Haemoplasmosis in Cats

Published: 01/01/2018
Last updated: 01/01/2021
Last reviewed: 01/11/2022

These guidelines were drafted by Séverine Tasker et al. and published in the Journal of Feline Medicine and Surgery 20, 2018, 256-261, http://journals.sagepub.com/doi/pdf/10.1177/1098612X18758594. This update was done by Séverine Tasker.

Synopsis

- *Mycoplasma haemofelis* is the most pathogenic of the three feline haemoplasma species.
- ' M. haemominutum' and '*Ca.* M. turicensis' infections are less pathogenic but can result in disease in immunocompromised cats.
- Male non-pedigree cats with outdoor access are more likely to be haemoplasma-infected.
- ' M. haemominutum' is more common in older cats.
- The natural mode of transmission of haemoplasma infection is not known; aggressive interactions and vectors are possibilities.
- Transmission by blood transfusion is possible and all blood donors should be screened for haemoplasma infection.
- Polymerase chain reaction (PCR) assays are the preferred diagnostic method for haemoplasma infections.
- Carrier cats that do not show clinical signs of infection exist for all feline haemoplasma species.
- Treatment with doxycycline for 2-4 weeks is usually effective for the treatment of *haemofelis*-associated clinical disease, but doxycycline treatment does not always clear infection. A protocol comprising 4 weeks of doxycycline followed by 2 weeks of marbofloxacin, for those cats that are still PCR-positive after the doxycycline treatment, has been described for clearance of chronic *M. haemofelis* infection. This protocol can be considered if clinical disease is severe and/or recurrent.
- Treatment of carrier cats that do not show any clinical signs is not recommended.
- Little information is currently available on the antibiotic responsiveness of ' M. haemominutum' and '*Ca.* M. turicensis'.

Agent properties

The haemoplasmas are haemotropic mycoplasmas, bacteria that parasitize red blood cells and can induce haemolytic anaemia. They are currently classified within the genus *Mycoplasma* in the *Mycoplasmataceae* family of bacteria. However, research suggests that although the haemoplasmas probably do belong to this family, they might be better placed in their own separate genus (Hicks et al., 2014a). In contrast to many 'classical' mycoplasmas, haemoplasmas are uncultivable. Their propagation is possible in living animals only, not *in vitro*.

Three main haemoplasma species known to infect cats are *Mycoplasma haemofelis*, '*Candidatus* Mycoplasma haemominutum' and '*Candidatus* Mycoplasma turicensis'. These mycoplasmas have a worldwide distribution. A canine haemoplasma species-like organism, described as '*Candidatus* Mycoplasma haematoparvum'-like, has also been reported in a small number of cats in two studies (Sykes et al., 2007; Martinez-Diaz et al., 2013). The clinical importance of this hemoplasma species in cats remains unclear.

Epidemiology

Prevalence

The prevalence of the feline haemoplasma species varies geographically. In general, looking at studies that have evaluated domestic cats for the presence of all three of the feline haemoplasma species by PCR, it is found that '*Ca.* M. haemominutum' is usually more prevalent (4.4 – 46.7% of cats are infected) than *M. haemofelis* (0.4 – 27.0% of cats) and '*Ca.* M. turicensis' (0 – 26.0% of cats). Reported prevalences vary with geographical variation and also differ quite widely because the cats sampled in different studies are very variable, i.e. some studies test only ill anaemic cats, whereas others sample healthy cats only, and some test stray feral cats whereas others focus on owned cats. Feline haemoplasma infections have been identified in prevalence studies performed in many countries in Europe including: Cyprus (Attipa et al., 2017), Denmark (Rosenqvist et al., 2016), Germany (Bauer et al., 2008; Bergmann et al., 2017), Iran (Ghazisaeedi et al., 2014), Ireland (Juvet et al., 2010), Italy (Gentilini et al., 2009; Persichetti et al., 2016; Ravagnan et al., 2017; Persichetti et al., 2018; Latrofa et al., 2020), Malta (Mifsud et al., 2020), Portugal (Martinez-Diaz et al., 2013; Mesa-Sanchez et al., 2020), Romania (Imre et al., 2020), Serbia (Sarvani et al., 2018), Spain (Roura et al., 2010; Ravicini et al., 2016; Diaz-Reganon et al., 2018; Mesa-Sanchez et al., 2020), Switzerland (Willi et al., 2006a), Turkey (Ural et al., 2009) and the UK (Tasker et al., 2003; Willi et al., 2006b; Peters et al., 2008).

Predisposing factors

Feline haemoplasma infections are usually more common in male, non-pedigree cats with outdoor access and cat bite abscesses. Additionally '*Ca.* M. haemominutum' is specifically more prevalent in older cats, presumably because cats have an increasing chance of acquiring chronic subclinical infection over their lifetime compared to the other haemoplasma species. Some studies have found an association between haemoplasma and feline immunodeficiency virus (FIV) infection (Macieira et al., 2008; Gentilini et al., 2009; Walker Vergara et al., 2016; Persichetti et al., 2018; Sarvani et al., 2018), whereas others have not (Willi et al., 2006a), and most studies have failed to show an association between haemoplasma infection and feline leukaemia virus (FeLV) infection (Willi et al., 2006a; Macieira et al., 2008; Gentilini et al., 2009). However, variable results have been seen regarding retroviruses as risk factors for haemoplasma infections, and other studies have suggested significant associations between these infections (Laberke et al., 2010; Attipa et al., 2017; Bergmann et al., 2017; Diaz-Reganon et al., 2018). Epidemiology studies suggest that the host phenotype (e.g. aggressive male phenotype) could drive some of these associations rather than infections being simple risk factors for each other (Carver et al., 2015). Additionally, *Felis catus* gammaherpesvirus 1 (FcaGHV1), a potential feline pathogen, has been found to be significantly associated with haemoplasma infection in studies (McLuckie et al., 2016; Novacco et al., 2019), suggesting similar transmission routes, but the significance of FcaGHV1 in cats has not yet been elucidated (Beatty et al., 2014).

Transmission

The clustered geographical distribution of infection in some studies supports the role of an arthropod vector in haemoplasma transmission (Sykes et al., 2007). The cat flea has been implicated in feline haemoplasma transmission, but only very transient *M. haemofelis* infection has been reported in one experimental study via the haematophagous activity of fleas, and clinical and haematological signs of *M. haemofelis* infection were not induced in the recipient cat (Woods et al., 2005). Additionally, one study found no evidence of haemoplasma transmission by fleas in an experiment involving the introduction of fleas into groups of cats housed together (Lappin, 2014). Mosquitoes were also investigated as potential vectors, but no evidence of biological transmission of feline haemoplasmas was found (Reagan et al., 2017). Similarly, although feline haemoplasma DNA has been found in ticks collected from cats (Duplan et al., 2018), no concrete evidence for their role in the natural transmission of feline haemoplasmas exists. Some observations have suggested that cat fights are involved in transmission. Subcutaneous inoculation of '*Ca.* M. turicensis'-containing blood resulted in infection transmission, whereas the same inoculation method using '*Ca.* M. turicensis'-containing saliva, did not (Museux et al., 2009). This suggests that haemoplasma transmission by social contact (saliva via mutual grooming etc.) is less likely than transmission by aggressive interaction (blood transmission during a cat bite incident) (Museux et al., 2009). However, one study (Lappin, 2014) found evidence of horizontal transmission of '*Ca.* M. haemominutum', but not *M. haemofelis*, by direct contact between cats in the absence of any apparent significant aggressive interaction and vectors. Blood transfusion is another potential route of transmission, and blood donors should be screened for haemoplasma infection (Pennisi et al., 2015). Vertical transmission has been strongly suggested for the canine haemoplasma species *Mycoplasma haemocanis* (Lashnits et al., 2019) but has not been definitively shown for feline hemoplasmas.

Pathogenesis

Mycoplasma haemofelis is the most pathogenic feline haemoplasma species as it can result in severe, sometimes fatal, haemolytic anaemia following acute infection in some cats, although others develop only mild anaemia, so variability in outcome occurs. This could be due to host response differences or *M. haemofelis* strain variation, but severe disease can occur including in immunocompetent cats (Tasker et al., 2009b). Chronic infection is usually not associated with significant anaemia, and carrier cats exist which show no

evidence of anaemia (Willi et al., 2006a; Laberke et al., 2010). In line with this, some epidemiological studies have not shown associations between anaemia and *M. haemofelis* infection (Willi et al., 2006a; Bauer et al., 2008; Juvet et al., 2010; Munhoz et al., 2018), probably due to the inclusion of chronically *M. haemofelis*-infected cats without clinical signs.

Although '*Ca.* M. haemominutum' infection can cause erythrocyte parameters (e.g. red blood cell count, haemoglobin, haematocrit) to decrease (Tasker et al., 2009b), anaemia is not commonly seen following infection unless the cat has concurrent problems, e.g. immunosuppression or is undergoing chemotherapy. Many carrier cats of '*Ca.* M. haemominutum' exist which do not show any clinical signs (Willi et al., 2006a). '*Ca.* M. haemominutum' has also been associated with the development of myeloproliferative disease in cats with FeLV infection in one experimental study (George et al., 2002). However, cases of anaemia have been reported in which only '*Ca.* M. haemominutum' infection was diagnosed and so it appears that in some cases, '*Ca.* M. haemominutum' can cause anaemia in the absence of concurrent diseases (Reynolds and Lappin, 2007; Weingart et al., 2016).

'*Ca.* M. turicensis' infection has caused anaemia or a mild decrease of erythrocyte parameters in some experimental studies (Willi et al., 2005), but generally anaemia is uncommon (Tasker et al., 2009b). Concurrent disease and immunosuppression are both thought to be involved in the pathogenesis of '*Ca.* M. turicensis' disease, similar to '*Ca.* M. haemominutum'.

Determining the pathogenicity of '*Ca.* M. haemominutum' and '*Ca.* M. turicensis' in naturally infected cats can be difficult as cats are often co-infected with other haemoplasma species, confounding disease associations.

Carrier cats often have subclinical infections, but reactivation of infection can occur, although rarely, and can result in clinical disease (Weingart et al., 2016). Reactivation can occur when the cat has failed to eliminate infection. One study found that cats that had previously recovered from *M. haemofelis* infection were protected from homologous re-challenge with *M. haemofelis*, confirming the presence of protective immunity (Hicks et al., 2014b), possibly in those that have previously eliminated the infection, and thus, reinfection seems unlikely. However, another study found that cats that had recovered from previous '*Ca.* M. turicensis' infection actually showed more severe and rapid *M. haemofelis* infection signs than naïve cats infected with *M. haemofelis* (Baumann et al., 2013). Thus, more research is required into the relationship between infection with different haemoplasma species and their pathogenesis and immunity.

Clinical signs

Common clinical signs associated with acute pathogenic haemoplasma infections are lethargy, weakness, reduced appetite, dehydration, weight loss and intermittent pyrexia (which can be high) (Tasker, 2010). Pallor, associated with anaemia, is also reported. Splenomegaly can be evident in some cats. Severe anaemia can result in tachycardia, tachypnoea and weak or bounding femoral pulses with haemic cardiac murmurs. Icterus is uncommon despite the haemolytic nature of the anaemia, possibly because the haemolysis is not severe enough to cause significant elevations in bilirubin concentrations. and the reasons for this are unknown as the haemolysis can be very severe in some cases. As mentioned above, chronic haemoplasma infection is usually not associated with clinical signs, although reactivation of infection is possible and can be associated with disease.

Diagnosis

Laboratory changes

Pathogenic haemoplasma infections typically cause a regenerative macrocytic hypochromic anaemia although pronounced reticulocytosis is not always evident (Kewish et al., 2004). Normoblasts can be present. White blood cell changes can also occur including leukopenia, lymphopenia, eosinopenia and monocytosis. Positive Coombs' test results can occur, particularly with cold agglutinins, and persistent autoagglutination has been reported in acute haemoplasmosis, indicating the presence of erythrocyte-bound antibodies. However, in experimental studies (Tasker et al., 2009b) these antibodies appear after the development of anaemia; the absence of erythrocyte-bound antibodies at the onset of development of anaemia could be due to reduced sensitivity for their detection or because erythrocyte-bound antibodies appear as a result of haemoplasma-induced haemolysis rather than mediating it. Indeed erythrocyte-bound antibodies disappear with antibiotic and supportive treatment alone, without glucocorticoid treatment. Hyperbilirubinaemia is seen occasionally, due to haemolysis. Hypoxic liver damage can result in increased activities of alanine aminotransferase. A polyclonal hypergammaglobulinaemia is also sometimes seen.

Blood smear cytology

Cytology of blood smears, stained with Romanowsky type stains, can reveal haemoplasmas on the surface of erythrocytes but this is known to be very unreliable for diagnosis. Sensitivity is a particular issue with figures of only 0% to 37.5% reported in various studies (Westfall et al., 2001; Tasker et al., 2003; Bauer et al., 2008). Specificity is usually higher, with values of 84 to 98% (Tasker et al., 2003; Bauer et al., 2008), although these figures are based upon board-certified clinical pathologists examining and interpreting blood smears (Tasker, 2010). If reliable blood smear interpretation analysis is available, the cytological detection of organisms during acute infection

can be useful, as a bench-side and immediate diagnostic test. However, in reality, many cases diagnosed as being haemoplasma-infected on the basis of blood smear interpretation in practice have been false positives, with stain precipitate, Howell-jolly bodies and artefacts due to slow blood smear drying being the most common reasons for error. Additionally, cytology cannot differentiate between haemoplasma species., and cytology cannot easily differentiate haemoplasma species.

Culture

Haemoplasmas are currently unculturable *in vitro* despite numerous attempts in experimental studies. A number of haemoplasmas have been subjected to whole genome sequencing, including sequencing of two feline haemoplasma species; M. haemofelis strain Langford 1(Barker et al., 2011) and 'Ca. M. haemominutum' strain Birmingham 1 (Barker et al., 2012). These data have highlighted the limited metabolic capabilities of these important pathogens (glucose is their only energy source), which likely contribute to the haemoplasmas' current uncultivatable status. Such knowledge of haemoplasma metabolic capabilities has allowed us to direct *in vitro* cultivation attempts but successful growth has not yet been possible.As haemoplasmas do not grow on bacteriological media, and *in vitro* culture is not possible.

PCR

Polymerase chain reaction (PCR) assays, to detect haemoplasma DNA, are now the diagnostic method of choice for haemoplasma infection. PCR is performed in specialised diagnostic laboratories following DNA extraction from submitted blood samples. PCR is far more sensitive and specific than cytology. Quantitative PCR (qPCR) assays allow quantification of haemoplasma DNA in the sample being analysed, allowing monitoring of response to treatment. Blood samples for PCR should be taken before antibiotic treatment is started as effective treatment can result in a rapid and dramatic fall in organism numbers within a few days, as shown in Figure 1, which could result in negative PCR results. It is also known that *M. haemofelis* blood organism numbers can fluctuate markedly in some cats for several months following infection; the reason for this is not known but could be related to antigenic variation (Tasker et al., 2006a; Tasker et al., 2009a). No evidence of significant tissue sequestration of *M. haemofelis*, to explain reduced blood organism numbers, has been found (Tasker et al., 2009a). This is in contrast to '*Ca.* M. turicensis', in which evidence of tissue sequestration was found in PCR-negative cats (Novacco et al., 2013).

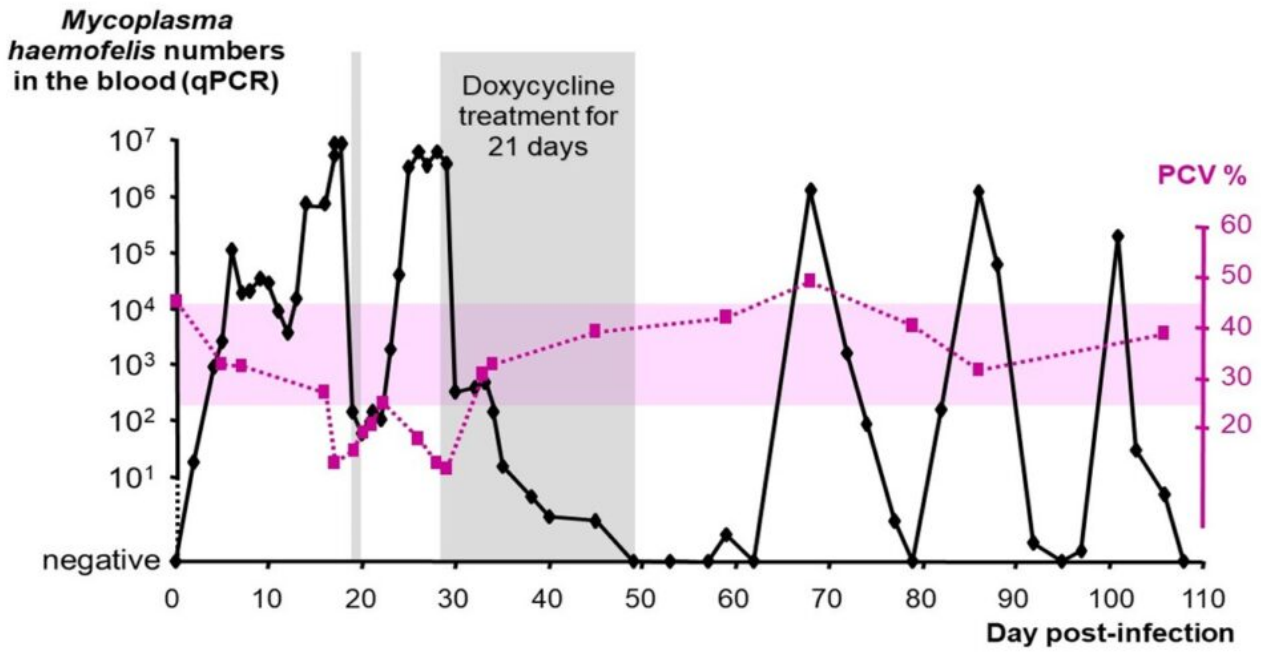

Fig. 1. Variation in M. haemofelis organism numbers in the blood of a cat, measured by quantitative polymerase chain reaction (qPCR), over time. The cat's packed cell volume (PCV) measurements are also shown over time, together with a pink shaded area illustrating PCV reference interval. The cat received doxycycline therapy (10/mg/kd PO SID; grey shaded areas) on day 19 post-infection and then again for 21 days from day 28 post-infection. It can be seen that there is a marked drop in organism numbers in the blood with doxycycline treatment. Cycles of increasing and decreasing organism numbers occurred following completion of the 21-day course of doxycycline, but these were not associated with anaemia. Figure adapted from Tasker (2008).

In-house PCR is not available, although a point-of-care machine (Hawley et al., 2018) that uses isothermal non-quantitative amplification of DNA to diagnose *M. haemofelis* infection has been described. This method requires in-house extraction of DNA from blood and the extraction technique markedly influences sensitivity, precluding routine recommendation of this method.

Haemoplasma antibody tests

Tests to detect antibodies to haemoplasma species have been difficult to develop due to the inability to culture haemoplasmas *in vitro* preventing the easy acquisition of significant amounts of haemoplasma proteins for use in antibody assays; they are currently only available for use in experimental studies. These antibody assays, based on a *M. haemofelis* dnaK protein, have suggested that antibody levels can differentiate between acute and chronic infection with *M. haemofelis* (Barker et al., 2010) and have been more sensitive than PCR in detecting haemoplasma exposure (as PCR-negative antibody-positive cats have been identified) (Novacco et al., 2011), but these assays are not appropriate for use in field cats yet due to cross-reactivity.

Treatment

Antibiotic treatment

Haemoplasmosis generally has a good prognosis if prompt appropriate treatment is instigated. However, as haemoplasmas lack a cell wall around their cell membrane, ß-lactams (e.g. penicillins, cephalosporins) are not effective in treatment**.** Tetracyclines (primarily doxycycline) and fluoroquinolones (e.g. marbofloxacin, pradofloxacin) are effective for the treatment of haemoplasmosis. The majority of studies have evaluated the response of *M. haemofelis* only to treatment. Doxycycline (10 mg/kg SID PO or 5 mg/kg BID PO) is often used as a 1st line treatment, typically for 2-4 weeks with longer treatment courses recommended by some experts to increase the chance of eliminating infection. Administration of the hyclate preparation of doxycycline should always be followed by food or water because of the possibility of it inducing oesophagitis in cats with incomplete swallowing. Figure 1 shows that when treatment is effective, it can be associated with a rapid fall in organism numbers in the blood. One study (Dowers et al., 2009) suggested that 2 weeks of pradofloxacin (at two doses; both the standard 5 mg/kg daily PO, as well as a higher dose of 10 mg/kg daily PO) can be more effective at clearing *M. haemofelis* than doxycycline. It has been found that '*Ca.* M. haemominutum' infection does not necessarily respond to antibiotics similarly to *M. haemofelis*; in one study (Tasker et al., 2006b) '*Ca.* M. haemominutum' organism numbers in the blood fell only temporarily during marbofloxacin (2 mg/kg SID PO) treatment, with organism numbers re-increasing to pre-treatment levels following completion of a 4 weeks course of treatment. The response of '*Ca.* M. turicensis' to antibiotic treatment has not been fully evaluated but doxycycline can be effective (Museux et al., 2009).

Azithromycin was not effective in the treatment of clinical haemoplasmosis in a partially controlled study of cats infected with M. haemofelis and/or 'Ca. M. haemominutum' (Westfall et al., 2001).

A study (Novacco et al., 2018) described a method for clearance of *M. haemofelis* infection, should this be required. Here doxycycline treatment was given for 28 days followed by monitoring of copy numbers in the blood by quantitative PCR; if the cat remained PCR-positive, treatment was switched to a fluoroquinolone (marbofloxacin was used in the study) for 14 days and this was associated with apparent clearance of infection. So, this study suggests that the use of doxycycline followed by marbofloxacin could be useful for clearance of *M. haemofelis*. Attempts to clear infection can be considered when *M. haemofelis*-associated clinical disease is particularly severe and/or has been recurrent. Moreover, clearance of *M. haemofelis* infection may be required in certain situations, such as for cats living in multicat environments together with *M. haemofelis*-naïve cats, since acute primary infection can lead to severe haemolytic anaemia, for cats with immunodeficiency, for cats to be used as blood donors and for cats living with immunocompromised persons. However, treatment of carrier cats that do not show any clinical signs is not generally recommended.

Corticosteroid treatment

Corticosteroids have been used as adjunct treatment for any immune-mediated component of haemoplasma-associated anaemia, although cats usually recover without any need for corticosteroid treatment, as antibiotic and supportive care alone is usually adequate. Thus, we do not recommend the use of corticosteroids for the treatment of haemoplasmosis.

Other supportive care

Other supportive care for haemoplasma-infected cats can be important; correction of dehydration with fluid therapy is important, as well as tempting the cat to eat. Blood transfusions may be required if the anaemia is very severe. However, anaemic cats are at risk of fluid overload due to increased circulating volume, particularly in the presence of occult cardiac disease (Barker, 2019), so care should be taken with intravenous fluid treatment and blood administration.

Prevention

Vaccination

There are no vaccines against feline haemoplasmosis.

Other preventive measures

Although vectors have not been proven to transmit haemoplasma infection, preventative flea and tick treatment is probably wise to help prevent infection in case vectors are involved.

Keeping cats indoors is also likely to prevent infection as outdoor status has been identified as a risk factor, but this is likely to be impractical in cats used to having outdoor access.

Blood donors should be screened for haemoplasma infection by PCR to prevent inadvertent transmission by blood transfusion from carrier cats that do not show any clinical signs (Pennisi et al., 2015). One study (Mesa-Sanchez et al., 2020) describing the screening of healthy, client-owned, indoor cats to become blood donors in Spain and Portugal found that in 4880 retroviral seronegative cats haemoplasmas were detected in 3.7% of cats (1.3% were positive for *M. haemofelis*; 2.3% for *'Ca*. M. haemominutum' and 0.12% for *'Ca*. M. turicensis').

Prognosis

Haemoplasmosis generally has a good prognosis if prompt appropriate treatment is instigated quickly. If infection is not cleared, cats may have subsequent reactivation of infection with recurrence of clinical disease.

Zoonotic risk

Haemoplasma infections with novel haemoplasma species have been described in humans (Steer et al., 2011; Maggi et al., 2013; Alcorn et al., 2020; Hattori et al., 2020), as well as with species that have possibly originated in animals, including the cat (Santos et al., 2008), raising the possibility of zoonotic infections, although we do believe that there is a significant risk of human infection with feline haemoplasma species.

Acknowledgement

ABCD Europe gratefully acknowledges the support of Boehringer Ingelheim (the founding sponsor of the ABCD), Virbac and IDEXX.

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