Hemotropic Mycoplasma

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KEYWORDS

• Hemoplasma • Hemoparasite • Infectious anemia • Vector-borne disease
• Zoonosis

KEY POINTS

- Hemoplasma infections are erythrocytic infections found in both cats and dogs but are more common, and more often associated with disease, in cats.
- *Mycoplasma haemofelis* is the most pathogenic species in cats, causing hemolytic anemia and fever in immunocompetent hosts, whereas *Mycoplasma haemocanis* usually only results in hemolytic anemia in dogs that are splenectomized or immunocompromised.
- Diagnosis is by polymerase chain reaction on blood samples because cytology is unreliable.
- Prompt treatment of clinical disease with supportive care and at least 2 weeks of doxycycline is usually successful.
- Transmission pathways have not been confirmed, but indirect, via vectors, and direct via bites/fights/predation are likely.

INTRODUCTION

The hemotropic mycoplasmas (hemoplasmas) are small (0.3–1.0 μm) wall-less gram-negative bacteria that infect erythrocytes; most species live on the erythrocyte surface (**Fig. 1**), but a porcine hemoplasma species has been shown to reside intracellularly within erythrocytes. Hemoplasmas infect a wide range of hosts worldwide including cats, dogs, rodents, pigs, cattle, sheep, horses, bats, beetles, and people. Infection can result in a hemolytic anemia of variable severity, depending on the host and the infecting hemoplasma species. Individual hemoplasma species can also comprise several genotypes,[1] so it is possible that different genotypes of a species influence pathogenicity.

HEMOPLASMA CLASSIFICATION

The hemoplasmas were initially classified as rickettsial organisms within the Haemobartonella and Eperythrozoon genera, but sequence analysis of the 16S rRNA gene of hemoplasmas resulted in their reclassification within the genus *Mycoplasma*.[2–4]

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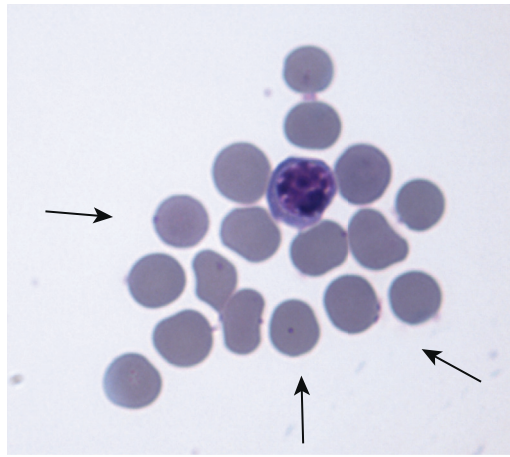

Fig. 1. Romanowsky-stained blood smear from an 8-year-old male neutered domestic shorthair cat showing epierythrocytic bacteria typical of *Mycoplasma haemofelis* (*arrows*), reproduced with permission.[159]

Although hemoplasmas share similarities with the mycoplasmas, such as small size, fastidious in vitro growth requirements, and absence of a cell wall, they also differ in their target cell (erythrocyte rather than mucosal cells). It has been proposed that hemoplasmas warrant being in a separate genus to that of the *Mycoplasma* species within the family Mycoplasmatale.[5]

HEMOPLASMA SPECIES INFECTING CATS AND DOGS

Several different species of hemoplasma exist, which vary in pathogenicity (**Table 1**).

Three major species infect cats:

- *Mycoplasma haemofelis*
- *'Candidatus* Mycoplasma haemominutum'
- *'Candidatus* Mycoplasma turicensis'

Two major species infect dogs:

- *Mycoplasma haemocanis*
- '*Candidatus* Mycoplasma haematoparvum'

Occasionally '*Ca* M turicensis',[6,7] '*Ca.* M. haemominutum',[6,8–10] and a species similar to the latter,[11] have been detected in dogs, as has the ovine *Mycoplasma ovis*,[12] the bovine '*Candidatus* Mycoplasma haemobos',[13–15] and the porcine *Mycoplasma suis*.[16] A '*Ca.* M. haematoparvum'-like organism has also been reported in a small number of cats.[17,18] Of these species *M. haemofelis* and *M. haemocanis* are the most pathogenic and important species in cats and dogs, respectively.

PREVALENCE OF HEMOPLASMAS IN CATS AND DOGS

Hemoplasma prevalence figures vary greatly in different studies; this may be due to differences in geography/climate (which may influence possible vector distribution), whether the cats and dogs sampled are healthy and/or anemic, sample types (eg, blood or tissue samples) and detection methods used (eg, cytology, polymerase chain reaction [PCR], and whether PCR assays detect/distinguish all hemoplasma species

Table 1
Hemoplasma species infecting cats and dogs, their prevalences determined by polymerase chain reaction (PCR) in global studies, and an outline of their pathogenicity

Hemoplasma Species Name	Host Species	Reported PCR Prevalence Range (Median)	Outline of Pathogenicity
Mycoplasma haemofelis	Cat	0.0%–28.6% (4.8%)	Acute infection can result in hemolytic anemia and fever in immunocompetent cats
'*Candidatus* Mycoplasma haemominutum'[a]	Cat	0.0%–66.7% (14.6%)	Acute infection induces a decrease in erythrocyte values, but hemolytic anemia does not usually result unless cat has comorbidities or is immunocompromised, eg, retrovirus infection, neoplasia
'*Candidatus* Mycoplasma turicensis'[a]	Cat	0.0%–10.0% (1.4%)	
Mycoplasma haemocanis	Dog	0.0%–52.4% (7.6%)	Infection can result in hemolytic anemia in splenectomized dogs
'*Candidatus* Mycoplasma haematoparvum'[a]	Dog	0.0%–33.3% (2.0%)	Hemolytic anemia does not usually result unless dog has concurrent disease or is immunocompromised, eg, chemotherapy

[a] Some species have the status *Candidatus*, which is the name used for newly described species for which genetic sequence data are available but which cannot be phenotypically characterized to the level required by the International Code of Nomenclature of Bacteria due to the inability to grow them in vitro.[160] The species *M. haemofelis* and *M. haemocanis* do not have the *Candidatus* status, even though they have not yet been grown in vitro, because they represent the previously existing *Haemobartonella felis* and *Haemobartonella canis* species, respectively. Bacterial nomenclature forbids the "demotion" of any bacterial species, including during renaming.

in that host animal). **Table 1** shows the major published prevalence ranges for each hemoplasma species based on the use of PCR as diagnosis:

- In cats, '*Ca.* M. haemominutum' is the most common species, followed by *M. haemofelis* and then '*Ca* M turicensis'
- In dogs, *M. haemocanis* is usually the more common species, then '*Ca.* M. haematoparvum'
- Dual, and triple in cats, hemoplasma species infections can occur. '*Ca.* M. turicensis'-infected cats are often dual infected with another hemoplasma species, especially '*Ca.* M. haemominutum'

WHAT RISK FACTORS EXIST FOR HEMOPLASMA INFECTION?

Feline Hemoplasmas

In cats, many studies have found that male, older, nonpedigrees with outdoor access are more likely to be infected with feline hemoplasmas (especially '*Ca.* M. haemominutum').[1,17,19–32] Some studies have also shown significant associations for all or some hemoplasma species and retrovirus infection,[17,18,20,22,23,28,29,33–35] especially feline immunodeficiency virus [FIV],[21,27,36–42] whereas others have not.[31,43,44] An association between anemia/reduced erythrocyte values and hemoplasma infection

(especially *M. haemofelis*) is sometimes seen in studies[24–26,32,33,38,40,42,45–47] but is often not present,[18–21,28,31,37,38,48–52] probably due to the existence of chronic subclinical infections. In one US study, '*Ca.* M. haemominutum'-infected cats were less likely to be anemic than non-'*Ca.* M. haemominutum'-infected cats.[17] Only a few studies have looked at the presence of vectors as risk factors for feline hemoplasma infection, and in these, no association has been found with either fleas[18,53] or ticks.[18]

Canine Hemoplasmas

In one large study, in dogs, kenneled, young crossbreeds and those with mange were more likely to be hemoplasma infected,[54] whereas other studies have found no association with age[21,55–62] or found that dogs older than one[63,64] or two[7] years were more likely to be infected. An association between being male and hemoplasma status has only been reported in a few canine studies,[7,56,65] whereas most do not find an association with gender,[11,15,21,41,54–62,66–68] in contrast to feline hemoplasmas. An association with anemia is not commonly found,[21,54–59,69,70] with pathogenicity largely confined to case reports of symptomatic dogs.

Hemoplasma infection is said to be common in fighting dogs,[70–72] which suggests that horizontal transmission may be possible between dogs. Potential vectors are also implicated as risk factors for canine hemoplasma infections. In some studies, associations exist between canine hemoplasma infections and both other vector-borne infections,[21,67] particularly *Babesia* spp (notably *Babesia vulpis* and *Babesia gibsoni*),[70,72–74] and the presence of ticks[15,65,67] or ectoparasites in general.[11,68] Other studies have failed to show any association with ticks,[56,57,63] so results are variable. Living in a rural[7,63] or free-roaming[13,41,67] setting may also be a risk factor for canine hemoplasma infection.

PATHOGENESIS OF HEMOPLASMA INFECTION

Mycoplasma haemofelis

This is the most pathogenic of the feline hemoplasma species, with acute infection causing severe hemolytic anemia (primarily extravascular, but occasionally intravascular is reported[75]) in immunocompetent cats with no other comorbidities. Osmotic fragility[75,76] and reduced erythrocyte lifespan[77] occur. Younger cats are likely to develop severe clinical disease.[78,] A regenerative response with reticulocytosis occurs following anemia.[29] Acute *M. haemofelis* infection can also be associated with the development of erythrocyte-bound antibodies, demonstrable by the presence of persistent autoagglutination or a positive Coombs' tests,[76,80,81] although the role of these antibodies in the development of anemia is not known[81] and cats with erythrocyte-bound antibodies respond to antibiotic and supportive treatment alone, without the need for specific glucocorticoid treatment. Experimental infections have shown that *M. haemofelis* blood organism numbers can markedly fluctuate over the course of a day or two in the first few weeks of infection, possibly due to antigenic variation and evasion of host immunity,[82] important to consider when interpreting PCR results. In addition, chronic *M. haemofelis* infection is usually subclinical with no anemia.[31]

'Ca. M. haemominutum'

This species is less pathogenic, rarely causing clinical anemia, but infection is associated with a small fall in erythrocyte numbers.[81] Cats with comorbidities (eg, lymphoma, immunosuppression or feline leukemia virus [FeLV] infection)[83,84] are more likely to develop anemia following '*Ca.* M. haemominutum' infection; however, splenectomized cats do not seem to be at an increased risk of developing disease.[85]

Nevertheless, there are reports of primary '*Ca.* M. haemominutum' anemia in cats without comorbidities.[86]

'*Ca* M. turicensis'

Our understanding of the pathogenesis of '*Ca.* M. turicensis' is more limited. Experimental infection can result in anemia[75] or a small decrease in erythrocyte numbers,[81] but generally clinical anemia is not common. Comorbidities are both thought to be involved in the pathogenesis of '*Ca.* M. turicensis' disease,[32,75] as for '*Ca.* M. haemominutum'.

M. haemocanis and 'Ca. M. Haematoparvum'

Less data are available on the pathogenesis of canine hemoplasma species, and anemia is not commonly associated with infection.[87] Infection with *M. haemocanis* and '*Ca.* M. haematoparvum' usually only results in hemolytic anemia in splenectomized or immunocompromised dogs.[88–96]

Subclinical Carrier Status of Hemoplasmas

Long-term subclinical carrier status can occur in both cats and dogs with hemoplasma infections.[30,55,97] Subclinical infections are particularly common with '*Ca.* M. haemominutum' infection, although clearance of infection can occur with and without antibiotic treatment.[31] Some *M. haemofelis*- and '*Ca.* M. turicensis'-infected cats spontaneously clear infection a few months following acute infection. The host immune response, as well as infecting species, is likely to be play a role in the outcome of hemoplasma infection. Reactivation of infection can result in clinical disease, but this seems to be rare.[78,98–100]

Immunity to Hemoplasmas

The existence of dual and triple hemoplasma infections in hosts suggests that cross-protection across the hemoplasma species does not occur. Indeed, a study has shown that not only were '*Ca.* M. turicensis'-recovered cats *not* protected against *M. haemofelis* challenge, they became PCR-positive for *M. haemofelis* significantly earlier than the naive cats, suggesting possible antibody-dependent enhancement.[101] Furthermore, passive immunization via transfusion of a small volume of pooled plasma from *M. haemofelis*-recovered cats failed to provide protection from infection with *M. haemofelis* and may have exacerbated clinical disease.[102] *M. haemofelis*- and '*Ca.* M. turicensis'-recovered cats are protected against rechallenge with the same species,[103,104] suggesting immunity due to previous infection; this may suggest that if animals do clear infection after acute hemoplasmosis, they may be immune to reinfection with the same species but still susceptible to infection by other hemoplasma species infections, possibly with more severe disease.

HOW ARE HEMOPLASMA SPECIES TRANSMITTED?

Multiple Modes of Transmission

The natural route of transmission of feline and canine hemoplasma species in the field has not yet been determined, and it may be that different routes predominate for different host and hemoplasma species. Indeed, recent pioneering work on the transmission of '*Ca.* M. haemominutum' in domestic and wild felids[1] suggests that multiple transmission pathways exist concurrently. These pathways include indirect spread (ie, vector-borne) and direct spread (via predation, of larger cats over smaller cats, or fighting), and it will be interesting for future work to evaluate other hemoplasmas using a similar approach.

Indirect Vector-Borne Transmission

Evidence for the presence of canine and feline hemoplasmas, usually via PCR studies amplifying hemoplasma DNA, has been found in fleas, ticks, and mosquitoes[53,79,105–113], although the numbers of samples testing positive vary widely. However, this does not confirm that these vectors mediate transmission, because the presence of hemoplasmas could simply reflect the vectors' hematophagous activity on infected hosts.

Fleas

Although *Ctenocephalides felis* has been implicated in hemoplasma transmission in cats, evidence for this is very limited. Only very transient *M. haemofelis* (and not '*Ca.* M. haemominutum') infection has been reported in a small study of cats experimentally infected via the hematophagous activity of fleas, and clinical and hematologic signs of *M. haemofelis* infection were not induced in the recipient cat.[114] Another study did not detect any evidence of transmission of either *M. haemofelis* or '*Ca.* M. haemominutum' to cats by the ingestion of hemoplasma-infected fleas.[115] In addition, there was no evidence of hemoplasma transmission when fleas were introduced into groups of cats housed together.[116]

Ticks

Published studies do support ticks being a vector for canine hemoplasma transmission. Experimental transmission of *M. haemocanis* by the brown dog tick, *Rhipicephalus sanguineus,* has been reported, although this study was performed before the development of sensitive and specific molecular diagnostic methods to confirm transmission.[106] The clustered geographic distribution of infection in some studies supports the role of an arthropod vector in feline hemoplasma transmission,[17] and hemoplasma prevalences in dogs can vary according to the presence of *R. sanguineus*.[54,55,61,65] Associations also exist between canine hemoplasma infections and other vector-borne infections, particularly *Babesia vulpis* and *Babesia gibsoni*, and ticks and other ectoparasites, also supporting vector transmission.

Direct Spread via Fighting

Fights and biting are likely to transmit hemoplasmas. Studies have found that subcutaneous inoculation of '*Ca.* M. turicensis'-containing blood resulted in infection transmission, whereas '*Ca.* M. turicensis'-containing saliva did not. A high prevalence of hemoplasma infection has also been reported in fighting dogs.[70,71] Thus hemoplasma transmission by social contact (saliva via mutual grooming, and so on) is less likely than transmission by aggressive interactions (blood transmission during a cat bite incident).[117]

Vertical Transmission

Vertical transmission of hemoplasmas in dogs and cats has not been definitively proven using molecular methods but has been strongly suggested for *M haemocanis*.[118]

Blood Transfusion

Fresh blood transfusions can transmit hemoplasmas[119] so blood donors should be screened for all hemoplasma species infection.[120–122]

CLINICAL SIGNS AND PHYSICAL EXAMINATION

When anemia results from hemoplasma infection, common clinical signs reported include lethargy, pallor, weakness, inappetence, dehydration, weight loss, and

intermittent fever. Splenomegaly may also be evident on physical examination, although dogs with clinical hemoplasmosis usually have a history of splenectomy (a predisposing factor in the development of clinical disease). Severe anemia may result in tachycardia, tachypnea, and weak or bounding femoral pulses with hemic cardiac murmurs. Icterus is uncommon despite the severe nature of the hemolytic anemia involved.

DIFFERENTIAL DIAGNOSIS

Hemoplasmosis should be considered as a differential diagnosis in cats or dogs presenting with regenerative anemia, especially with fever. Other diagnoses to consider are primary (nonassociative) immune-mediated hemolytic anemia,[93,94] secondary (associative) immune-mediated hemolytic anemia (eg, to drugs, neoplasia, other infectious diseases including feline infectious peritonitis), babesiosis, cytauxzoonosis (cats), retroviral infection (cats), Heinz body-associated hemolysis (cats), hypophosphatemia, and inherited red blood cell disorders (eg, pyruvate kinase deficiency, and red cell fragility disorders).

DIAGNOSIS

Hematology

Hematology typically reveals a macrocytic hypochromic regenerative anemia, although sometimes the reticulocytosis is minimal.[123] Nucleated erythrocytes may also feature on hematology. Other features of hematology tend to remain within the reference range. Manual reticulocyte counts should be interpreted with care because hemoplasma-infected erythrocytes can appear like reticulocytes in blood smears stained with new methylene blue. As mentioned earlier, cases with erythrocyte-bound antibodies can give positive Coombs' test results or show persistent autoagglutination.

Blood Smear Cytology

Cytologic examination of blood smears may show hemoplasmas on the surface of erythrocytes, but cytology, although quick and possible in-house, is unreliable especially for those without experience of reading blood smears. Specificity is an issue because it is difficult to differentiate hemoplasma organisms from stain precipitate (careful staining with filtered Romanowsky-type stain solutions [eg, Wright-Giemsa or Diff-Quik] is essential), Howell-Jolly bodies, and basophilic stippling. Specificity is good at 84% to 98% when smears are examined by specialist clinical pathologists.[26,30,45,124] Cytology is very insensitive (0%–37.5%),[26,30,45,124,125] and only when huge numbers of organisms are present in the blood (likely only early in acute infections) can they be visualized on blood smears; indeed '*Ca.* M. turicensis' has never been seen on blood smears due to the low numbers of organisms present in the blood during infection.[31,126] Blood smear examination cannot differentiate between hemoplasma species.[127] It is advisable to submit blood smears to an external laboratory with expertise in their interpretation to maximise specificity, despite the delay in reporting results that this may bring. As *M. haemocanis* organisms tend to form chains (**Fig. 2**), they can be more readily recognized on cytology because chain formation allows differentiation from stain precipitate and erythrocyte morphologic changes.

Serum Biochemistry

Biochemistry may reveal hyperbilirubinemia, due to hemolysis, although this is not usually severe. Hypoxic damage to the liver may result in increased activities of alanine

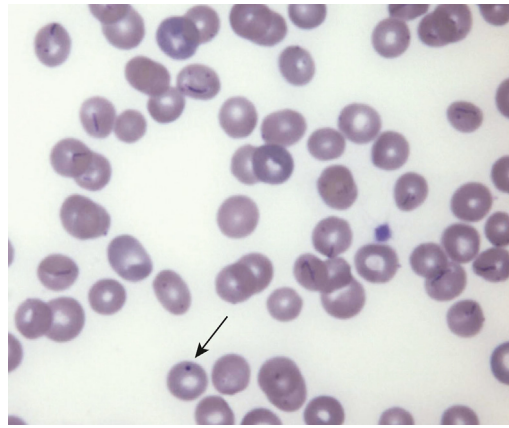

Fig. 2. Romanowsky-stained blood smear showing chains of epierythrocytic bacteria typical of *M. haemocanis*. A Howell-Jolly body is also present (*arrow*), reproduced with permission.[159]

aminotransferase and aspartate transaminase. Hyperproteinemia, due to a polyclonal gammopathy, sometimes occurs.[7,101]

Retrovirus Testing

Tests for FeLV and FIV infection may be positive, especially in cats showing more severe clinical signs than expected.

Urinalysis

Urinalysis is usually unremarkable. Bilirubinuria may be present where hyperbilirubinemia is present.

Culture

Despite numerous attempts by researchers, it has not been possible to culture veterinary hemoplasmas in vitro,[128,129] thus culture (and antimicrobial sensitivity) testing cannot be used diagnostically.

Polymerase Chain Reaction

PCR assays, performed on DNA extracted from ethylenediaminetetraacetic acid blood samples, are the most reliable diagnostic test for hemoplasma infection due to their sensitivity and specificity. Blood samples should ideally be taken before any antibiotic treatment is started because organisms can decrease rapidly if antibiotic treatment is successful.[130]

Many PCR assays exist, both conventional and real-time quantitative PCR (qPCR), which are generally based on detection of segments of the 16S rRNA gene; increasingly, hemoplasma PCR assays are duplexed with a host housekeeping gene PCR[56,131] as an internal control, so that false-negative results due to the failure of DNA extraction, presence of PCR inhibitors, or setup errors are recognized. Others amplify host housekeeping genes in a separate PCR (ie, not duplexed),[7] which is less optimal. Well-designed PCR assays, run in high-quality laboratories, can detect low numbers of organisms in the blood, allowing for detection of subclinical carrier cats and dogs. Samples need to be sent to an external laboratory for analysis, which typically takes a few days. The detection of subclinical carrier status by PCR means

that a positive PCR result does not equate with hemoplasmosis being the cause of disease in the animal being tested. Thus, positive PCR results must be interpreted in conjunction with the clinical signs shown by the animal being tested (anemia, pyrexia), clinicopathological results, any concurrent disease or immunosuppression, and the pathogenicity of the hemoplasma species detected by PCR. Last, large numbers of hemoplasmas (reported by qPCR) may be more consistent with clinical hemoplasmosis, but the marked fluctuations in organism numbers in acute *M. haemofelis* infection makes qPCR interpretation more difficult. However, the detection of low numbers of organisms in an animal with appropriate clinical signs, in the absence of another cause of the anemia, could well be reflective of clinical hemoplasmosis, warranting treatment.

Isothermal Assay

A new point-of-care machine, using isothermal nonquantitative amplification of DNA to diagnose *M. haemofelis* infection has been evaluated in a small study.[132] However, in-house extraction of DNA from blood is needed, and the extraction kit used affects the sensitivity of the assay, possibly limiting the usefulness of this assay.

Serology

Although serologic assays to detect antibodies against hemoplasmas were more sensitive than PCR in detecting exposure to '*Ca.* M. turicensis' in one study,[133] and have been used in research,[133,134] none are commercially available.

TREATMENT

Overview

Prompt antibiotic treatment (**Table 2**) is indicated for cats and dogs with clinical signs and clinicopathological abnormalities consistent with clinical hemoplasmosis. However, although clinical improvement in the anemia is seen, clearance of infection is rare. Most studies evaluating antibiotics have centered on *M. haemofelis* infection, and information is then extrapolated to guide treatment for other hemoplasma species. However, the response of different hemoplasma species, and indeed probably different strains/genotypes of the same species, to antibiotics varies, so clinicians should always be aware that a change in treatment may be required if a clinical response is not seen within a few days.

Tetracyclines

Tetracyclines, particularly doxycycline,[92,135] are indicated as first-line antibiotic treatment of clinical hemoplasmosis. Because of the possibility of esophagitis in cats, administration of the hyclate preparation of doxycycline should always be followed by food or water. Doxycycline is typically given for 2 weeks, with clinical improvement within 3 days. In simple cases that show a rapid response, the 2-week course of doxycycline is usually adequate with no further monitoring required. However, if the hemoplasmosis is a reactivated infection, or comorbidities are present and/or clinical signs do not improve within 3 days, ideally blood organism numbers should be monitored by qPCR to determine if they are decreasing with doxycycline. The results of qPCR, alongside repeat hematology, can guide whether a longer doxycycline course (up to 4 weeks) is required if only a partial response has occurred, or whether a second-line antibiotic is needed if little response is seen. In one study, '*Ca.* M. haemominutum' infection was not as effectively treated by doxycycline as *M. haemofelis*,[85] highlighting the varying response of different hemoplasma species to the same antibiotic.

Table 2
Suggested drug dosages for antibiotic treatment of acute clinical hemoplasmosis in cats and dogs

Antibiotic Class & Name	Dosage (mg/kg)[a]	Route & Frequency[b]	Comments
Tetracycline: doxycycline	5 10	PO q 12 h PO q 24 h	Commonly used first-line antibiotic for acute hemoplasmosis. Can be associated with gastrointestinal side effects when dosed q 24 h. Can be associated with esophagitis if incompletely swallowed so always follow with food or water
Fluoroquinolone: marbofloxacin	2–5.5	PO q 24 h	Reserve fluoroquinolones as second-line antibiotics. Reported use in combination (sequentially) with doxycycline to clear *M haemofelis*[140]
Fluoroquinolone: pradofloxacin	3–5	PO q 24 h	Reserve fluoroquinolones as second-line antibiotics. May be more efficacious at clearing *M haemofelis* than doxycycline[139]
Fluoroquinolone: enrofloxacin	5	PO q 24 h	Reserve fluoroquinolones as second-line antibiotics. Enrofloxacin is not a preferred fluoroquinolone in cats as it has potential for irreversible retinal toxicity as idiosyncratic reaction

Abbreviations: PO, by mouth; q, every.
[a] Licensed dosages (eg, for marbofloxacin) and drug availability vary by formulation and country.
[b] Two-week courses are usually adequate for treatment of uncomplicated hemoplasmosis: courses can be extended if only a partial clinical response occurs.

Fluoroquinolones

Fluoroquinolones, notably marbofloxacin and pradofloxacin,[135–139] are also effective but are reserved as second-line treatments. Again, these are given typically for 2 weeks with improvement occurring within a few days. Pradofloxacin may be more efficacious at clearing *M. haemofelis* infection than doxycycline.[139] Although marbofloxacin treatment is known to result in a marked and sustained decrease in blood *M haemofelis* organisms in cats and clinical response,[138] it only caused a temporary decrease of '*Ca.* M. haemominutum' organisms[137] and PCR positive results for '*Ca.* M. haemominutum' have remained following either enrofloxacin or doxycycline treatment,[18] thus highlighting the varying response of different hemoplasma species.

Treatment of Hemoplasmosis in the Absence of a Published Evidence Base

Little evidence exists on the response of *M. haemocanis*, '*Ca.* M. haematoparvum' and '*Ca.* M. turicensis' to antibiotics, but one report described a successful response of '*Ca.* M. turicensis' to doxycycline,[31] and doxycycline is generally used as a first-line treatment of all infections. Some cases seem to be refractory to tetracyclines, and in 1 *M. haemocanis* case report,[91] oxytetracycline, and subsequent enrofloxacin, did not markedly reduce organism numbers, although clinical signs did improve. It is important to focus on the clinical response to treatment but to be prepared to try an alternative antibiotic if the clinical response is inadequate, preferably alongside

qPCR results if finances allow, to document hemoplasma organism numbers to further help assess response to treatment.

Low numbers of hemoplasma organisms are often detectable by qPCR following antibiotic treatment, even if a good clinical response is seen. Some have suggested using longer courses of antibiotics (eg, 6 weeks) to try and clear infection and obtain a negative qPCR result, although antibiotic stewardship should always be considered to limit inappropriate antibiotic use. Recently a protocol to clear chronic *M. haemofelis* infection in cats has been described,[140] comprising a 4-week course of doxycycline (5 mg/kg by mouth every 12 hours) and then, if still qPCR positive (repeated testing on multiple occasions), a 2-week course of marbofloxacin (2 mg/kg by mouth every 24 hours). Treatment breaks of up to 4 weeks between the courses of antibiotics did not influence the outcome. This protocol is an option for cases in which reactivation of infection or particularly severe disease (eg, with comorbidities) has occurred.

Supportive Treatment

As well as antibiotics, supportive therapy is important for the successful management of acute hemoplasmosis in cats and dogs. Intravenous fluid therapy to correct dehydration and blood products (packed red blood cells if available, or whole blood) for severe anemia may be required if tachycardia, weakness, and/or tachypnea are present.

Glucocorticoids

Glucocorticoids are not usually required for hemoplasmosis treatment, even if erythrocyte-bound antibodies are documented. Efficacious antibiotic treatment is adequate in these cases[81] and immunosuppressive glucocorticoids have actually been used experimentally to enhance bacteremia and to try and induce reactivation of subclinical hemoplasma infection.[78,135,139–141] Glucocorticoids would only be indicated in cases in which the response to antibiotics was not appropriate and primary immune-mediated hemolytic anemia was a likely diagnosis.

PROGNOSIS

The prognosis for acute hemoplasmosis is generally good if effective antibiotic and supportive treatment is started promptly, with clinical improvement occurring within 3 days of starting treatment. Many animals remain subclinical hemoplasma carriers following recovery, and reactivation of disease is possible months or years later.

PREVENTION

The lack of definitive knowledge on how hemoplasmas are transmitted in the field makes it difficult to make firm recommendations to prevent infection, but risk factors for hemoplasma infection should be avoided if possible. Prevention of fighting, control measures for flea and tick infestations, and screening of blood donors by PCR should be helpful.

PUBLIC HEALTH ASPECTS

Molecular techniques have confirmed infections in humans with hemoplasma species already reported in animal hosts such as cats,[142] dogs,[143,144] pigs,[145–147] and sheep,[144,148] suggesting that zoonotic transmission is possible. Most reports have suggested that hemoplasma-associated clinical signs are more likely in immunocompromised humans, and clinically ill people have often had coinfections with *Bartonella henselae*.[142,143,148] Further investigation is warranted into the effects of *B. henselae* coinfection on transmission and disease.[149]

More recently, human infections with a novel hemoplasma species have been described[144,150–153]; this species was named '*Candidatus* Mycoplasma haemohominis,' and has since been found in bats[153–158] with zoonotic transmission by direct contact with bats believed to have occurred. '*Flying fox hemoytic fever*' is the name recently given to the '*Ca* M haemohominis'-associated syndrome in humans, characterized by febrile splenomegaly, weight loss, life-threatening autoimmune hemolytic anemia, and hemophagocytosis in New Caledonia.[153] These patients usually had a history of contact with bats (via hunting/food preparation primarily), and '*Ca.* M. haemohominis' was found in a significant number of bats tested. Interestingly, these patients were not immunocompromised before succumbing to '*Ca.* M. haemohominis' disease and usually recovered if treated promptly with a 3-week course of doxycycline.

Until further information is available on zoonotic potential and transmission, veterinarians should handle blood and tissues from animals suspected to be hemoplasma infected with caution.

SUMMARY

Hemotropic mycoplasmas (hemoplasmas) exist worldwide and are wall-less bacteria. The main pathogenic species in dogs and cats are *M. haemocanis* and *M. haemofelis*, respectively. The species infect erythrocytes and induce hemolytic anemia and fever. Their natural mode of transmission has not been confirmed, but likely includes vertical, fighting/biting, and vector-borne transmission. Reliable diagnosis is by PCR on blood samples because cytology is insensitive. Prompt treatment of clinical disease with supportive care and at least 2 weeks of doxycycline is usually successful. Subclinical carrier status is common, but reactivation of clinical disease is rare. Zoonotic infection is possible, most likely via direct contact with bats.

CLINICS CARE POINTS

- Consider hemoplasmosis in cats and splenectomized or immunocompromised dogs presenting with a regenerative anemia and fever
- In-house blood smear examination (cytology) for diagnosis is generally unreliable unless interpreted by someone with experience in cytology
- PCR is the diagnostic method of choice, performed on EDTA blood samples collected before antibiotic treatment is started
- A 2-week course of doxycycline is usually successful for treatment, with supportive care (including a blood transfusion) if needed; an improvement is usually seen within 3 days. If the response is inadequate to doxycycline, pradofloxacin or marbofloxacin treatment can be used as a second-line treatment
- Glucocorticoid treatment is not usually required
- Despite a clinical response to treatment, clearance of infection may not result from treatment; subclinical-infected animals remain at risk of reactivation of infection, but this seems to be rare

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