported in a cats infected with *R. equi* (Aslam *et al*., 2019; Gunew, 2002). Abnormalities in the tracheobronchial and retrosternal lymph nodes and abdominal organs especially liver and kidney have been reported in a recent studies of cats diagnosed with R. equi (Aslam *et al*., 2019; Passamonti *et al*., 2011).

Haematology and biochemistry findings in different species

In human patients, haematological and biochemical findings are not specific nor sensitive for *R. equi* because of the opportunistic type of infection in already sick or immunocompromised patients. An average white blood cell (WBC) count in human cases documented 8.1 x 10^9/L with a range of 3.8 – 19.1 x 10^9/L (Doig *et al*., 1991). CD4+ has been checked in many previous studies and looked retrospectively also with an average of 35/µL (range 01–183/µL). Most of the time, this infection occurs in HIV patients with <200/µL CD4+ cells and chronic pulmonary cavitary lesion/s (Torres-Tortosa *et al*., 2003; Vechi *et al*., 2018). None of the previous human study on *R. equi* could demonstrate any consistent striking biochemistry pattern.

Steeve Giguère & Prescott (1997) described complete blood count (CBC) with hyperfibrinogenaemia (consistent finding) and biochemistry profiles highly useful parameters to raise the index of suspicion in foals infected with *R. equi* with supportive clinical signs. Another study also (Leclere *et al*., 2011) reported a specificity of 86% for white blood cells and 92% for fibrinogen if leukocyte count is >20,000 cells/µL and hyperfibrinogenaemia of >700 mg/dL. In differential cell count, neutrophilia with or without monocytosis was most a common finding.

Previous study (Steeve Giguère *et al*., 2003) reported that white blood cell count has significantly greater diagnostic performance as compared to fibrinogen concentration in foals. These parameters have lots of variations when compared with cases of similar clinical signs produced by other infectious agents. Thrombocytosis can be seen with acute or chronic inflammation and it was reported as significant parameter in foals infected with In *R. equi*, but this was also declared quite a variable parameter later on (Steeve Giguère & Prescott, 1997). Elevated globulin levels were also seen in some cases of foals (Hines, 2014). Increased white blood cells are significantly correlated with EPDs of foals. Cases of foals with bronchopneumonia or with non-specific clinical signs carrying significantly high number of WBCs should warrant further detailed investigation to look for EPDs (Reuss *et al*., 2009).

Based on the reported clinical signs in previously available studies, neutrophilic changes with left shift ± monocytosis and/or lymphocytosis and mild to moderate anaemia can be possible findings in haematology as it is consistently seen in infectious feline pyothorax (Barrs *et al*., 2005; Demetriou *et al*., 2002). Neutropenia can also

be seen in cases with degenerative left shift (Barrs & Beatty, 2009). Common serum biochemistry profile changes in cats diagnosed with pyothorax are, hypoalbuminaemia with hyperglobulinaemia, low sodium, chloride and calcium levels and mild elevations of aspartate aminotransferase (AST) and bilirubin level (Barrs & Beatty, 2009; Demetriou *et al*., 2002). Leukocytosis because of neutrophilia with/without left-shift, monocytosis and thrombocytopenia were prominent findings in hematology reports of cats infected with *R. equi*. In serum biochemistry changes in the proteins level were predominant findings causing low albumin to globulin ratio (Aslam *et al*., 2019).

Cytological findings

Cytology is considered as supportive diagnostic along with microbiological culture. Cytological characteristics are described quite similar in all reported species. An intra- or extracellular gram-positive pleomorphic (cocci to coccobacillus) rod on cytological evaluation of infected or contaminated specimen supports the presence of *R. equi* (Heidmann *et al*., 2006; Hines, 2014). In foals, identification of these bacteria is highly specific (91%) from tracheal aspirate but sensitivity (35%) of the test is quite poor (Leclere *et al*., 2011). Commonly these bacteria are seen in histiocytes, macrophages and neutrophils on cytological examination as shown here in Figure 1. In previous studies of different species, intrahistiocytic presence was reported in goat sample (Stranahan *et al*., 2018), macrophages and neutrophils carrying pleomorphic bacteria had been reported in dogs (Bryan *et al*., 2017) and cats (Fairley & Fairley, 1999). It is not necessary that bacteria will be present in all cytological samples as they can be low in number or may be difficult to detect. On a routine basis, a combination of cytology of tracheal aspirate and microbiological culture can be adapted as valuable tools to improve the quality of diagnosis. In a previous study, confirmed *R. equi* was cultured for 48 samples but only 61% of the samples were positive on tracheal aspirate cytology (Anzai *et al*., 1997; Sweeney *et al*., 1987).

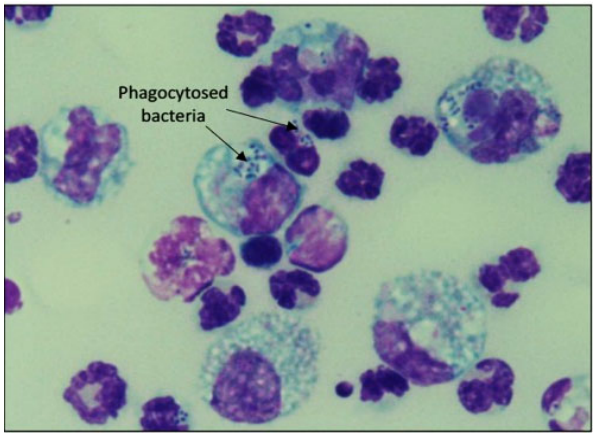

Figure 1. A cytological smear of *R. equi* from thoracic fluid of a cat presented with severe respiratory distress due to bilateral pleural effusion. Pyogranulomatous inflammation was diagnosed due to the presence of abundant neutrophils and macrophages. Pleomorphic phagocytosed bacteria noticed in macrophage. (1000x, Wright's stain, UVH, FPV, UPM, Malaysia)

Pathological findings in different species

A typical and common *R. equi* lesion is abscesses formation in pulmonary parenchyma (McCracken, 2015). In humans also pneumonia is the most common presentation which is further confirmed by radiological procedures and cytological examination of samples of lesions on lung parenchyma. Necrotizing pneumonia with abscess formation is characteristic lesion in pulmonary form (Emmons *et al*., 1991). This lesion, histopathologically termed as malakoplakia (acquired granulomatous disease) is characterized by heavy infiltration of histiocytes and concentric scattered basophilic Michaelis-Gutmann bodies (Alfano *et al*., 2019). Histopathology of extra-pulmonary lesions were also described in human reports, where biopsies taken from caecum, ascending and transverse colon showed similar type of cellularity and heavy infiltration of histiocytes (Hamrock *et al*., 1999).

In foals, because of the virulence-associated severity and endemic nature of the disease, lesions are well described and demonstrated in previous studies. Firm nodular lesions were seen as in multiple dispersion or giant coalescing form, are characteristics of gross lung lesions. These lesions (often described as abscess) are separated from atelectatic or congested lung lobes. Miliary pyogranulomatous lesions can also be seen in some cases. Distribution can vary on both sides of the lungs or it can be throughout the lungs. Sometimes pleural fluid is also noticed. Thoracic lymphadenopathy is often seen in such cases, characterized by oedematous, caseous and necrotic in appearance (Hines, 2014).

Histopathologically in foals, bronchiolitis, necrosis of alveolar septum with infiltration of macrophages, giant cells and neutrophils are seen at earlier stages with or without engulfed intact bacteria. Lymphocytes and plasma cells are also seen in interstitial zones and alveolar septum. In later stages, spectrum of alveolar septal necrosis increase in larger areas of the pulmonary parenchyma and produce caseous necrotic material termed as pyogranulomatous lesions. Oedema, congestion, interstitial fibrosis and hyperplasia of type II pneumocytes are also noticed commonly in histopathological lesions (Hines, 2014; Lakritz *et al*., 1993). Pyogranulomatous and/or suppurative lesions are usually seen in most of the extra-pulmonary disorders listed in Table 3.

With regards to cats, similar type of cell population was noticed in lung and subcutis histology in previously reported cases. Alveolar septal necrosis, detached pneumocytes, macrophages engulfing pleomorphic bacteria, neutrophils, giant cells, lymphocytes and plasma cells were noticed in histopathological section of lung (Passamonti *et al*., 2011). In subcutis histopathological section, macrophages engulfing pleomorphic bacteria with clear cytoplasm and neutrophils were reported

(Fairley & Fairley, 1999). In a single cat study, report of gross lung lesions appearance for *R. equi* infection was white foci scattered multifocally all over the lungs field with increased consistency without any prominent consolidation. Mucopurulent exudate and mild oedema were noticed from cut surfaces of the lung lobes. Tracheobronchial lymphadenopathy, pale colour enlarged liver and renomegaly were also reported in the same study (Passamonti *et al*., 2011).

TREATMENT CONTROL AND PREVENTION

Generally, best medical practice is to preform antibiotic susceptibility test for the rationale use of antimicrobial therapy in all species presented with infectious diseases. In humans, despite the use of broad spectrum, lipophilic antibiotics with high penetration ability, mortality rate is still high as most of the cases carry concurrent immunosuppressive disorders (Donisi *et al*., 1996). *R. equi* is an intracellular pathogen and replicating in macrophages, hence antibiotics having good penetrating ability in cells and have strong lipophilic properties are tested as best treatment choices. Many drugs show high *in-vitro* sensitivity but are reasonably poor in *in-vivo* efficacy, as demonstrated by a previous study where penicillin and gentamicin therapies resulted in high mortality, despite tested as highly sensitive drugs against *R. equi* strain in infected foals (Sweeney *et al*., 1987).

A wide range of antibiotics have been shown to be effective in many reported cases and retrospective studies in the past (Kedlaya *et al*., 2001) but combination of macrolide (erythromycin, azithromycin, clarithromycin) and rifampin remain the therapy of choice for *R. equi* infection in humans and horses (S. Giguère *et al*., 2011; Steeve Giguère & Prescott, 1997; Khurana, 2015). In this combination, clarithromycin-rifampin is superior as compared to azithromycin and erythromycin with rifampin (Giguére *et al*., 2004). In cats, amoxicillin, gentamicin and lincomycin have been recommended in previously reported studies (Passamonti *et al*., 2011). Gunew (2002) used doxycycline to treat *R. equi* related pyothorax in a cat. Fairley & Fairley (1999) tested combination of erythromycin and rifampin in a cat diagnosed with *R. equi* and proved effective. In the same study, another four cats were treated successfully with amoxicillin clavulanic-acid combination for musculoskeletal pathologies related to *R. equi*. Aslam *et al*., (2019) reported significant resistance in cats tested against cephalexin, clindamycin, tetracycline, metronidazole and potentiated amoxicillin as treatment choices for *R. equi*. On the other hand combinations of the rifampin with macrolides and/or fluoroquinolones were considered acceptable options as some cases improved and/or recovered with these combinations. Only antimicrobial therapy is not sufficient for management of feline rhodococcosis cases a number of factors can impart in final outcome of disease like pyothorax management and oxygen therapy.

Since 2007, significant increase in resistance (P <0.001) of *R. equi* towards erythromycin and rifampin is seen especially from tracheobronchial aspirate, lungs and musculoskeletal samples in foals (Huber *et al*., 2018). Consensus statements of the ACVIM suggested poor or worse prognosis for foals infected with resistant strains of *R. equi* (S Giguère *et al*., 2011).

In humans, mortality rate depends on the immune status of the host and reported almost 11%, 50 – 55% and 20 – 25% in immunocompetent, HIV-infected immunodeficient and non-HIV immunodeficient cases, respectively (Kedlaya *et al*., 2001). An overall survival rate of 60 – 90% reported with current amicrobial therapies with their resistance status in foals (Hines, 2014). On the other hand, an overall survival rate of 72% was reported in another retrospective study (Ainsworth *et al*., 1998) from 115 foal cases. In cats, data about survival and outcome is quite variable because of limited number of cases and studies. Most of the cases with extra-pulmonary disorders survived and responded well to antibiotics as compared to pulmonary cases where only one study showed complete resolution of pulmonary manifestation (Fairley & Fairley, 1999; Gunew, 2002; Passamonti *et al*., 2011). On the other hand, Aslam *et al*., (2019) reported a recovery rate of only 32.5% in 40 cats diagnosed with pulmonary and extra-pulmonary form of the disease. In the same study all 4/4 cats with cutaneous form of the disease died because of the poor response to antimicrobial therapy.

Control and preventions are very important and documented well in natural host of this bacterium because of the severity of the diseases and losses attached with this infection but weightage is not given in human host studies as it is opportunistic for them. In cats, there are no data available on control and prevention. In human cases, prophylactic usage of macrolides against mycobacterium tuberculosis complex in immunocompromised hosts might have also given some support to control this infection. Exposure should be reduced as much as possible and infected patients should be isolated to prevent nosocomial spread (Weinstock & Brown, 2002). While in foals, screening tests for example, white blood cell count and ultrasound for early detection of the disease, environmental management, active and passive immunization, and chemoprophylaxis are control and preventive methods documented comprehensively by Hines (2014) and also recommended by consensus statements of American College of Veterinary Internal Medicine (S. Giguère *et al*., 2011).

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