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# A Review on Emerging Zoonotic *Mycoplasma*

**Neelam Rani*, PiyushTomar, P. K. Kapoor and Y. Singh**

Department of Veterinary Public Health and Epidemiology

College of Veterinary Sciences

Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar-125004 (Haryana)

*Corresponding Author E-mail: neelamvet2011@gmail.com

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**ABSTRACT**

*Haemoplasma is a zoonotic mycoplasma and act as a cofactor in the progression of retroviral, neoplastic and immune-mediated disease. Haemoplasmas can be transmitted horizontally as well as vertically.The relapse of the haemoplasmosis may coincide with the introduction of systemic glucocorticoids in the treatment of various other diseases. For the identification and control of emerging zoonotic haemoplasmal diseases we require a "One Health" approach, which demands combined efforts of physicians, veterinarians, epidemiologists, public health workers and urban planners. Collaborative international routine surveillance strategies prompt reliable genetic identification techniques, and optimization of the treatment regiments will ensure the prevention and management of such infections. This review highlights the important haemoplasmas species, classification, diagnosis and their remedy for control of the diseases caused by haemoplasmas.*

***Key words:*** *Haemoplasma, Mycoplasma, Immuno-suppression, Zoonotic pathogens*

## INTRODUCTION

Haemoplasmas is a group of uncultivated, erythrocyte parasitizing bacteria of the genus *Mycoplasma* within the Mollicutes class that can result in infectious anaemia[15]. Disease manifestations in animals are most often reported in association with drug- or retrovirus-induced immuno-suppression, with stressors such as poor nutrition, pregnancy, or lactation, or with concurrent infection with another, more virulent pathogen[12,16,21,30,23]. Hemotropic *Mycoplasma* spp. represent emerging, zoonotic pathogens that pose poorly defined health risks for animals and humans throughout the world[22,20,4].

No other group of prokaryotes has been so involved in controversy and in establishing a clear pathogenic niche as the mycoplasmas. Their virulence determinants are complex and their unique biological properties likely challenge the host differently from typical bacterial pathogens[10,28]. Due to lack of *in vitro* cultivation systems for the isolation of these haemoplasmas has hampered and delayed their detection and characterization in humans and animals.

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The development of new and improved molecular techniques, particularly PCR amplification and DNA sequencing, has facilitated improved diagnostic detection, as well as the recognition of several zoonotic animal haemoplasmas. In this review classification of zoonotic mycoplasma, its pathogenicity, transmission and diagnosis have been reviewed.

**Classification of Haemoplasmas:**

Haemoplasmas are classified within the genus Mycoplasma based on 16S rRNA gene and RNase P RNA gene phylogeny[15,13,17]. They are divided, based on phylogeny (rather than pathogenicity or host specificity), into two groups: a haemominutum group and a haemofelis group[17,25]. In many domestic and wild animal species, haemoplasmas have been identified to cause haemolytic anaemia[1,7,8,13,14,19,31]. Previously, based upon molecular confirmation, only five hemotropic *Mycoplasma* spp. were described as causes of human infections: *Mycoplasma haemofelis*-like, *Mycoplasma suis*-like Yuan *et al*.[33], *Mycoplasma ovis*[21], "*Candidatus* Mycoplasma haemohominis"[18], and "*Candidatus* Mycoplasma haematoparvum"[11], organisms.

**Mechanisms of Pathogenicity:**

It is well established that the haemoplasmas attach to the surface of the red cells but may under certain conditions penetrate this host cell[9]. The pathogenic potential of haemotropic mycoplasmas as a cause of human disease has not been clearly understood but these emerging zoonotic pathogens may pose a more serious public health concern. Many mycoplasmal pathogens exhibit filamentous or flask-shaped appearances and display prominent and specialized polar tiporganelles that mediate attachment to host target cells[9]. These are the complex structures, composed of a network of interactive proteins, designated adhesins, and adherence accessory proteins. These proteins cooperate structurally and functionally to mobilize and concentrate adhesins at the tip and permit mycoplasmal colonization of mucous membranes and eukaryotic cell surfaces, probably through host sialoglyco-conjugates and sulfated glycolipids[6]. It appears that mycoplasmal cytadherence-related proteins represent a superfamily of genes and proteinsthat have been conserved through horizontal gene transfer from an ancestral gene family. This protein network resembles a specialized cytoskeleton like apparatus, which may represent the precursor to mammalian cytoskeletal and extracellular matrix like complexes. Other *Mycoplasma* species lack distinct tip structures yet are capable of cytadherence, and they may use related genes or proteins or alternative mechanisms of surface parasitism[6].

Survival of pathogenic mycoplasmas within mammalian cells has been debated for many years. The mycoplasmas are highly fastidious and dependent upon the host microenvironment and complex culture medium for growth; have been observed in close contact with mammalian cell surfaces and within target cells; may be capable of initiating fusion with host cells through their cholesterol-containing unit membranes; and survive long-term recommended antimicrobial treatment in humans and tissue cultures[27]. In addition to the evidence supporting vector transmission, poor sanitary settings appear to increase the risk.

Other biological properties of mycoplasmas have been implicated as virulence determinants and include 1) generation of hydrogen peroxide and superoxide radicals by adhering mycoplasmas, which induces oxidative stress, including host cell membrane damage; 2) competition for and depletion of nutrients or biosynthetic precursors by mycoplasmas, which disrupts host cell maintenance and function; 3) existence of capsule-like material and electron-dense surface layers or structures, which provides increased integrity to the mycoplasma surface and confers immunoregulatory activities; 4) high-frequency phase and antigenic variation, which results in surface diversity and possible avoidance of protective host immune defenses; 5) secretion or introduction of mycoplasmal enzymes, such as phospholipases, ATPases,

hemolysins, proteases, and nucleases into the host cell milieu, which leads to localized tissue disruption and disorganization and chromosomal aberrations; and 6) intracellular residence, which sequesters mycoplasmas, establishes latent or chronic states, and circumvents mycoplasmicidal immune mechanisms and selective drug therapies[27].

**Transmission routes:**

Haemoplasmas may be transmitted by transfer of infected blood (blood transfusion or use of contaminated needles, surgical instruments, herd or flock management equipment) or via arthropod vectors such as lice, flies, ticks, and mosquitoes[3]. Vertical transmission from mother to offspring has been reported in cats, swine, and camelids[3]. Direct transmission associated with fighting is suspected in cats and supported by studies reporting presence of hemoplasma DNA in saliva, on gingiva, and on claw beds of infected cats[3].

**Disease in humans and animals**

The Haemoplasmas vary in their ability to cause clinically significant hemolytic anemia. These bacteria induce persistent asymptomatic intravascular infections in wild and domestic animals and are not considered to be highly pathogenic[3]. Therefore, hemotropic mycoplasma infections are often chronic in nature; however, hemolytic anemia of variable severity, often in association with other infectious or non infectious diseases, has been reported in animals[3].The clinical signs depend on the stage of infection, degree of anemia, and the immune status of infected animals. The *M. haemominutum* infections are more severe in case of coinfection by feline leukemia virus. The most common clinical signs are pale mucous membranes, inappetence, depression, weakness, and icterus and splenomegaly. Inacutely infected cats fever also occurs and may be intermittent in some chronically infected cats. Evidence of coexisting disease may be present. Weight loss is common in chronically infected cats[3]. In chronic phase of cats disease can be subclinically present and have recurrence of clinical disease following periods of stress. A greater percentage of cats with fever are infected with *M. haemofelis* than cats without fever suggesting the organism can be associated with fever of unknown origin. The macrocytic normochromic anemia occurs in haemoplasmosis but may be macrocytic, hypochromic if coinfections leading to chronic inflammation exist. Chronic non-regenerative anemia is unusual in haemoplasmosis. The disease is rare in humans and manifests with fever, swollen lymph nodes, an enlarged spleen and liver, worsening anemia, leucopenia, thrombocytopenia and sometimes mild hepatitis and subclinical myocarditis[3].

This disease in animals are most often reported in association with retrovirus or drug induced immunosuppression, with stressors such as poor pregnancy, nutrition, or lactation, or with concurrent infection with another, more virulent pathogen. After an initial infection is controlled, either naturally or after antibiotic treatment, protective immunity develops against repeat *M. haemofelis* infection. Hemoplasmas are capable of causing a hemolytic anemia, but the severity varies greatly[21]. In healthy adult animals asymptomatic infections tend to occur, and more severe acute anemias are associated with splenectomy, immunocompromise, concurrent diseases (such as feline leukemia virus or feline immunodeficiency virus in cats), or multiple hemoplasma species coinfection. The *M. haemofelis* is the main exception, which causes acute hemolytic anemia in healthy cats. The severe anemia may be present and occasionally fatal. Typical clinical signs include lethargy, anorexia, and fever, with splenomegaly and icterus occurring less often. Acute hemolysis in dogs that are splenectomized occurs due to *M. haemocanis* infections, but infections are usually asymptomatic in healthy dogs. In neonatal pigs, feeder pigs, and pregnant sows; *M suis* causes hemolytic anemia accompanied by icterus. Poor growth rates, decreased conception rates, reproductive failure, and decreased milk production occurs in chronic infection. The sheep and goats that are infected with *M. ovis* infection are often asymptomatic, but hemolytic anemia can occur

in young animals, especially those with heavy intestinal worm burdens. Poor weight gain, exercise intolerance, decreased wool production, and mild anemia are the common sequalae in chronic infection. Sykes *et al*.[21], reported a first case of human infection in a veterinarian with an

*M. ovis*-like organism who was coinfected with *B. henselae* reported. In camelids, haemoplasma infection can cause a severe hemolytic anemia in young ones. The chronic infection prevalence is high in sheep, pigs, and kennel-raised dogs and outbreaks of acute disease have been reported in animals during research studies.

**Diagnosis:**

Diagnosis of haemoplasmosis in animals has historically relied on cytological aspiration of enlarged lymph node and peripheral blood smear showing typical rings or cocci organisms. But the observation of organisms on erythrocytes in blood smears is known to be unreliable compared to PCR. In particular, sensitivity is very poor ranging from 0 to 37.5%[2,24,25,29]. Although specificity is higher, with values of 84–98% reported, it must be noted that these figures are based upon experienced board-certified veterinary clinical pathologists interpreting blood smears and that lower specificity is common when smears are examined by individuals lacking experience in haemoplasma diagnosis[2,24,26]. Based upon the visualization of organisms on stained blood smears only, researchers in Inner Mongolia, China, reported regional human hemotropic mycoplasma infection rates as high as 35.3% (population tested, 1,529 people), with infection rates of up to 57.0% in local pregnant women and 100% in new borns from infected mothers[32]. Similarly, a high prevalence of infection was found among farmers and veterinarians working with swine in China, most specifically in Shanghai, where 32 of 65 workers (49%) were PCR positive for an *M. suis*-like infection[32]. All three of these published reports from China support a greater risk of haemotropic mycoplasma infection among farmers, veterinarians, and other individuals who have frequent and close contact with domestic animals that serve as reservoir hosts[32]. PCR is now the preferred method of diagnosis[17]. The hemoplasma infections results in hemolysis which is typically extravascular and results in a regenerative anemia. Erythrocyte agglutination may be present, and Coombs' test results are often positive in cats infected with *M haemofelis*. The positive Coombs' test could also be found in splenectomized dogs with acute hemolysis along with agglutination and spherocytosis due to *M haemocanis*. Hypoglycemia secondary to glucose consumption by the pathogen has been reported in heavily parasitized pigs, sheep, llamas, and calves; however, rapid bacterial glycolysis in vitro may also cause artifactually decreased blood glucose concentrations.

**Treatment and Control:**

The tetracyclines (doxycycline, oxytetracycline) have been the choice of treatment for acute infections. Enrofloxacin and marbofloxacin have also been effective against *M haemofelis*[3]. The erythro-phagocytosis could be decreased by giving Glucocorticoids and may be useful to in cases of severe hemolysis whereas some animals may require blood transfusion[3]. Periodic clinical relapses are common in treated patients. To prevent transmission of haemoplasmas, blood donors should be screened using PCR-based DNA assays. Properly sterilized needles and equipment should be used to avoid iatrogenic transmission. Entry of arthropod vectors should also be controlled, as is minimizing stress in herd and flock situations[3].

## CONCLUSIONS

Haemoplasmas act as a cofactor in retroviral, neoplastic and immune-mediated disease. The relapse of the hemoplasmosis may coincide with the introduction of systemic glucocorticoids in the treatment of various other diseases. The limitation in *in vitro* cultivation systems for the isolation of these cell wall-deficient bacteria has hampered and delayed their detection and characterization in humans and animals. The development of new

and improved molecular techniques, particularly PCR and DNA sequencing, has facilitated improved diagnosis as well as the recognition of zoonotic haemoplasmas but there is a need for additional research and documentation of role of vectors in disease transmission. For the identification and control of emerging zoonotic haemoplasmal diseases we require a"OneHealth" approach, which demands combined efforts of physicians, veterinarians, epidemiologists, public health workers and urban planners. Collaborative international routine surveillance strategies prompt reliable genetic identification techniques, and optimization of the treatment regiments will ensure the prevention and management of such infections.

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