

# GUIDELINE for Hepatozoonosis

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The Hepatozoonosis guidelines were first published in the Journal of Feline Medicine and Surgery (2015) 17, 642-644 by [Albert Lloret](#) et al. The present update was drafted by Albert Lloret.

## Synopsis

Hepatozoonosis of domestic cats has been reported in several countries, mainly as a subclinical infection.

The infection has been described mostly in the same areas where canine infection is present and, in recent years, different species *Hepatozoon felis* and *Hepatozoon silvestris*, have been identified by molecular techniques.

The vector for feline hepatozoonosis remains unknown and the pathogenesis has not been elucidated.

Feline hepatozoonosis is mainly a subclinical infection, but a few cases have been reported with clinical signs associated with the infection.

The diagnosis of hepatozoonosis in cats can be made by observation of parasite gamonts in blood smears, parasite meronts in muscles by histopathology and detection of parasite DNA in blood and tissue by PCR.

No specific treatment is recommended, but one case has been treated successfully with imidocarb and doxycycline.

Although the mode of transmission and the type of vector are not known, preventive treatment against blood sucking vectors (fleas and ticks) is advised.

## Agent properties

*Hepatozoon* species are apicomplexan parasites (family Hepatozoidae) with a blood-sucking arthropod final host and a vertebrate intermediate host (Smith, 1996). In general, the agent is acquired by ingestion of the infected arthropod (e.g. *Rhipicephalus sanguineus* in *H. canis* and *H. americanum* infections of dogs), but meat eating and hunting are also routes of infection (*H. americanum*), as well as transplacental transmission (*H. canis*, *H. felis*) (Baneth, 2011).

More than 340 species of *Hepatozoon* have been described, not only in mammals but also in amphibians, reptiles, birds and marsupials.

The first report in a domestic cat dates from 1908 when the parasite was named *Leucocytozoon felis domestici* (Patton, 1908). Later it was reclassified in the genus *Hepatozoon* (Wenyon, 1926) as a result of the similarities to the species infecting dogs and wild canids. For some time, reports of the infection in cats referred to *Hepatozoon* spp. or *Hepatozoon-like* spp.

More recently, with the use of molecular techniques, *H. felis* (two different genotypes, *H. felis* genotype I and *H. felis* genotype II) was identified as a distinct and predominant species in cat infections (Criado-Fornelio et al., 2006; Tabar et al., 2008; Pawar et al., 2012). It is a matter of discussion whether there are two *H. felis* genotypes or they represent different species or lineages that should be referred as *H. felis-like* complex (Harris et al., 2019). Moreover, there is also evidence that *H. canis* and *H. silvestris* can infect cats (Jittapalapong et al., 2006; Criado-Fornelio et al., 2007; Baneth et al., 2013; Kegler et al., 2018). *H. silvestris* was first reported in wild cats from Bosnia Herzegovina (Hodžić et al., 2017) and then in healthy domestic cats in Italy (Giannelli et al., 2017) and more recently in a severely ill cat in Switzerland (Kegler et al., 2018).

## Epidemiology

Feline hepatozoonosis has been reported in several countries worldwide, including India, South Africa, Nigeria, USA, Brazil, Israel, Spain,

France, Portugal, and more recently Italy, Turkey, Cape Verde archipelago, Cyprus, Switzerland and Austria (Patton, 1908; Klopfer et al., 1973; Ewing, 1977; Leeflang and Ilemobade, 1977; Van Amstel, 1979; Beaufils et al., 1998; Perez et al., 2004; Tabar et al., 2008; Criado-Fornelio et al., 2009; Vilhena et al., 2013; Otranto et al., 2017; Kegler et al., 2018; Basso et al., 2019; Pereira et al., 2019). The prevalence of the infection varies depending on the geographical area, cat lifestyle and type of samples tested.

Two studies showed a high prevalence of infection in Israel. In one study, meronts were found in the myocardium of 36 % of cats examined post mortem (Smith, 1996). A more recent study showed hepatozoon DNA in blood in 36 % of cats tested (Baneth et al., 2013).

In Spain, in studies using blood PCR, prevalence values were much lower, but varied depending on the study populations: 0.6 % in domestic cats, 16 % in a colony of feral cats and 4 % in a group of privately owned cats visiting a referral hospital (Criado-Fornelio et al., 2006; Ortuño et al., 2008; Tabar et al., 2008).

Two recent studies in Portugal found *H felis* DNA in blood samples in 15.6 % of randomly sampled cats and 8.6 % of owned and shelter cats (Vilhena et al., 2013; Maia et al., 2014a). A highest prevalence of 37.9% hepatozoon DNA positive cats has been observed in a vector-borne pathogens prevalence study conducted in Cyprus (Attipa et al., 2017a).

A significant association between infection and outdoor access has been reported, but no association with gender, age or FIV infection has been observed (Baneth et al., 2013). However, other studies found a significant association between FIV and FeLV infection and hepatozoonosis in cats (Baneth et al., 1998; Beaufils et al., 1998; Ortuño et al., 2008).

The route of transmission has not been fully elucidated yet, but the association with outdoor access suggests transmission by some ubiquitous vectors such as the common flea, mite or ticks, or predation as in other species.

The arthropod vectors of *H felis* remain unknown, but recently *H felis* DNA was detected in ticks (*Rhipicephalus sanguineus*) in Turkey and Portugal (Aktas, 2014; Maia et al., 2014b), *H silvestris* in an *Ixodes hexagonus* in Wales (Duplan et al., 2018) and in fleas (*Ctenocephalides felis*) in Israel (Kamani et al., 2018). In Maio island (Cape Verde) the only tick species present is *Rhipicephalus sanguineus*, but no association between infected cats and presence of ticks was found (Pereira et al., 2019). So far, no *H felis* oocysts have been detected in any arthropod vector.

Transplacental transmission of *H felis* has been suggested and could be an important route of transmission (Baneth et al., 2013).

## Pathogenesis

There have been no published studies on the pathogenesis of infection in cats.

Two forms of the parasite have been found in the cat: intracellular gamonts in neutrophils and monocytes in blood smears and meronts in several tissues.

*H felis* usually results in infection of myocardial and skeletal muscles (Klopfer et al., 1973; Beaufils et al., 1998). The infection does not lead to significant inflammatory reaction around the parasite meronts, so the cat rarely develops clinical signs (Klopfer et al., 1973; Beaufils et al., 1998; Baneth et al., 2013). The presence of meronts has been observed in many other tissues as well as skeletal muscle and myocardium, for example lungs, liver, pancreas, bone marrow, lymph nodes, placenta and amniotic fluid (Baneth et al., 2013).

However, a case of fatal histiocytic and lymphoplasmacytic myocarditis associated with the presence of *H silvestris* meronts has been reported in Switzerland. No immunosuppression or underlying diseases were found suggesting that *H silvestris* infections in domestic cats could be more virulent and even fatal (Kegler et al., 2018).

The level of parasitaemia is low, with less than 1 % of neutrophils and monocytes containing *H felis* gamonts (Baneth et al., 1998; Pereira et al., 2019).

Some studies have shown that there is no correlation between the presence of gamonts in blood smears and meronts in muscular tissues (Klopfer et al., 1973; Baneth et al., 1998; Jittapalapong et al., 2006).

## Clinical presentation

Feline hepatozoonosis caused by *H. felis* is mostly subclinical; a high proportion of cats appears to be infected with no overt clinical signs (Baneth et al., 2013; Giannelli et al., 2017).

Scarce clinical information on the disease in cats is based on a few case reports describing systemic disease; liver and/or kidney disease were present and hepatozoon-like parasites were demonstrated in liver or blood (Ewing, 1977; Van Amstel, 1979; Baneth et al., 1995). The remaining reported cases have been infected cats with no clinical signs.

In a retrospective study of 7 cats with *Hepatozoon* spp. detected in blood smears, diverse clinical signs (lethargy, fever, weakness, lymphadenopathy) and clinicopathological abnormalities (anaemia, thrombocytopenia) were described. However, all 7 cats were suffering from other diseases, which could explain the clinical signs. Four of the cats were co-infected with retroviruses and 2 with haemoplasmas, suggesting that the clinico-pathological abnormalities were not associated with hepatozoon infection. Interestingly, 5 of the cats had clinico-pathological abnormalities suggesting muscular damage (elevated levels of creatinine kinase and lactate dehydrogenase) (Baneth et al., 1998).

One cat recently reported in Turkey showed some clinico-pathological abnormalities (anaemia, leukocytosis, hepatomegaly, icterus, fever). The cat was FIV positive, so immunosuppression might have been associated with the presence of clinical signs (Tuna et al., 2018).

Observation of *H. felis* gamonts in a cat blood smear might be a sign of immunosuppression; so retrovirus testing and investigations for other co-infections and diseases (leishmaniosis, haemoplasmosis, babesiosis, cytauxzoonosis) (Maia et al., 2014a; Attipa et al., 2017a) may be indicated.

In an epidemiological study in Barcelona, 4 cats that tested positive for *H. felis* were sick (attributed to other diseases) and one had leishmaniosis (Tabar et al., 2008), suggesting that immunosuppression and/or another disease could be risk factors for hepatozoon infection. There were similar observations in the Cyprus study where non-healthy cats were three times more likely to be hepatozoon infected compared to healthy cats, although the cause of the disease was not investigated and co-infections were frequent (Attipa et al., 2017a).

A cat diagnosed of leishmaniosis in Cyprus that was also positive to haemoplasma and hepatozoon DNA was treated only for the leishmaniosis and clinical signs got into remission, although the cat remained positive to haemoplasma and hepatozoon (Attipa et al., 2017b).

One cat reported in Switzerland died shortly after showing no specific signs of disease. At necropsy severe myocarditis associated to the presence of *H. silvestris* meronts was found. No other significant lesions were observed (Kegler et al., 2018).

One cat recently reported in Austria had kidney and liver disease showing icterus, high SDMA levels, anaemia, leukopenia and thrombocytopenia with the presence of *H. felis* gamonts within neutrophils confirmed by PCR testing. In this cat no co-infections nor causes of immunosuppression were found, suggesting that in some cases *H. felis* may be a primary pathogen also in cats (Basso et al., 2019).

## Diagnosis

In clinical practice, diagnosis is usually made by the observation of *Hepatozoon* spp. gamonts in the cytoplasm of neutrophils and monocytes in blood smears stained with Diff-Quick or May-Grunwald Giemsa methods. *H. felis* gamonts have an ellipsoidal shape and are 10.5 x 4.7 µm in size (Fig. 1); they are less prominent and so are easily missed compared with the larger *H. canis* gamonts in dogs.

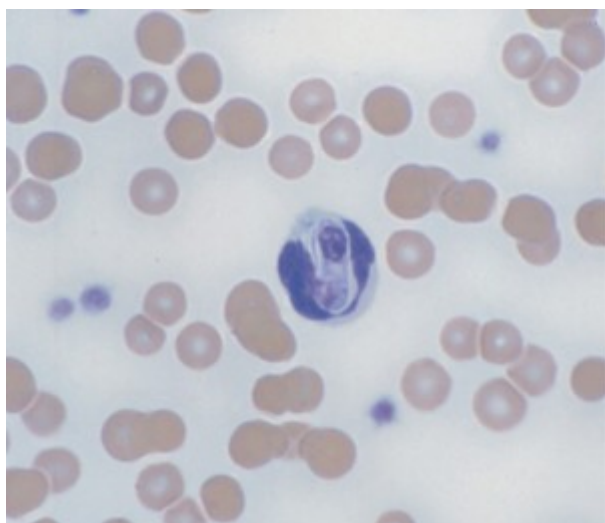


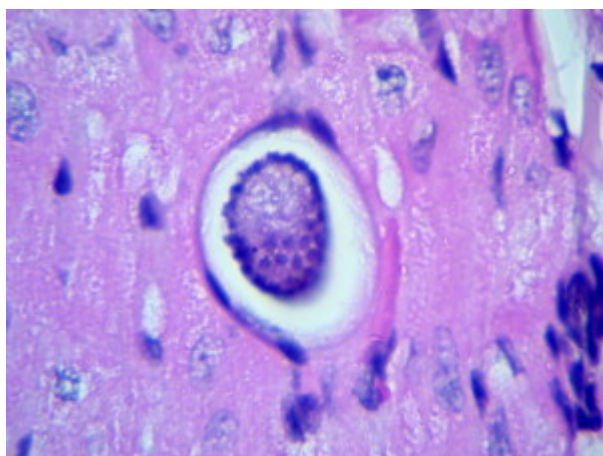
Fig. 1. *Hepatozoon felis* gamont within a neutrophil in a cat blood smear. Courtesy of Prof. Gad Baneth, School of Veterinary Medicine, Hebrew University, Jerusalem, Israel.

Several studies have shown that blood smears have low sensitivity for diagnosis of infection compared to PCR detection of DNA. In one study in Thailand, 32 % of 300 cats were PCR positive, but only in 0.7 % of cats were gamonts observed in blood smears (Jittapalpong et al., 2006). In a recent study in the Maio island (Cape Verde) 12 cats out of 80 (12.5 %) were *H felis* PCR positive and no gamonts were detected in blood smears (Pereira et al., 2019). Similarly, in a study in Israel, none of the cats with meronts in the myocardium tested positive when blood smears were examined (Klopfer et al., 1973).

Therefore, blood PCR should be considered the diagnostic test of choice for confirming hepatozoon infection when blood smears do not show parasites and it is the best tool for prevalence and epidemiological studies.

However, positive DNA results should be interpreted in the light of the clinical picture, as it is highly possible that any clinical signs present are associated with another infectious agent. A quantitative PCR test has been developed that has shown improved sensitivity of detection compared to standard PCR in a group of dogs and cats (Criado-Fornelio et al., 2007).

Meronts (round to oval parasites surrounded by a thick membrane with a length of 39 x 34.5 µm) in skeletal muscle (Fig. 2) might be detected in cats in which muscle biopsies are obtained during investigations of muscle pain or polymyositis, but this scenario has not been reported so far. The detection of meronts in skeletal and myocardial muscle histologically might occur as incidental or unexpected findings in the necropsy of cats in endemic areas.



*Fig. 2. Hepatozoon felis meront within myocardial muscle in a cat. Courtesy of Prof. Gad Baneth, School of Veterinary Medicine, Hebrew University, Jerusalem, Israel.*

## Treatment

There have been no prospective controlled studies on the treatment of feline hepatozoonosis, so all information is based on a few published historical case reports. Doxycycline was used in one case with no clear benefits on the outcome (Ewing, 1977) and a combination of oxytetracycline and primaquine in another case led to a successful outcome (Van Amstel, 1979).

Other drugs frequently used in canine hepatozoonosis have not been studied in cats. However, in the case report recently published from Austria imidocarb dipropionate at 6 mg/kg two doses 14 days apart combined with doxycycline at 5 mg/kg q12h for 4 weeks was effective for clinical signs remission, and also for clearing the parasite from the blood (Basso et al., 2019).

## Prevention

No clear guidelines on the prevention of infection can be made, as the routes of transmission in cats remain unknown. It is likely that, as in dogs, transmission is related to ingestion of blood sucking vectors, as well as to the consumption of meat and vertical transmission. Therefore, preventive treatment against external parasites (fleas, ticks, others) is strongly recommended in any cat, not only but especially in cats with outdoor access.

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