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## **The role of vector-borne pathogens in development of fever in cats**

### **Part 2 – Tick and sand fly associated diseases**

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## **Abstract**

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 like signs of depression and loss of appetite.

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

## **Introduction**

In Part 1 of this two-part article series, the 2 major differentials for elevated body temperatures (>39.2°C, 102°F) in cats – hyperthermia and fever (pyrexia) – were reviewed and the infectious disease agents proven or likely to be vectored by fleas were summarized.<sup>1</sup> In Part 2, the infectious disease agents vectored by ticks or sand flies are discussed. Emphasis is placed on common clinical and laboratory findings, optimal diagnostic tests, treatments, and strategies for prevention.

## **Tick-borne agents associated with fever**

### *Anaplasma phagocytophilum*

Wild caught adult *Ixodes scapularis* in the United States are commonly positive for *A. phagocytophilum* DNA and experimentally infested cats have been shown to be susceptible to *A. phagocytophilum* infection.<sup>2,3</sup> Cats do not develop permanent immunity to *A. phagocytophilum* and repeated infections have been documented in experimentally infested cats.<sup>4</sup> DNA of *A. phagocytophilum* or antibodies against the agent have been detected in naturally exposed cats in most countries with *Ixodes* spp..<sup>5,13</sup> *Ixodes* spp. also often carry *B. burgdorferi* and co-infections with *A. phagocytophilum* are likely common.<sup>12</sup>

Cats infected with *A. phagocytophilum* after infestation with *I. scapularis* have not developed clinical signs of illness.<sup>2,4</sup> Cats living in endemic areas are commonly seropositive but most do not have clinical signs of disease. When illness is recognized fever, anorexia, and lethargy are the most common clinical abnormalities in naturally infected cats.<sup>4,6,9</sup>

Cats with fever residing in *Ixodes* spp. endemic areas should have blood smears examined cytologically attempt to find morulae (Figure 1).<sup>9</sup> Many commercial laboratories offer PCR assays to amplify *A. phagocytophilum* DNA from blood and these assays are more likely to be positive than serological tests in acute illness (Table 1).<sup>2</sup> One commercial assay for detection of *A. phagocytophilum* antibodies in dog serum (SNAP 4DXPlus, IDEXX Laboratories) has been shown to detect these antibodies in feline sera.<sup>2</sup> 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.<sup>5</sup>



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

Several antibiotics have been administered to naturally infected cats with suspected anaplasmosis, but all cats in 2 studies became clinically normal within 24 to 48 hours after initiation of tetracycline or doxycycline administration and recurrence was not reported.<sup>5,6,9</sup> Two cats were still PCR positive 17 days and 90 days after treatment (of 21 to 30 days duration) while clinically normal, which suggests that treatment with tetracyclines for 21 to 30 days may be inadequate for eliminating this pathogen from some cats.<sup>5</sup>

Infection of 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*.<sup>12</sup> In that study, it appeared that owners of treated, seropositive cats did not administer the acaricide year round. It is also possible that owners of cats with known exposure, and possibly previous infections, were more likely to purchase an acaricide.

### *Anaplasma platys*

A number of cats have been shown to be infected by *A. platys*.<sup>14-17</sup> This agent is suspected to be tick-borne, possibly by *Rhipicephalus sanguineus*. However, whether this agent induces fever in cats alone or as a coinfection has not been determined. Serological tests have not been validated for this organism in cats. Thus, the diagnosis currently is



based on 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 risk of exposure.

### *Babesia* spp.

In South Africa and parts of Asia, there is a high number of *Babesia* spp. that infect cats. In Europe, *Babesia vogeli* or *Babesia vulpes* DNA was amplified from ticks collected from cats and antibodies reactive to *Babesia vulpes* were detected in cats.<sup>13,18-20</sup> In the Americas, *B. vogeli*, *Babesia gibsoni*, and mixed infections have been described in cats.<sup>21,22</sup> *Babesia 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. Serological 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 were reviewed.<sup>23</sup> Use of acaricides should lessen risk of exposure except for *B. gibsoni* which may be transmitted directly.

*Borrelia* spp.

Many cats exposed to *Ixodes* spp. 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.<sup>24</sup> Fever can be associated with *B. burgdorferi* or *B. persica* infections in cats.<sup>12,24,25</sup> However, since many cats have exposure to *Ixodes* spp., it can be difficult to determine whether clinical illness is resulting from *A. phagocytophilum* or *B. burgdorferi* or both.<sup>12</sup>

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.<sup>24</sup> 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, Portland Maine, USA) titrated for use with dog sera.<sup>2,4</sup> However, a positive *B. burgdorferi* antibody assay result only proves exposure, not necessarily clinical borreliosis.

Cats with fever from suspected borreliosis generally respond to administration of doxycycline at 5 mg/kg, PO, q12h or 10 mg/kg, PO, q24h.<sup>12,25</sup> The effectiveness of different acaricides for the prevention of transmission of *Borrelia* spp. to cats has not been

compared but, based on experiences in dogs, all should be helpful in preventing borreliosis in cats if used appropriately.<sup>20</sup>

*Cytauxzoon* spp.

Cats in the United States, Brazil and Europe can be infected by *Cytauxzoon* spp..<sup>10,26-32</sup> It is apparent that *Cytauxzoon felis* infections in the United States (transmitted by *Amblyomma americanum*) can be very pathogenic when compared with the *Cytauxzoon* spp. infections occurring in cats in other countries. This may represent different species in different countries.<sup>33</sup> While fatal *C. felis* infections are common in some regions in the United States, cats that survive or have subclinical infections are also common.<sup>34,35</sup> These findings suggest that a wide range of clinical presentations may occur with differences amongst 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 between 36 and 48 hours of tick attachment, and ingestion of *A. americanum* did not induce infections.<sup>36</sup>

In the United States, clinical infections are recognized most commonly in the spring, summer and fall. Owners of cats report non-specific complaints as lethargy and anorexia frequently. The infected cats have fever or hypothermia if presented in the final

shock phase. Common physical examination findings that might lead to consideration of this agent as a differential diagnosis include unresponsive fever, pale mucous membranes, icterus, splenomegaly, and hepatomegaly.<sup>10,28</sup> Discomfort, clinical evidence of central nervous system disease including seizures, tachypnea with or without respiratory distress, and sudden death on manipulation all occur in some cats. Recently, ocular involvement of cytauxzoonosis has been described.<sup>37</sup>

*Cytauxzoon* spp. can be seen on the 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 the piroplasmas on erythrocytes, cytological demonstration of shizonts in spleen, liver, or bone marrow samples, or by PCR of *Cytauxzoon* spp. DNA in blood or tissue aspirates.<sup>28</sup>

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.<sup>38,39</sup> This combination is superior to diminazene or imidocarb protocols.<sup>40</sup> Minimal restraint techniques should be used during 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. It is always better to prevent a vector-borne disease rather than attempt to treat it after illness has begun. Use of acaracides appropriately should lessen the risk of transmission of this agent.<sup>41</sup> One commercially available flea and tick collar containing flumethrin (Seresto<sup>®</sup>, Bayer Animal Health) and a topical product containing sarolaner (Selamectin Plus, Zoetis) were shown to block transmission of *C. felis* by *A. americanum*.<sup>41,42</sup>

#### *Ehrlichia* spp.

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 *E. canis* infections in dogs, has *E. canis* infections in cats. Naturally exposed cats in many countries have been shown to have *Ehrlichia*-like bodies or morulae in peripheral lymphocytes or monocytes, have had DNA consistent with *E. canis* amplified from the blood or tissues, or have had antibodies that react to *E. canis* morulae or peptides.<sup>10,22,43-55</sup> There have been field cases that have been positive for DNA identical to *E. canis* at 2 genes that never seroconverted.<sup>45</sup> Another study in Brazil 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.<sup>50</sup> In Sicily, *E. canis* DNA was amplified from ticks collected from some cats.<sup>54</sup>

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.<sup>43,44,49,55</sup> Almost every abnormality noted in dogs with clinical ehrlichiosis has been detected in cats, including monoclonal gammopathy.

A validated serological assay is not currently available and some cats with *E. canis*-like DNA in blood were seronegative.<sup>45</sup> 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* spp. 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.<sup>43-45</sup> Moreover, a positive response to treatment was a criterion for the diagnosis of ehrlichiosis for some cats. The current recommendation of the American College of Veterinary Internal Medicine

Infectious Disease Study Group ([www.acvim.org](http://www.acvim.org)) 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; when this occurs in dogs it may not respond to treatment.<sup>45</sup>

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 hours after tick attachment.<sup>55</sup> This short transmission time shows the importance of using acaricides that either rapidly kill attached ticks or, preferably, prevent ticks from biting in the first place.

#### *Francisella tularensis*

Cats in the United States can develop fever after infection by *F. tularensis*.<sup>56</sup> Cats are often infected by *F. tularensis* by carnivorousism but tick-borne transmission could occur. Infection can be proven by culture, amplification of specific DNA by PCR assay, or rising antibody titers.<sup>57</sup> Clinically ill cats should respond to doxycycline or quinolones. Cats in endemic areas should be provided tick control year round and hunting behavior should be minimized if possible.

#### *Hepatozoon* spp.

A number of investigators have amplified *Hepatozoon* spp. DNA from cats and the agent has been detected in ticks collected from cats.<sup>3,30,52,59-61</sup> In a recent report from cats in southern Italy, 3 different *Hepatozoon* spp. were detected.<sup>60</sup> In dogs, *H. americanum* infection is induced by ingestion of the ticks or ingestion of prey species like rabbits.<sup>62</sup> Whether carnivorousness results in infection of cats with any *Hepatozoon* spp. has not been determined. Fever associated with *Hepatozoon* spp. has not been studied extensively in cats; however, in dogs in the United States with *H. americanum* infection, fever is common. In one study from Israel, fever was reported as one of the potential clinical manifestations in cats.<sup>59</sup> PCR assays can be used to help confirm the diagnosis but optimal treatment protocols for cats with hepatozoonosis are unknown. Use of acaricides should lessen the potential for transmission of these agents amongst cats.

#### *Rickettsia* spp.

*Rickettsia conorii* and *Rickettsia massiliae* DNA was amplified or antibodies reacted to *R. conorii* from the blood of cats in Spain and Italy.<sup>53,63</sup> In one study of cats in the USA with fever, the *R. rickettsii* antibody prevalence rate in cats was 6.6%, but DNA of the agent was not amplified from blood.<sup>64</sup> Similar results were seen in a study of cats in St. Kitts, West Indies where 22 of 52 feral cats had *R. rickettsii* antibodies in serum but were



all negative for specific DNA in blood.<sup>22</sup> These results prove that cats are sometimes exposed to tick-borne spotted fever group organisms but further data are needed to determine significance of diseases associations like 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 amongst cats.

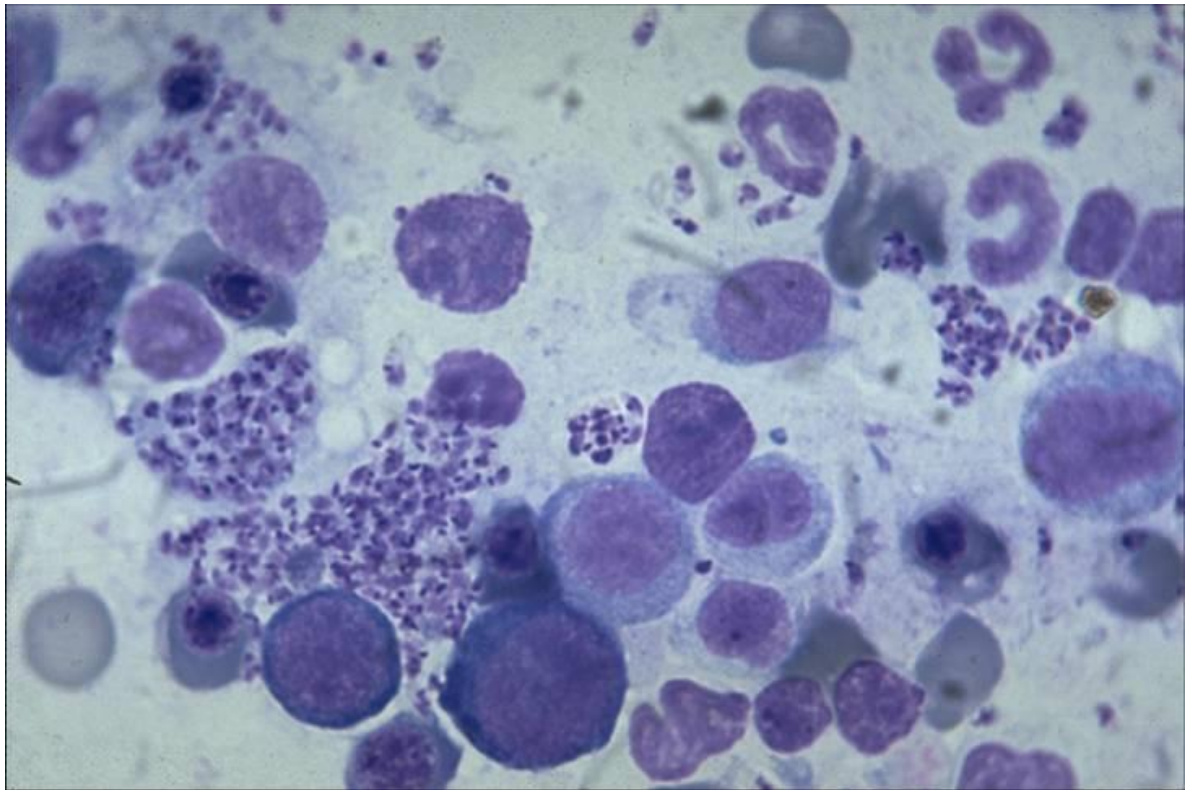
### **Sand fly borne agents associated with fever**

*Leishmania* spp.

Feline leishmaniosis has been globally reported.<sup>61,654-75</sup> 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. Recently, a cat with fever that may have related to leishmaniosis was reported.<sup>76</sup>

The diagnosis of leishmaniosis in cats, in the presence of suspected clinical signs, can be achieved using direct techniques like cytology, histopathology and PCR assays (Figure 2). Alternately, serological techniques such as indirect fluorescent antibody assays

or ELISA that evaluate the immune response of the cat against *Leishmania* spp. can be used indirectly to support the diagnosis. In contrast to dogs that can have very high antibody levels even when subclinical carriers, low positive titer in cats can be considered highly suggestive of diagnosis.<sup>77</sup>



**Figure 2.** Cytology of an arthrocentesis in a dog with polyarthritis showing *Leishmania* amastigotes in macrophages. Courtesy of Dr. Arturo Font, Barcelona, Spain

The information about the best management of feline leishmaniosis 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 sand fly control, is recommended to reduce the number of cats infected with *Leishmania* in endemic areas.<sup>787,798</sup>

## **Conclusions**

Some tick and sand fly 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 that consistent use of products that either rapidly kill vectors or, preferably, prevent vectors from biting a cat is desirable.

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### **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. In addition, no animals or humans are identifiable within the publication and, therefore, additional consent for publication was not required.

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**Table 1. Concurrent findings and diagnostic plan suggestions for feline tick or sand fly borne pathogens associated with fever.**

Pathogens	Concurrent Findings	Diagnosis*		Comments
		Direct identification techniques	Serology	
<i>Anaplasma phagocytophilum</i>	- Lethargy - Lameness - Thrombocytopenia	- Blood or joint fluid cytology - PCR assay on blood	- Several techniques - Available in some laboratories - Canine SNAP 4DX Plus used in one experimental study	- Morulae in neutrophils
<i>A. platys</i>	- Lethargy - Thrombocytopenia	- Blood cytology - PCR assay on blood	- Not commercially available	- Whether canine serological assays cross react with infected cats is unknown
<i>Babesia</i> spp.	- 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 4DX Plus used in one experimental study	- 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> spp.	- Anemia - Dyspnea - Findings consistent with shock	- Blood smear cytology - PCR assay on blood	- Not commercially available	

<i>Ehrlichia</i> spp.	<ul style="list-style-type: none"> <li>- Anemia</li> <li>- Thrombocytopenia</li> <li>- Pancytopenia</li> <li>- Hyperglobulinemia</li> <li>- Uveitis</li> <li>- Other</li> </ul>	<ul style="list-style-type: none"> <li>- Blood smear cytology</li> <li>- PCR assay on blood</li> </ul>	- Available in some USA laboratories	<ul style="list-style-type: none"> <li>- Cytology commonly falsely negative</li> <li>- Morulae in mononuclear cells</li> <li>- Serum antibodies have been falsely negative in some cats</li> <li>- Most clinical findings in dogs have been described in cats</li> </ul>
<i>Francisella tularensis</i>	- Lymphadenopathy	<ul style="list-style-type: none"> <li>- Cytology</li> <li>- Fluorescent antibody staining</li> <li>- Culture</li> <li>- PCR assay</li> </ul>	- Available in some laboratories	<ul style="list-style-type: none"> <li>- Lymph nodes, abscesses, airway washing used for direct identification techniques</li> <li>- Rising titers can be used to confirm recent infection if direct techniques are negative</li> </ul>
<i>Hepatozoon</i> spp.	- Currently unknown	<ul style="list-style-type: none"> <li>- Blood smear cytology</li> <li>- PCR assay on blood</li> </ul>	- Not commercially available	
<i>Rickettsia rickettsii</i> <i>R. conorii</i> , <i>R. 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
<b>Sand fly associated</b>				
<i>Leishmania</i> spp. (mainly <i>L. infantum</i> )	<ul style="list-style-type: none"> <li>- Skin lesions</li> <li>- Hyperglobulinemia</li> <li>- Lymphadenopathy</li> <li>- Uveitis</li> </ul>	- PCR assay on aspirates or imprints	- Available in some laboratories	- In contrast to dogs, even a low antibody titer likely proves infection

	- Other			
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\*The results of the direct tests (cytology, other staining techniques, culture, PCR assays) confirm infection when they are positive. However, for some agents like *Ehrlichia* spp. and *Hepatozoon* spp. there can be a carrier phase in healthy cats and so the positive test results do not confirm disease induced by the agent. The same problem is known for most positive antibody test results that indicate past or current infection but do not confirm current infection or disease.

### **Suggested pull quotes**

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

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