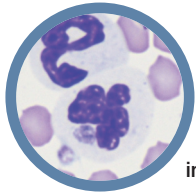




ROLE OF VECTOR-BORNE PATHOGENS IN THE DEVELOPMENT OF FEVER IN CATS

2. Tick- and sandfly-associated diseases



Practical relevance: There has been increasing identification of vector-borne pathogens in cats presented to veterinary clinics around the world for evaluation of fever and the associated secondary effects, such as signs of depression and loss of appetite.

Aim: The aim of this article is to summarize the clinically relevant information concerning fever in cats that is associated with pathogens vectored by ticks or sandflies, with an emphasis on presenting clinical abnormalities and optimal diagnostic, treatment and prevention strategies.

Fever in cats associated with pathogens known or suspected to be vectored by fleas was discussed within Part 1 of this two-part article series.

Keywords: *Anaplasma*; *Bartonella*; *Borrelia*; *Ehrlichia*; *Leishmania*; sandfly; tick

INTRODUCTION

In Part 1 of this two-part article series, the two major differentials for elevated body temperature ($>39.2^{\circ}\text{C}$, 102.5°F) in cats – hyperthermia and fever (pyrexia) – were discussed and the infectious disease agents proven or likely to be vectored by fleas were summarized.¹ Here, in Part 2, which reviews the infectious disease agents vectored by ticks or sandflies, emphasis is placed on common clinical and laboratory findings, optimal diagnostic tests, treatments and strategies for prevention.

Cats do not develop permanent immunity to *Anaplasma phagocytophilum* and repeated infections have been documented experimentally.

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TICK-BORNE AGENTS ASSOCIATED WITH FEVER

Anaplasma, *Ehrlichia* and *Rickettsia* species

Anaplasma phagocytophilum

Wild-caught adult *Ixodes scapularis* in the USA are commonly positive for *Anaplasma phagocytophilum* DNA and experimentally infested cats have been shown to be susceptible to *A phagocytophilum* infection.^{2,3} Cats do not develop permanent immunity to *A phagocytophilum* and repeated infections have been documented in experimentally infested cats.⁴ DNA of *A phagocytophilum* or antibodies against the agent have been detected in naturally exposed cats in most countries with *Ixodes* species.^{5–13} *Ixodes* species also often carry *Borrelia burgdorferi* and coinfections with *A phagocytophilum* are likely common.¹²

A small number of cats experimentally infected with *A phagocytophilum* after infestation with *I scapularis* in two studies did not develop clinical signs of illness.^{2,4} Cats living in endemic areas are commonly seropositive but most do not have clinical signs of disease. However, when illness is recognized in naturally infected cats, fever, anorexia and lethargy are the most common clinical abnormalities, and lameness is likely to occur.^{4,6,9}



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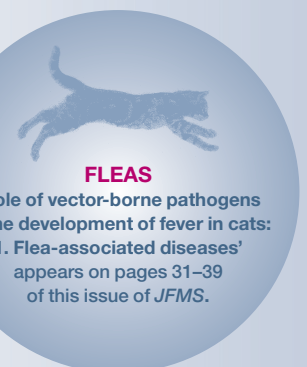
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FLEAS

'Role of vector-borne pathogens in the development of fever in cats: 1. Flea-associated diseases' appears on pages 31–39 of this issue of JFMS.

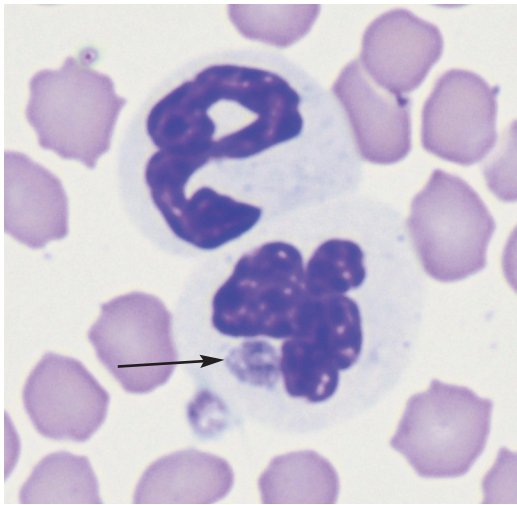


Figure 1 *Anaplasma phagocytophilum* morula (arrow) in a neutrophil of an experimentally infected cat

Cats with fever, with or without thrombocytopenia, residing in *Ixodes* species-endemic areas should have blood smears examined cytologically to attempt to find morulae (Figure 1).⁹ Many commercial laboratories offer PCR assays to amplify *A phagocytophilum* DNA from blood and these assays are more likely to be positive than serologic tests in acute illness (Table 1).² One commercial assay for the detection of *A phagocytophilum* antibodies in dog serum (SNAP 4DXPlus; IDEXX Laboratories) has been shown to detect these antibodies in feline serum.² Approximately 30% of cats with proven clinical infections induced by *A phagocytophilum* are seronegative when first assessed serologically, but most of the proven cases evaluated to date have ultimately seroconverted.⁵

Several antibiotics have been administered to naturally infected cats with suspected anaplasmosis. In two studies all cats became clinically normal within 24–48 h of initiation of tetracycline or doxycycline administration and recurrence was not reported.^{5,6,9} Two cats were still PCR positive 17 days and 90 days after treatment (of 21–30 days' duration) while clinically normal, which suggests that treatment with tetracyclines for ≤30 days may be inadequate for eliminating this pathogen from some cats.⁵

The risk of infection in cats by *A phagocytophilum* should be reduced by appropriate use of an acaricide. However, in one study, purchase of a topical acaricide was not associated with a lessened risk of having antibodies against *A phagocytophilum* or *B burgdorferi*.¹² In that study, it appeared that owners of treated, seropositive cats did not administer the acaricide all year round. It is also possible that owners of cats with known exposure, and possibly previous infections, were more likely to purchase an acaricide.

Any country that has *Ehrlichia canis* infections in dogs likely also has *E canis* infections in cats.



Anaplasma platys

A number of cats have been shown to be infected by *Anaplasma platys*.^{14–17} This agent is suspected to be tick-borne, possibly by *Rhipicephalus sanguineus*. However, whether this agent induces fever in cats alone or as a co-infection has not been determined. Serologic tests have not been validated for this organism in cats. Thus, the diagnosis currently is based on the detection of morulae in platelets or amplification of specific DNA by PCR assay. Optimal treatments are unknown for cats, but doxycycline should be effective. Use of acaricides should lessen the risk of exposure.

Ehrlichia species

While canine ehrlichiosis is well characterized, less is known about the agents associated with disease in cats. It is likely that any country that has *Ehrlichia canis* infections in dogs also has *E canis* infections in cats. Naturally exposed cats in many countries have variously been shown to have *Ehrlichia*-like bodies or morulae in peripheral lymphocytes or monocytes, had DNA consistent with *E canis* amplified from the blood or tissues, or had antibodies that react to *E canis* morulae or peptides.^{10,13,18–30} There have been field cases that have been positive for DNA identical to *E canis* at two genes that never seroconverted.²¹ Another study reported that cats at greater risk for *R sanguineus* infestation were more likely to have higher prevalence rates (9.4%) of PCR positivity for *E canis* DNA.²⁶ In Sicily, *E canis* DNA was amplified from ticks collected from cats.³¹

Fever, lethargy and inappetence are commonly reported clinical abnormalities in cats with suspected ehrlichiosis and so testing may be indicated in cats showing these signs. Thrombocytopenia, anemia and monocytosis appear to be the most common clinical laboratory findings in naturally infected cats.^{19,20,25,30} Almost every abnormality noted in dogs with clinical ehrlichiosis has been detected in cats, including monoclonal gammopathy.

A validated serologic assay is not currently available and some cats with *E canis*-like DNA in blood have been seronegative.²¹ Positive serologic test results occur in both healthy and clinically ill cats, and so a diagnosis of clinical ehrlichiosis should not be based on serologic test results alone. *Ehrlichia* species PCR and gene sequencing can be used in cats with suspicious clinical signs to confirm infection and should be considered the tests of choice at this time. However, not all cats that are PCR positive are clinically ill.

Clinical improvement after treatment with tetracycline, doxycycline or imidocarb dipropionate has been reported for most cats with suspected ehrlichiosis.^{19–21} The current recommendation of the American College of

Table 1 Concurrent findings and diagnostic plan suggestions for feline tick- or sandfly-borne pathogens associated with fever

		Diagnosis*		
	Concurrent findings	Direct identification techniques	Serology	Comments
Tick-associated pathogens				
<i>Anaplasma phagocytophilum</i>	❖ Anorexia ❖ Lethargy ❖ Lameness ❖ Thrombocytopenia	❖ Blood smear or joint fluid cytology ❖ PCR assay on blood	❖ Several techniques ❖ Available in some laboratories ❖ Canine SNAP 4DXPlus used in two experimental studies^{2,4}	❖ Morulae in neutrophils
<i>Anaplasma platys</i>	❖ Lethargy ❖ Thrombocytopenia	❖ Blood smear cytology ❖ PCR assay on blood	❖ Not commercially available	❖ Whether canine serologic assays cross react with infected cats is unknown
<i>Babesia</i> species	❖ Hemolytic anemia	❖ Blood smear cytology ❖ PCR assay on blood	❖ Not commercially available	❖ Cytology is likely falsely negative frequently
<i>Borrelia burgdorferi</i>	❖ Lethargy ❖ Lameness	❖ PCR assay on skin affected by tick bites ❖ PCR assay on synovial fluid	❖ Several techniques ❖ Available in some laboratories ❖ Canine SNAP 4DXPlus used in two experimental studies^{2,4}	❖ PCR assay on blood of affected dogs is generally negative; unknown in cats
<i>Borrelia persica</i>	❖ Anemia ❖ Thrombocytopenia	❖ Blood smear cytology ❖ PCR assay on blood	❖ Not commercially available	
<i>Cytauxzoon</i> species	❖ Anemia ❖ Dyspnea ❖ Findings consistent with shock	❖ Blood smear cytology ❖ PCR assay on blood	❖ Not commercially available	
<i>Ehrlichia</i> species	❖ Anemia ❖ Thrombocytopenia ❖ Pancytopenia ❖ Hyperglobulinemia ❖ Uveitis ❖ Other	❖ Blood smear cytology ❖ PCR assay on blood	❖ Available in some US laboratories	❖ Cytology commonly falsely negative ❖ Morulae in mononuclear cells ❖ Serum antibodies have been falsely negative in some cats ❖ Most clinical findings in dogs have been described in cats
<i>Francisella tularensis</i>	❖ Lymphadenopathy	❖ Cytology ❖ Fluorescent antibody staining ❖ Culture ❖ PCR assay	❖ Available in some laboratories	❖ Lymph nodes, abscesses, airway wash samples used for direct identification techniques ❖ Rising titers can be used to confirm recent infection if direct techniques are negative
<i>Hepatozoon</i> species	❖ Currently unknown	❖ Blood smear cytology ❖ PCR assay on blood	❖ Not commercially available	
<i>Rickettsia rickettsii</i> <i>Rickettsia conorii</i> <i>Rickettsia massiliae</i>	❖ Currently unknown	❖ PCR assay on blood	❖ Not commercially available	❖ <i>Rickettsia rickettsii</i> is the predominant species in the USA and others exist in Europe
Sandfly-associated pathogens				
<i>Leishmania</i> species (mainly <i>Leishmania infantum</i>)	❖ Skin lesions ❖ Hyperglobulinemia ❖ Lymphadenopathy ❖ Uveitis ❖ Other	❖ PCR assay on aspirates or imprints ❖ Cytology ❖ Histopathology	❖ Available in some laboratories	❖ In contrast to dogs, even a low antibody titer likely proves infection

*Results of direct tests (cytology ± staining techniques, culture, PCR assays) confirm infection when they are positive. However, for some agents, such as *Ehrlichia* species and *Hepatozoon* species, there can be a carrier phase in healthy cats and so positive test results do not confirm disease induced by the agent. Similarly, most positive antibody test results merely indicate past or current infection but do not confirm current infection or disease

Veterinary Internal Medicine Infectious Disease Study Group is to administer doxycycline (10 mg/kg PO q24h or 5 mg/kg PO q12h for 28 days). Pancytopenia can occur in cats with ehrlichiosis;²¹ in dogs, pancytopenia may not respond to treatment.

This pathogen is another example of why acaricides should be used to attempt to

avoid infection with vector-borne disease agents. It has been shown in dogs that *E. canis* can be transmitted within 3 h of tick attachment.³² This short transmission time indicates the importance of using acaricides that either rapidly kill attached ticks or, preferably, prevent ticks from biting in the first place.

Rickettsia species

Rickettsia conorii and *Rickettsia massiliae* DNA was amplified or antibodies reacted to *R conorii* from the blood of cats in Spain and Italy.^{13,33} In one study of cats in the USA with fever, the *Rickettsia rickettsii* antibody prevalence rate was 6.6%, but DNA of the agent was not amplified from blood.³⁴ Similar results were seen in a study of cats in St Kitts, West Indies where 22/52 feral cats had *R rickettsii* antibodies in serum but were all negative for specific DNA in blood.¹⁸ These results prove that cats are sometimes exposed to tick-borne spotted fever group organisms, but further data are needed to determine the significance of disease associations such as fever. Because clinical illness in cats has not been documented, optimal treatment is unknown. However, based on results in dogs, doxycycline or a fluoroquinolone would be logical choices. Use of acaricides should lessen the potential for transmission of these agents to cats.

Other bacteria

Borrelia species

Many cats exposed to *Ixodes* species in North America and parts of Europe develop antibodies against *B burgdorferi*. Some cats are also infected by *Borrelia persica* from infestation by *Ornithodoros tholozani* in some parts of the Middle East.³⁵ Fever can be associated with *B burgdorferi* or *B persica* infections in cats.^{12,35,36} However, since many cats have exposure to *Ixodes* species, it can be difficult to determine whether clinical illness is resulting from *A phagocytophilum* or *B burgdorferi* or both.¹²

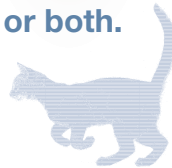
Cats with fever and suspected *B persica* infections should have peripheral blood smears evaluated for spirochetes and the infection can be confirmed by PCR assay.³⁵ While not approved for this use, serum from cats with fever and suspected *B burgdorferi* infection can be screened with a commercially available kit (SNAP 4DXPlus; IDEXX Laboratories) titrated for use with dog sera.^{2,4} However, a positive *B burgdorferi* antibody assay result proves only exposure, and not necessarily clinical borreliosis.

Cats with fever from suspected borreliosis generally respond to the administration of doxycycline at 5 mg/kg PO q12h or 10 mg/kg PO q24h.^{12,36} The effectiveness of different acaricides for the prevention of transmission of *Borrelia* species to cats has not been compared but, based on experiences in dogs, potentially all should be helpful in preventing borreliosis in cats if used appropriately.³⁷

Francisella tularensis

Cats in the USA can develop fever after infection by *Francisella tularensis*.³⁸ Cats are often infected by *F tularensis* through carnivorousism but tick-borne transmission can occur. Infection

Since many cats have exposure to *Ixodes* species, it can be difficult to determine whether clinical illness is resulting from *Anaplasma phagocytophilum* or *Borrelia burgdorferi* or both.



can be proven by culture, amplification of specific DNA by PCR assay or rising antibody titers.³⁹ Clinically ill cats should respond to doxycycline or fluoroquinolones. Cats in endemic areas should be provided with tick control all year round and hunting behavior should be minimized if possible.

Protozoa

Babesia species

In South Africa and parts of Asia, there is a high number of *Babesia* species that infect cats. In Europe, *Babesia vogeli* or *Babesia vulpes* DNA have been amplified from ticks collected from cats and antibodies reactive to *B vulpes* detected in cats.^{13,31,37,40} In the Americas, *B vogeli* and *Babesia gibsoni* have been described in cats as both single and mixed infections.^{18,41} *B vogeli* and *Babesia canis* are likely more prevalent in areas with high infestation rates for *R sanguineus*. However, whether these agents induce fever in cats alone or as a coinfection has not been determined.

Serologic tests have not been validated for these agents in cats. Thus, the diagnosis currently is based on detection of piroplasms in erythrocytes or amplification of specific DNA by PCR assay. Optimal treatments are unknown for cats but options primarily extrapolated from canine babesiosis have been reviewed.⁴² Use of acaricides should lessen the risk of exposure, except for *B gibsoni* which may be transmitted directly.

Cytauxzoon species

Cats in the USA, Brazil and Europe can be infected by *Cytauxzoon* species.^{10,43–49} It is apparent that *Cytauxzoon felis* infections in the USA (transmitted by *Amblyomma americanum*) can be very pathogenic when compared with the *Cytauxzoon* species infections occurring in cats in other countries. This may represent different species in different countries.⁵⁰ While fatal *C felis* infections are common in some regions of the USA, cats that survive or have subclinical infections are also common.^{51,52} These findings suggest that a wide range of clinical presentations may occur, with differences among cats perhaps related to inoculation dose, pre-existing immunity, strain variations, or as yet unidentified variations in immune response of the cat. A recent study showed that *C felis* could be transmitted after 36–48 h of tick attachment, and that ingestion of *A americanum* did not induce infections.⁵³

In the USA, clinical infections are recognized most commonly in the spring, summer and fall. Owners of clinically affected cats report non-specific complaints, such as lethargy and anorexia, frequently. Cats have fever or hypothermia if presented in the final shock phase of infection. Common physical examination findings that might lead to consideration of this agent as a differential diagnosis include unresponsive

fever, pale mucous membranes from shock or anemia, icterus, splenomegaly and hepatomegaly.^{10,45} Discomfort, clinical evidence of central nervous system disease including seizures, tachypnea with or without dyspnea, and sudden death on manipulation may all occur. Recently, ocular involvement of cytauxzoonosis has been described.⁵⁴

Cytauxzoon species can be seen on erythrocytes frequently, but cytology can be falsely negative in the acute stages of illness. The serious clinical signs of disease relate to the development of shizonts in the tissues. The syndrome can be diagnosed by cytological demonstration of piroplasms on erythrocytes or shizonts in spleen, liver or bone marrow samples, or by amplification of *Cytauxzoon* species DNA in blood or tissue aspirates by PCR.⁴⁵

To date, clinically affected cats have shown the best response to a combination of azithromycin at 10 mg/kg PO q24h and atovaquone at 15 mg/kg PO q8h, with approximately 60% of treated cats responding.^{55,56} This combination is superior to diminazene or imidocarb protocols.⁵⁷ Minimal restraint techniques should be used during the administration of supportive care to lessen the likelihood of sudden death.

The poor overall treatment response in clinical cytauxzoonosis cases is a perfect example of why tick control can be so important. Again, as referred to earlier in this article series, it is always better to prevent a vector-borne disease than attempt to treat it after illness has begun. Appropriate use of acaracides should lessen the risk of transmission of this agent.⁵⁸ One commercially available flea and tick collar containing flumethrin (Seresto; Bayer Animal Health) and a topical product containing sarolaner (Selamectin Plus; Zoetis) were shown to block transmission of *C felis* by *A americanum*.^{58,59}

Hepatozoon species

A number of investigators have amplified *Hepatozoon* species DNA from cats and the agent has been detected in ticks collected from cats.^{3,28,47,60–62} In a recent report on cats in southern Italy, three different *Hepatozoon* species were detected.⁶¹ In dogs, *Hepatozoon americanum* infection is induced by ingestion of ticks or ingestion of prey species such as rabbits.⁶³ Whether carnivorous results in infection of cats with *Hepatozoon* species has not been determined.

Fever associated with *Hepatozoon* species has not been studied extensively in cats; however, in dogs in the USA with *H americanum* infection, fever is common. In one study from Israel, fever was reported as one of the potential clinical manifestations of hepatozoonosis in cats.⁶⁰ PCR assays can be used to help confirm the diagnosis but optimal treatment protocols for cats with *Hepatozoon* species infections are unknown. Use of acaricides should lessen the potential for transmission of these agents among cats.

The poor overall treatment response in clinical cytauxzoonosis cases is a perfect example of why tick control can be so important.



SANDFLY-BORNE AGENTS ASSOCIATED WITH FEVER

Leishmania species

Feline leishmaniasis has been reported globally.^{62,64–74} Traditionally skin lesions have been described as the most frequent clinical manifestation and sometimes were the only finding on physical examination. However, more recently cats have been described that do not have cutaneous manifestations but rather have other clinical signs, and in general these cases appear to be associated with a worse prognosis. A case of fever in a cat that may have related to leishmaniasis has been reported.⁷⁵

The diagnosis of leishmaniasis in cats, in the presence of suspected clinical signs, can be achieved using direct techniques such as cytology (Figure 2), histopathology and PCR assays. Alternatively, serologic techniques such as indirect fluorescent antibody assays or ELISAs that evaluate the immune response of the cat against *Leishmania* species can be used indirectly to support the diagnosis. In contrast to dogs that can have very high antibody levels even when subclinical carriers, a low positive titer in cats can be considered highly suggestive of a diagnosis of leishmaniasis.⁷⁶

Information about the best management of feline leishmaniasis is mostly based on single case reports. Long-term administration of allopurinol (10–20 mg/kg q12h or q24h) is usually clinically effective, but meglumine antimoniate has also been used successfully in a few cases. However, in the majority of cats the infection cannot be cleared, so the use of adequate prevention, including sandfly control, is recommended to reduce the number of cats infected with *Leishmania* species in endemic areas.^{77,78}

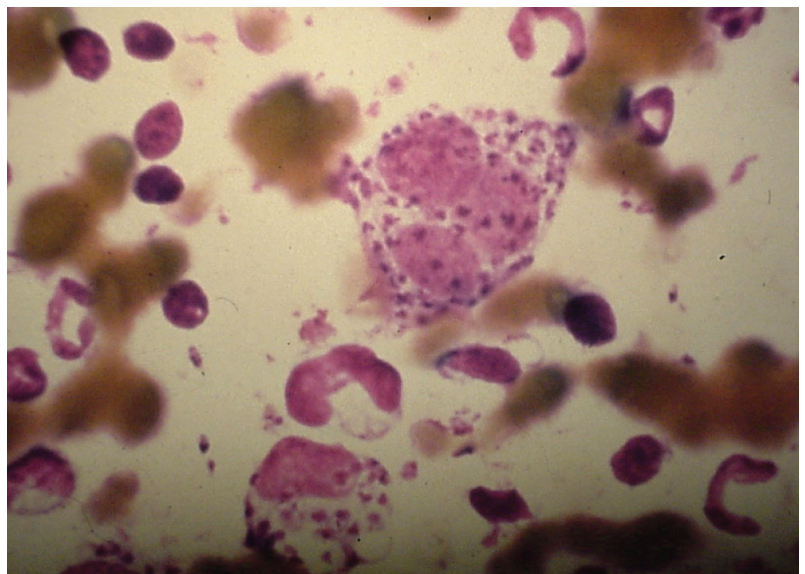


Figure 2 Cytology sample showing *Leishmania* species amastigotes in macrophages

KEY POINTS

- ✦ Some tick- and sandfly-associated pathogens can be associated with fever in cats and the history and concurrent clinical signs can trigger a diagnostic work-up and, ultimately, appropriate therapy.
- ✦ Prevention of these infections is preferred and there is mounting evidence to show that consistent use of products that either rapidly kill vectors or, preferably, prevent vectors from biting a cat is desirable.



ACKNOWLEDGEMENTS

The authors thank Dr Susanne Siebert and Dr Annette Boegel for their support and encouragement as well as editorial comments.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article.

ETHICAL APPROVAL

This work did not involve the use of animals and therefore ethical approval was not required.

INFORMED CONSENT

This work did not involve the use of animals and therefore informed consent was not required. No animals or humans are identifiable within the publication and therefore additional consent for publication was not required.

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