Management of feline vector borne diseases

Michael R. Lappin, DVM, PhD, DACVIM
The Kenneth W. Smith Professor in Small Animal Clinical Veterinary Medicine
College of Veterinary Medicine and Biomedical Sciences
Colorado State University, Fort Collins Colorado

There are multiple vector borne diseases in cats; those transmitted by ticks (multiple agents), fleas (multiple agents), mosquitoes (*Dirofilaria immitis*) or sandflies (*Leishmania* spp.) are among the most common. The Companion Animal Parasite Council (www.capcvet.org), European Scientific Counsel Companion Animal Parasites (www.esccap.org/guidelinies/) and the Companion Vector Borne Diseases (www.cvbd.com) are excellent sources of information about vector borne diseases.

There are multiple tick-borne agents that have been grown or amplified from blood or have induced serum antibodies in the serum of normal cats or those with clinical signs like fever. Most of the tick-borne diseases diagnosed in dogs have now been found in cats. In some countries, thorough evaluation of cats for tick-borne disease agents has not been completed. In those situations, dog results can be used as evidence for the presence of individual agents in the region that could potentially infect cats. Results of studies from regional ticks can also be used as evidence for risk in cats (Skarphédinsson et al, 2007; Smith and Wall, 2013; Pennisi et al, 2015). The purpose of this review is to provide an update on the diagnosis and management of feline tick borne diseases of significance. *Anaplasma phagocytophilum, Borrelia* spp., *Cytauxzoon* spp., *Ehrlichia* spp., and *Rickettsia* spp. will be discussed. It is less clear how important *Hepatozoon* spp. infections are in cats (Díaz-Regañón et al, 2017) and how often *Francisella tularensis* infections are transmitted to cats by ticks and so they are not presented in depth.

**Feline granulocytotropic anaplasmosis.** Canine anaplasmosis has been recognized for many years. Cats have shown to be susceptible to *A. phagocytophilum* infection after experimental inoculation (Lappin et al, 2015). DNA of *A. phagocytophilum* DNA has been amplified from blood of naturally exposed cats in multiple countries (Bjöersdorff et al, 1999; Lappin et al, 2004; Adaszek et al, 2013; Bergmann et al, 2016; Lee et al, 2016; Savidge et al, 2016). The easiest way to remember the distribution of *A. phagocytophilum* infections in cats is to remember the range of *Ixodes* spp. or Lyme disease in people or dogs. In the United States, *Ixodes scapularis* transmits both *A. phagocytophilum* and *B. burgdorferi* but some of the current evidence suggests that *A. phagocytophilum* is the more likely cause of the clinical and laboratory abnormalities.

While the pathogenesis of disease associated with *A. phagocytophilum* in cats is unknown, some cats experimentally inoculated with *A. phagocytophilum* developed anti-nuclear antibodies and increased IFN-gamma mRNA suggesting that an immune pathogenesis of disease may contribute to the clinical findings (Foley et al, 2003). Fever, anorexia, and lethargy are the most common clinical abnormalities in naturally infected cats (Savidge et al, 2016). Whether or not this agent is associated with chronic recurrent fever in cats is unknown. In a recent experimental study, cats infected with *A. phagocytophilum* by exposure to wild caught adult *Ixodes scapularis* from Rhode Island remained clinically normal over the 70 day study period in spite of being PCR positive for *A. phagocytophilum* DNA in blood for several weeks (Lappin et al, 2015). In a
larger unpublished study, we infested 10 cats with *I. scapularis* twice and induced *A. phagocytophilum* or *Borrelia burgdorferi* infection in all 10 cats (Lappin et al, 2017). While repeated or new infections with both organisms occurred, all cats remained clinically normal. Since both studies were performed using ticks from the same region, it is possible a less pathogenic strain of the organism was present (Rejmanek D et al, 2013).

Cats with fever in endemic areas can have blood smears examined cytologically but morulae are not always detected in cats with clinical signs of anaplasmosis. Some commercial laboratories offer serologic testing or PCR assays to amplify *A. phagocytophilum* DNA from blood. In experimental infections, DNA is amplified from blood prior to seroconversion for most cats (Lappin et al, 2015). 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. Therefore, cats with suspected anaplasmosis may need convalescent serum samples to prove infection. Alternately, antibody testing could be combined with PCR testing of whole blood in acute cases. The SNAP4DX Plus (IDEXX Laboratories) has been shown to be accurate for the detection of *A. phagocytophilum* antibodies in cats but is not labeled for this purpose (Lappin et al, 2015). In addition, another peptide (P44-4) than the one used on the commercial assays detected antibodies even sooner.

Several antibiotics have been administered to naturally infected cats, but most cats treated in the field become clinically normal within 24 to 48 hours after initiation of tetracycline or doxycycline administration and recurrence has not reported in any cat to my knowledge (Lappin et al, 2014; Savidge et al, 2016). While clinically normal, the organism DNA can still be amplified from the blood of some cats which suggests that treatment with tetracyclines for 21 to 30 days may be inadequate for eliminating the organism from the body. In one of our recent studies, the fact that an owner paid for a tick control product was not associated with decreased risk of having *A. phagocytophilum* antibodies in serum (Hoyt et al, 2017). These results suggest lack of compliance or lack of efficacy. As repeat new infections can occur, it is imperative to maintain tick control at all times, even in cats that have been previously infected (Lappin et al, 2017).

DNA homologous with *A. platys* has been amplified from the blood of cats in some countries with *Rhipicephalus sanguineus* (Lima et al, 2010; Qurollo et al, 2014). Further studies will be required to determine if disease associations exist with this agent in cats.

**Feline borreliosis.** *Borrelia burgdorferi* is the cause of Lyme disease and is transmitted by *Ixodes* spp. Clinical illness in dogs and people is most common in the United States. While *B. burgdorferi* antibodies have been detected in the serum of cats for years, whether the agent induces illness in cats is still controversial (Burgess EC, et al 1992; Levy et al, 2003; Magnarelli et al, 2005; Krupka and Straubiner, 2010).

Recently, 2 manuscripts have attempted to ascribe clinical illness to *B. burgdorferi* infection in cats (Pantchev et al, 2016; Hoyt et al, 2017). The cats that were positive for *B. burgdorferi* antibodies in Belgium, Sweden and Germany had weakness, ataxia and lameness as the most common clinical signs and doxycycline was apparently effective for treatment (Pantchev et al, 2016). The biggest limitation in that study was the failure to report results of assays for other
feline disease agents that may be responsive to doxycycline, in particular *A. phagocytophilum*. The cats in Maine with suspected borreliosis were seropositive to *B. burgdorferi* C6 peptide but negative for *A. phagocytophilum* antibodies, had fever, weakness, lameness, lethargy and inappetance as clinical signs, and had apparent responses to doxycycline (Hoyt et al, 2017). The biggest limitations in that study was the failure to perform *A. phagocytophilum* PCR or other diagnostic assays to evaluate for other feline disease agents that may be responsive to doxycycline. Recently, use of cefovecin was shown to be effective for the treatment of borreliosis in dogs (Wagner et al, 2015). Whether this will prove to be true for cats needs to be determined.

*Borrelia garinii* and *afzelii* have been amplified from ticks collected from cats in the United Kingdom (Unpublished data, Richard Walls, ISFM Congress 2017). Whether these agents are associated with clinical disease in cats is unknown.

There are currently no feline *B. burgdorferi* vaccines. In dogs, use of acaracides can block transmission of the agent and repeat infections can occur in cats (Honsberger et al, 2016; Lappin et al, 2017). Thus, use of acaracides is imperative for the control of this agent.

**Feline cytauxzoonosis.** Cats in the United States and Europe are infected by *Cytauxzoon* spp. (Carli et al, 2012; Díaz-Regañón et al, 2017). Excellent review articles from European authors (Lloret Aet al, 2015) and American authors (Sherrill and Cohn, 2015) are recently available.

It is apparent that *Cytauxzoon felis* infections in the United States (transmitted by *Amblyomma americanum*) can be very pathogenic when compared to the *Cytauxzoon* spp. infections occurring in cats in other countries. This may represent different species in different countries (Gallusová M et al, 2016). However, *C. felis* strain variations also play a role in whether clinical disease occurs within countries as well. For example, while fatal *C. felis* infections are common in some regions in the United States, cats that survive or have subclinical infections are also common (Meinkoth et al, 2000; Rizzi et al, 2015). A recent study showed the *C. felis* could be transmitted between 36 and 48 hours of tick attachment and ingestion of *A. americanum* did not induce infections (Thomas et al, 2017).

In the United States, clinical infections are recognized most commonly in the spring, summer and fall. Non-specific complaints of lethargy and anorexia are reported frequently by owners. 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 pale mucous membranes, icterus, splenomegaly, and hepatomegaly. 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.

Piroplasmas can be seen on the erythrocytes frequently, but can be falsely negative in the acute stages of illness. The serious clinical signs of disease relate to the development of the shizonts in 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 (Sherrill and Cohn, 2015).
To date, clinically affected cats have the best response to the combination of azithromycin at 10 mg/kg, PO, q24 hours and atovaquone at 15 mg/kg, PO, q8 hours (Cohn et al, 2011; Schreeg et al, 2015) with approximately 60% of treated cats responding. This combination is superior to diminezene or imidocarb protocols (Cohn et al, 2011; Lewis et al, 2014). Minimal restraint techniques should be used during administration of supportive care to lessen the likelihood of sudden death.

The poor overall treatment responses 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 that attempt to treat it after illness has begun. Use of acaracides appropriately should lessen the risk of transmission of this agent (Reichard et al, 2013).

**Feline monocytotropic ehrlichiosis.** 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 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, and have had antibodies that react to *E. canis* morulae or peptides in many countries (see select reference list). However, in 2 separate experimental studies, we have failed to amplify monocytotropic *Ehrlichia* spp. from blood or detect seroconversion in cats inoculated SQ with different strains of cultured *E. canis* (Lappin and Breitschwerdt, unpublished observations, 2007; Lappin and Little, unpublished observations, 2010). These results indicate the *E. canis*-like DNA amplified from naturally-infected cats may be from a different *Ehrlichia* spp. more infective to cats, not all *E. canis* stains will infect cats, not all cats are susceptible to infection by *E. canis*, or SQ inoculation is not an effective method for infecting cats with *E. canis*. In addition, we have had field cases that have been positive for DNA identical to *E. canis* at 2 genes that never seroconverted (Breitschwert et al, 2002). It is likely that cats at greater risk for *Rhipicephalus sanguineous* infestation are more likely to have higher prevalence rates for *E. canis* in cats like in Brazil where 9.4% of cats were PCR positive in 1 study (Braga et al, 2014). In Sicily, *E. canis* DNA was amplified from ticks collected from some cats (Pennisi et al, 2015).

Fever, lethargy, and inappetance are commonly reported clinical abnormalities detected in cats with suspected ehrlichiosis and so testing may be indicated in these cats. Thrombocytopenia, anemia, and monocytosis appear to be the most common clinical laboratory findings in naturally infected cats (Bouloy et al, 1994; Peavy et al, 1997; Beaufils et al, 1999; Braga et al, 2013). Almost every abnormality noted in dogs with clinical ehrlichiosis has been detected in cats, including monoclonal gammapathy (Neer et al, 2002).

A validated serological assay is not currently available and some cats with *E. canis*-like DNA in blood were seronegative (Breitschwert et al, 2002). 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 to confirm infection and should be considered the tests of choice at this time.

Clinical improvement after therapy with tetracycline, doxycycline, or imidocarb dipropionate was reported for most cats with suspected monocytotropic ehrlichiosis. However, for some cats a
positive response to therapy was a criterion for the diagnosis of ehrlichiosis. The current recommendation of the ACVIM Infectious Disease Study Group (www.acvim.org) is to administer doxycycline (10 mg/kg PO q24h or 5 mg/kg PO q12h for 28 days). For cats with treatment failure or those intolerant of doxycycline, imidocarb dipropionate can be administered (5 mg/kg IM or SQ twice, 14 days apart). Salivation and pain at the injection site are the common adverse effects and imidocarb efficacy is in question for the treatment of canine monocytotropic ehrlichiosis.

Pancytopenia occurs in cats with ehrlichiosis and when occurs in dogs, may not respond to treatment (Breitscherdt et al, 2002). This is another example of why acaracides should be used to attempt to avoid infection with vector borne disease agents.

**Feline tick borne rickettsiosis.** *Rickettsia* spp. are obligate intracellular gram negative bacteria that are divided into the spotted fever group and the typhus group. In the United States, cats can be infected by *Rickettsia felis* and have been shown to have antibodies against *R. rickettsii* which is tick-borne (Bayliss et al, 2009). In Spain, *R. conorii* and *R. massiliae* antibodies were found in cat serum and DNA amplified from cat blood, suggesting cats could play a role in the life cycles of these agents, or be clinically affected (Segura et al, 2014). In one study of cats with fever we showed *R. felis* and *R. rickettsii* antibody prevalence rates in cats in the USA to be 5.6% and 6.6%, respectively but DNA of neither organism was amplified from blood. These results prove that cats are sometimes exposed to spotted fever group organisms but further data are needed to determine significance of diseases associations. Because clinical illness in cats from spotted fever organisms has not been documented, optimal treatment is unknown. However, based on results in dogs with *R. rickettsii* infection, doxycycline or a fluoroquinolone would be logical choices. The evidence for spotted fever agents in cats in the United States and Europe provides further evidence that acaracides should be used in cats as these agents are zoonotic to humans.

**Summary.** Tick control is warranted for cats as well as dogs. Products with efficacy against fleas should also be used as fleas can be vectors for several *Bartonella* spp., potentially the hemoplasmas, potentially *Coxiella burnetii*, (Cypress), *R. felis* and *Yersinia pestis*.

**Select references**


Foley JE, Leutenegger CM, Dumler JS, Pedersen NC, Madigan JE. Evidence for modulated


Feline flea associated diseases

Michael R. Lappin, DVM, PhD, DACVIM
The Kenneth W. Smith Professor in Small Animal Clinical Veterinary Medicine
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As high as 80% of fleas collected from cats contain at least one organism that could induce illness in cats or people. The purpose of this review is provide an update on the diagnosis and management of feline flea borne diseases of significance. *Bartonella* spp., hemoplasmas, and *Rickettsia* spp. infections of cats will be discussed. Please also see the AAFP Panel report on feline bartonellosis www.catvets.com.

**Feline bartonellosis.** A number of *Bartonella* spp. including *B. henselae*, *B. clarridgeiae*, *B. koehlerae*, *B. quintana* and *B. bovis* have been cultured or amplified from client-owned cats with fever. Fever following experimental inoculation with *B. henselae* has been documented in a number of studies including a recent study in our laboratory where the CSU-1 strain of *B. henselae* induced significant fever in three of six cats after exposure to infected *C. felis*. None of the six cats administered imidacloprid-moxidectin in that study became infected or febrile. However, not all strains or *Bartonella* spp. induce fever in all cats; for example in the imidacloprid-moxidectin study, cats inoculated with the same strain intravenously failed to develop fever. Whether fever will occur during *Bartonella* spp. infection is likely a complex interaction that is influenced by both host and organism factors.

As *B. henselae*, *B. clarridgeiae*, *B. koehlerae* are transmitted by fleas, bacteremia and antibody positive rates can be very high. For example, serum antibodies were detected in 93% of cats housed in a North Carolina shelter and *Bartonella* spp. DNA was amplified from the blood of > 50% of cats housed in Alabama or Florida shelters. The majority of these cats were thought to be normal which emphasizes that fever from bartonellosis cannot be documented by test results alone. In one study of pair matched cats with or without fever, serum *Bartonella* antibodies detected by ELISA or Western blot immunoassay were not correlated to the presence of fever. In addition, serum antibody test results are negative in between 3 and 15% of bacteremic cats. Thus, if a cat with fever is to be evaluated for *Bartonella* spp. infection the combination of blood culture or PCR assay on blood, and serologic testing will detect the greatest number of cats that are currently or previously infected. Febrile cats that are seronegative and negative for *Bartonella* spp. in blood by culture or *Bartonella* spp. DNA in blood are unlikely to have the organism as the cause of fever. However, addition of blood culture using BAPGM media is more sensitive that routine culture (www.galaxydx.com).
Fever, lymphadenopathy, uveitis, endocarditis, myocarditis, osteomyelitis, and hyperglobulinemia appear to be the most common manifestations of bartonellosis in cats. Osteomyelitis has recently been documented in infected cats. Upper respiratory tract disease, stomatitis, conjunctivitis, and pancreatitis do not seem to be associated with feline bartonellosis.

If fever or other acute signs from bartonellosis is suspected in a cat, administration of doxycycline is usually effective but does not eliminate infection. The AAFP Panel Report on Bartonellosis (www.catvets.com) recommended doxycycline at 10 mg/kg, PO, daily for 7 days as the initial therapeutic trial. If gastric irritation is occurring, dividing the drug into 2 doses per day is acceptable. If a positive response is achieved, continue treatment for 2 weeks past clinical resolution of disease or for a minimum of 28 days. If a poor response is achieved by day 7 or doxycycline is not tolerated and bartonellosis is still considered a valid differential diagnosis, fluoroquinolones are appropriate second choices. In experimental or field studies, administration of enrofloxacin or orbifloxacin have led to rapid resolution of fever in cats with presumed bartonellosis. Azithromycin is now considered contraindicated because of rapid induction of resistance. Pradofloxacin (Veraflox; Bayer Animal Health) at 7.5 mg/kg, PO, once daily is considered by many to be the optimal drug for treatment of clinical bartonellosis as it is the least likely to induce resistant strains. Use of imidacloprid containing products (Advantage Multi [Advocate] or Seresto Collars; Bayer Animal Health) have been shown to block transmission of *B. henselae* amongst research cats.

Frequent contact with animals infested with *C. felis* is likely a common way to people to acquire bartonellosis and veterinarians have increased risk. Cat scratch disease has been the greatest concern over the years but is actually not the most important manifestation in veterinarians. It is now recognized that *Bartonella* spp. infections of people is associated with endocarditis and many chronic inflammatory disease syndromes that can be confused with other infection or immune mediated diseases like polyarthritis. Neurobartonellosis with headaches and blurred vision is common. If an animal care provider has an undiagnosed chronic inflammatory disease, they should be tested for bartonellosis. The most sensitive techniques include culture and PCR (www.galaxydx.com).

**Feline hemoplasmosis.** Fever or hemolytic anemia are the most common manifestations of *Mycoplasma haemofelis*, ‘*Candidatus Mycoplasma haemominutum*’, or ‘*Candidatus M. turicensis*’. In multiple studies of experimentally infected cats, *M. haemofelis* is apparently the most pathogenic species. Dual infection with hemoplasmas may potentiate pathogenesis of disease. In one study, cats with chronic ‘*Candidatus Mycoplasma haemominutum*’ infection had more severe anemia and longer duration of anemia when experimentally infected with *M. haemofelis* when compared to cats infected with *M. haemofelis* alone. In one abstract, we reported an association between *M. haemofelis* and fever in cats without anemia. Clinical signs of disease depend on the degree of anemia, the stage of infection, and the immune status of infected cats. Direct transmission may occur with the hemoplasmas and so the agents should be on the differential list for cats with a history of fighting.

Diagnosis of hemoplasmosis is based on demonstration of the organism on the surface of erythrocytes on examination of a thin blood film or by PCR assay results. Organism numbers fluctuate and so blood film examination can be falsely negative up to 50% of the time. The
organism may be difficult to find cytologically, particularly in the chronic phase. Thus, PCR assays are the tests of choice due to sensitivity.

Doxycycline is often administered as a flavored suspension (to avoid esophageal strictures) at 10 mg/kg, PO, every 24 hours for a minimum of 7 - 10 days. In cats intolerant of doxycycline, enrofloxacin given at 5 mg/kg, PO, every 24 hours for 14 days was tolerated by cats and is equally effective or more effective than doxycycline. Administration of marbofloxacin or orbifloxacin gives similar results. Pradofloxacin (Veraflox; Bayer Animal Health) at 7.5 mg/kg, PO, once daily is considered the optimal drug for treatment of clinical hemoplasmosis as it is the only antibiotic shown to clear M. hemofelis bacteremia. However, negative PCR assay results were not achieved in all cats. Azithromycin was not effective for the treatment of hemoplasmosis in one study. Most drug protocols have failed to eliminate infection and so at this time there is no clinical utility to repeat PCR testing. The owners should be warned that recurrences may occur but are unusual.

**Feline rickettsiosis.** *Rickettsia spp.* are obligate intracellular gram negative bacteria that are divided into the spotted fever group and the typhus group. Cats can be infected by *Rickettsia felis* and have been shown to have antibodies against *R. rickettsii*. *Rickettsia felis* DNA has been amplified from *C. felis, C. canis,* and *Pulex irritans*; these fleas have a worldwide distribution. *Ctenocephalides felis* is a biological vector for *R. felis*; the organism can be transmitted transovarially and transtadially within the flea. Rickettsial infection is suspected to cause fever in cats but this has not been well documented. While we have commonly amplified *R. felis* from *C. felis* (67.4% of flea extracts in one study), we have not amplified the organism from the blood of healthy cats or cats with fever. However, in one study of cats with fever we showed *R. felis* and *R. rickettsii* antibody prevalence rates in cats in the USA to be 5.6% and 6.6%, respectively but neither organism was amplified from blood. Similar prevalence rates have been documented in Spain. These results prove that cats are sometimes exposed to spotted fever group organisms but further data are needed to determine significance of diseases associations. It is now known that dogs are a more important reservoir for this agent. Because clinical illness in cats has not been documented, optimal treatment is unknown. However, based on results in dogs with *R. rickettsia* infection, doxycycline or a fluoroquinolone would be logical choices.

**Summary.** Flea and tick control is warranted for cats as well as dogs. In addition to those agents discussed previously, there are other infectious agents of cats that are vector and can be associated with illness in cats with appropriate clinical findings and geographical locale including *Coxiella burnetii, Cytauxzoon felis, Francisella tularensis,* Hepatozoon spp., *Leishmania* spp., and *Yersinia pestis*.

**Select references**


