Effect of Doxycycline or Orbifloxacin Administration on *Bartonella* spp and Hemoplasma Assay Results in Naturally Exposed Cats

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ABSTRACT

The purpose of this study was to evaluate the effect of successful treatment for *Bartonella* spp, *Mycoplasma hemofelis* or *Candidatus* Mycoplasma haemominutum infection of cats on results of diagnostic test results commonly available to veterinary practitioners through commercial diagnostic laboratories. Evidence of infection or exposure to *Bartonella* spp, *M hemofelis* or *Candidatus* M. haemominutum was detected in 15 cats with fever. Doxycycline (50 mg) or orbifloxacin (22.7 mg) were administered empirically by mouth for 28 days to 12 cats with laboratory evidence of *Bartonella* spp infection alone and three cats with laboratory evidence of *Bartonella* spp and M. hemofelis or *Candidatus* M. haemominutum co-infection with the laboratory tests repeated on Day 35 and 58 (10 cats) or Day 35 alone (5 cats). While clinical illness in all 15 cats rapidly resolved, all nine cats that were PCR positive for *Bartonella* spp on Day 0 were still PCR positive on Day 35. Four of the six cats tested on Day 58 were still positive. Only one cat that was positive for *Bartonella* spp antibodies detected by ELISA on Day 0 was negative on Day 35 and Day 58. Of the 3 cats that were PCR positive for *M. hemofelis* or '*Candidatus* M. haemominutum' on Day 0, only 1 cat (*Candidatus* M. haemominutum') was PCR positive on Day 35 or Day 58. The results of the study support the recommendation that cats with suspected clinical bartonellosis should be evaluated concurrently by PCR (or culture) and serology. There appears to be little indication for following *Bartonella* spp assay results within the first 30 days using the treatment protocols described herein.

INTRODUCTION

Fever in cats is a clinical manifestation that can be associated with infectious disease agents. If other abnormalities like vomiting, diarrhea, coughing, sneezing, genital discharges, uveitis, or wounds are detected concurrently, the infectious cause of fever can be easy to determine. However, many

cats have fever without an obvious cause on physical examination. Feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV) can be associated with fever, but generally have prevalence rates of < 5% and are relatively easy to diagnose.[1] The vector borne diseases *Bartonella* spp, hemoplasmas (*Mycoplasma haemofelis* and '*Candidatus* M. haemominutum,' or '*Candidatus* M. turicensis'), *Anaplasma phagocytophilum*, and *Ehrlichia* spp are detected in some cats with fever but evidence of infection can also be detected in healthy cats.[2-5]

Cats have been shown by culture or DNA amplification to be infected by a number of *Bartonella* spp.[5-9] *Bartonella henselae* is the main etiological agent associated with Cat Scratch Disease in immunocompetent people as well as bacillary angiomatosis and peliosis hepatis, which are common disorders in people with AIDS.[5] *Bartonella* spp infections have also been associated with a number of other chronic disease syndromes in immunocompetent people.[5,10] *Bartonella henselae*, *B clarridgeiae*, and *B koehlerae* are transmitted amongst cats by *Ctenocephalides felis*, so the prevalence in cats is greatest in regions where fleas are common.[5]

For example, in a study performed in Alabama, Maryland, and Texas, blood in EDTA, and fleas were collected from cats. Total DNA was extracted from the blood and fleas, and the total DNA was assayed in a polymerase chain reaction (PCR) assay specific for *Bartonella* spp DNA.6 The prevalence of *B henselae* DNA in cats and their fleas were 34.8% and 22.8%, respectively. The prevalence of *B clarridgeiae* DNA in cats and their fleas were 20.7% and 19.6%, respectively. When results of *Bartonella* spp., *M. haemofelis*, and '*Candidatus* M. haemominutum' PCR assays were combined, 60.9% of the cats had DNA of 1 or more of the organisms amplified from blood.[6] In another study of cats housed in shelters in Florida and Alabama, *Bartonella* spp DNA was amplified from 56.9% of the cats and 100% of the *C. felis* collected from the cats.[7]

Bartonella spp infections of cats have recently been associated directly or indirectly with a variety of clinical manifestations like fever, lethargy, lymphadenopathy, uveitis, gingivitis, myocarditis, endocarditis, hyperglobulinemia, and neurological diseases.[5,8,9,11-13] Hemoplasmas are most commonly associated with anemia with or without fever.[14,15,a] As these syndromes are common in client-owned cats, veterinarians often have *Bartonella* spp or hemoplasmas on differential diagnosis lists. Accordingly, many Veterinary Diagnostic Laboratories offer PCR assays for *Bartonella* spp and hemoplasmas as well as serological assays for *Bartonella* spp antibodies. The use of these assays in the diagnosis of bartonellosis or hemoplasmosis has been reviewed.[5,15] However, whether there is clinical utility in following *Bartonella* spp or hemoplasma laboratory tests after treatment of client-owned cats is currently unknown.

When clinical illness from bartonellosis is suspected, the AAFP Panel Report on Feline Bartonellosis recommends the use of doxycycline as the initial therapeutic trial, with fluoroquinolones being used as a rescue drug class for those that fail to respond to doxycycline.[5,b] The same recommendations have been made for the treatment of hemoplasmas.[15] However, treatment recommendations for these flea-borne organisms have been made largely from anecdotal experiences. For example, there has not been a drug comparison study in client-owned cats with suspected clinical bartonellosis or hemoplasmosis. In addition, it is unknown whether treatment of client-owned cats eliminates *Bartonella* spp bacteremia, thus decreasing the risk of *Bartonella* spp transmission to other family members in the future. It is similarly uncertain if medical treatment impacts hemoplasma bacteremia or lessens the potential for future disease recurrence.[5] To date, *Bartonella* spp and hemoplasma treatment studies have been completed in small numbers of experimentally inoculated cats, often just using one strain of the organism.[5,11,16-23] In addition, only one treatment study has been performed in cats

that were infected via the natural route of transmission.[11] In that study, three cats that developed *B. henselae* associated fever after exposure to infected *C. felis* rapidly responded to oral enrofloxacin administration. Due to gaps in the existing literature, there is a significant need for additional *Bartonella* spp and hemoplasma treatment information.

Orbifloxacin is a fluoroquinolone antibiotic approved for use in cats.[c] There is one report of this antibiotic being used in combination with doxycycline in a cat with *B henselae* associated endocarditis.[12] However, there is no information available on the use of orbifloxacin in the management of cats with hemoplasma infections or the effect of treatment on *Bartonella* spp and hemoplasma test results.

The primary hypothesis to be tested is that *Bartonella* spp and hemoplasma. test results are changed by doxycycline or orbifloxacin administration. To address this hypothesis, the primary objective of this study was to administer doxycycline or orbifloxacin to client-owned cats with fever to determine the effect on *Bartonella* spp and hemoplasma test results 7 days and 30 days after the administration of 28 days of treatment.

MATERIALS AND METHODS

The study was approved by the Institutional Animal Care and Use Committee at Colorado State University. Veterinary hospitals located in states with high flea prevalence rates were contacted for participation in the study.[5] Client-owned adult cats (> 6 months of age) with rectal body temperature of > 102.5°F (39.2°C), but without an obvious cause of elevated body temperature based on history or physical examination, were considered for the study. Cats with a likely cause of fever and those with elevated body temperature that was likely to be hyperthermia from excitement, seizures, or environmental factors were excluded. When an appropriate cat was identified, the owner was offered participation in the study. To be included, the owner was required had to sign a consent form and be willing to administer a flea control product monthly (selected and prescribed by the attending veterinarian), administer one of the two study drugs daily by mouth, return for two scheduled recheck evaluations, and return sooner if clinical signs did not resolve quickly or if drug toxicities were suspected.

After consent was obtained, the owners were trained to administer the drugs. The first dose of flea control product was administered, blood samples were collected, and the cats screened for FeLV antigen and FIV antibody in serum using a commercially available kit.[d] Cats that were seropositive for FeLV or FIV were excluded from the study. Cats with fever residing in states with high *C. felis* rates were purposefully selected to aid in identifying cats with laboratory evidence of exposure to *Bartonella* spp or hemoplasmas.[5]

Experimental Design

Each participating clinic was sent a package of materials that included the standard operating procedures, consent forms, submission forms, clot tubes, EDTA tubes, prepaid and labeled shipping boxes, orbifloxacin, doxycycline, cold packs, syringes, and needles. Qualifying cats were administered doxycycline (50 mg; ½ of a 100 mg tablet, PO, q24 hours) or orbifloxacin (22.7 mg tablets; 1 tablet, PO, q24 hours) based on a predetermined randomization schedule. An empirical dose was chosen to mimic what often is used in clinical practice. To avoid esophageal strictures, each tablet was coated in butter or a vitamin supplement when administered or at least 6 ml of water was delivered orally by syringe after tablet administration.[24,25,e] Cats that were intolerant of the initial drug or failed to show a clinical response by day 5 were switched to the alternate drug. The drug potentially associated with a response to therapy (resolution of fever) was administered to cats positive for *Bartonella* spp or hemoplasmas for 28 days.

Sample Collection and Assays

Samples (1 ml blood in EDTA; 0.5 ml serum) were collected on day 0, day 35 (7

days post-treatment), and approximately on day 58 (30 days post-treatment). The samples were shipped by overnight express on a cold pack to Colorado State University.[f]

Total DNA was extracted from each blood sample as previously described and assayed in PCR assays for *Bartonella* spp, hemoplasmas, *Ehrlichia*/*Anaplasma* spp, and *Rickettsia* spp.[2,3,26,27] Serum antibodies against *Bartonella* spp and *Toxoplasma gondii* were measured using previously reported ELISAs.[13,28] The *T gondii* serology was included in an attempt to exclude another infectious cause of fever in cats from the differential list that would not be expected to respond to doxycycline or orbifloxacin. Based on sample availability, a group of *Bartonella* spp IgG ELISA positive cats (four treated with doxycycline and five cats treated with orbifloxacin) were selected to evaluate the *Bartonella* spp antigen recognition patterns before and after treatment using a previously reported Western blot immunoassay.[13]

Statistical Analysis

The primary outcome assessed was evidence of elimination of *Bartonella* spp or hemoplasma infections as defined as negative PCR assay results on Days 35 or 58 and changes in *Bartonella* spp antibody results as determined by ELISA. We employed a chi-square test to determine difference in outcomes between treatment groups, with statistical significance defined as $p < 0.05$. Results of the *Bartonella* spp Western blot immunoassay before and after treatment are presented descriptively.

RESULTS

A total of 24 cats from six different clinics in California, Florida, and Texas were included. All of the cats were negative for *T gondii* IgM and IgG in serum. *Bartonella* spp antibodies, DNA, or both, were detected in samples from 16 (66.7%) of the cats (Table 1). The *Bartonella* spp DNA amplified from blood of 11 of the 24 cats (45.8%) on Day 0 was *B henselae*. *Bartonella clarridgeiae* DNA was amplified from one cat on Day 35. Overall, hemoplasma DNA was amplified from the blood of four of 24 cats (16.7%). *Mycoplasma hemofelis* DNA was amplified from two cats, one of which was positive concurrently for *B henselae* DNA. '*Candidatus* M. haemominutum' DNA was amplified from the blood of two cats, one of which was positive concurrently for *Bartonella* spp antibodies. Overall, evidence of infection by or exposure to *Bartonella* spp or hemoplasmas was present in 18 of 24 cats (75%). The owners of 17 of the 18 cats with evidence of *Bartonella* spp or hemoplasma spp infection started antibiotic therapy (Doxycycline in five cats; Orbifloxacin in 12 cats) and the owners of 15 cats returned for one or both recheck samples (Table 2).

When pre- and post-treatment results

Table 1. *Distribution of Bartonella spp. PCR assay results, Bartonella spp. serum antibody results, and hemoplasma. PCR assay results in 24 cats with fever.*

Bartonella Assay result	Number of cats
PCR positive, Antibody positive	5 (20.8%)
PCR negative, Antibody positive+	5 (20.8%)
PCR negative, Antibody negative*+	8 (33.3%)
PCR positive, Antibody negative*	6 (25%)
Any test positive	16 (66.7%)

*Overall, 4 of 24 cats (16.7%) were PCR positive for haemoplasma. DNA in blood. *Mycoplasma haemofelis DNA was amplified from the blood of 1 of these cats.*
+'Candidatus M. haemominutum' DNA was amplified from the blood of 1 of these cats.
Overall, evidence of infection by or exposure to Bartonella spp. or a hemoplasmas was present in 18 of 24 cats (75%).

Table 2. *Distribution of Bartonella and haemoplasma assay results before and after administration of doxycycline or orbifloxacin for 28 days.*

		***Bartonella* IgG**			***Bartonella* PCR**			**Mhf PCR**			**Mhm PCR**		
Cat	**Drug**	**Day 0**	**Day 35**	**Day 58**	**Day 0**	**Day 35**	**Day 58**	**Day 0**	**Day 35**	**Day 58**	**Day 0**	**Day 35**	**Day 58**
1	Doxy	64	128	64	Pos	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg
2	Doxy	64	1024	512	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Neg
3	Doxy	Neg	128	512	Pos	Pos	Pos	Pos	Neg	Neg	Neg	Neg	Neg
4	Doxy	Neg	64	64	Pos	Pos	NS	Neg	Neg	NS	Neg	Neg	NS
5	Doxy	128	1024	NS	Neg	Neg	NS	Neg	Neg	NS	Neg	Neg	NS
6	Orbax	64	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
7	Orbax	256	128	256	Neg	Neg	Neg	Neg	Neg	Neg	Pos	Pos	Pos
8	Orbax	Neg	Neg	64	Neg	Neg	Neg	Neg	Neg	Neg	Pos	Neg	Neg
9	Orbax	Neg	128	128	Pos	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg
10	Orbax	128	512	256	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Neg
11	Orbax	Neg	1024	1024	Pos	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg
12	Orbax	Neg	256	NS	Pos	Pos	NS	Neg	Neg	NS	Neg	Neg	NS
13	Orbax	Neg	64	NS	Pos	Pos	NS	Neg	Neg	NS	Neg	Neg	NS
14	Orbax	512	1024	NS	Neg	Pos	NS	Neg	Neg	NS	Neg	Neg	NS
15	Orbax	64	64	NS	Neg	Neg	NS	Neg	Neg	NS	Neg	Neg	NS

Mhf = Mycoplasma haemofelis; Mhm = 'Candidatus M. haemominutum'; Neg = negative; Pos = positive; NS = no sample submitted; grey shaded cells contain positive test results; Doxy = doxycycline; Orbax = orbifloxacin

within and between treatment groups were compared, the proportions of *Bartonella* spp PCR positive cats or *Bartonella* spp IgG ELISA positive cats were not statistically different (Table 2). One cat that was *Bartonella* spp seropositive but PCR negative on Day 0, but was positive for *B clarridgeaie* DNA on Day 35, was administered orbifloxacin (Table 2). Each of the six *Bartonella* spp PCR positive, seronegative cats on Day 0 was positive for *Bartonella* spp antibodies by Day 35. Of the eight cats with *Bartonella* spp antibodies in serum on Day 0, seven cats were still positive on Day 35, and the titers had not decreased > 2-fold. The one seronegative cat had been administered orbifloxacin. Of the 13 cats with *Bartonella* spp antibodies in serum on Day 35, all eight cats with serum submitted from Day 58 were still positive for *Bartonella* spp antibodies. Each of the nine cats with *B henselae* DNA amplified from blood on Day 0 were also PCR positive on Day 35. Of these cats, two of the six cats (one cat administered doxycycline and one cat administered orbifloxacin) with samples submitted on Day 58 were PCR negative. The cat with *B henselae* and *M hemofelis* DNA amplified from blood concurrently on Day 0 was positive for *B. henselae* DNA on Day 35 and Day 58 but negative for *M. hemofelis* after administration of doxycycline. Of the two cats that were positive for '*Candidatus* M haemominutum' DNA on Day 0 and administered orbifloxacin, one cat was negative on Day 35 and Day 58 and one cat was positive on both post-treatment days.

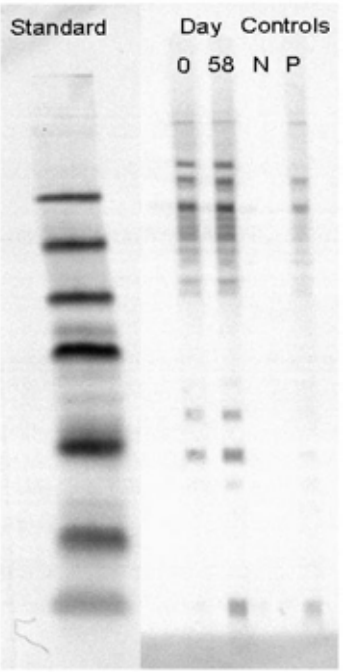
Of the nine cats treated with either doxycycline (four cats) or orbifloxacin (five cats) and evaluated on Day 0 and 58 by Western blot immunoassay, seven cats had increased numbers of *Bartonella* antigens recognized on Day 58 compared to Day 0 (Figure 1). Of the two cats with a decreased number of *Bartonella* antigens recognized on Day 58, both were still considered positive.[13]

All five of the doxycycline treated cats had resolution of clinical abnormalities by Day 5 as did 10 of the 12 cats administered orbifloxacin. One *B henselae* PCR positive, seronegative cat that was still clinically ill on Day 5 of orbifloxacin administration was switched to doxycycline and prednisolone and ultimately became clinically normal. One cat (*B henselae* PCR positive and seropositive) was still clinically ill by Day 5, but the owners chose to euthanize the cat rather than change to doxycycline. A necropsy was not performed. Thus, the cause of fever could not be determined definitely. It is, therefore, unknown whether the cat had a concurrent disease that would not respond to orbifloxacin administration. Overall, there were no significant differences between the doxycycline or orbifloxacin clinical response rates on Day 5 ($p = 1.0$).

DISCUSSION

Most cats did not become *Bartonella* spp seronegative or PCR negative after administration of either doxycycline or orbifloxacin for 28 days using this empirical protocol. It is possible that the cats develop repeated infection over the course of the study. However, this possibility is unlikely provided the owners administered the flea control products appropriately as trained. It was previously shown that administration of imidacloprid and moxidectin blocked transmission of *B. henselae* amongst cats exposed to *C. felis*.[11] Thus, the failure of most cats to become *Bartonella* spp. or hemoplasma PCR negative or *Bartonella* spp. seronegative over the course of the study likely relates to the persistence of the primary infection or antibody producing B lymphocytes. As the drugs were administered by lay persons, it is possible that the cats were not treated appropriately. In addition, the doses and duration of therapy chosen may not effectively eliminate either infection consistently. However, these findings are similar to other studies of cats experimentally infected with *Bartonella* spp or hemoplasmas and treated with tetracyclines or other fluoroquinolones.[11-18,20,21] As the majority of cats

Figure 1. *Representative Western blot immunoassay from the same Bartonella henselae infected cat before and after administration of 28 days of doxycycline therapy.*



treated with doxycycline or orbifloxacin in this study had no changes in *Bartonella* spp antibody assay results (ELISA or Western blot) or PCR assay results in the time period studied, there appears to be little clinical utility for repeating these assays in previously positive cats that have had apparent responses to antimicrobial therapy at least in the short term (< 60 days).

In studies of healthy cats, *B clarridgeaie* and *B. henselae* DNA often amplified in similar proportions.[6,7,29] In this study, *B henselae* DNA was amplified from all but one of the cats proven to *Bartonella* spp infected. Further studies should be performed to evaluate whether *B henselae* is more pathogenic to cats than *B. clarridgeaie*. Amplification of *B henselae* DNA from blood prior to serum antibodies in six cats suggests that the infection was acute in these cats. This finding supports the use of serology and PCR (or culture) concurrently in cats with suspected clinical bartonellosis.[5]

As this was an uncontrolled study, the data presented concerning potential treatment responses should be interpreted carefully as it possible that the cats improved spontaneously or the cats responded to the drugs for other reasons like the anti-inflammatory properties of doxycycline or the presence of other infectious responsive to either doxycycline or orbifloxacin.

Many factors should be considered when choosing empirical antibiotic therapy in a cat with fever.The most important is that there is a reasonable expectation that an infection exists that may be antibiotic responsive. In this study, 75% of the cats had evidence of infection or exposure to a *Bartonella* spp or hemoplasma. While there are no tests that document clinical illness induced by these genera, historical information in other papers of experimentally infected or naturally infected cats supports the role of these agents as causes of fever.[2,5,11,13-15,a] In addition, none of the cats in the study described herein had other known causes of fever, and all but two cats were clinically normal by Day 5 of the administration of antibiotics in classes with known activity against *Bartonella* spp or hemoplasmas. There were no significant differences in clinical response rates between the two antibiotics on Day 5. The cat switched to doxycycline with a positive response was also administered prednisolone and so whether the apparent response over time was due to doxycycline, prednisolone or spontaneous remains unknown.

The results described here suggest that administration of either orbifloxacin or doxycycline would be potentially effective in FeLV and FIV seronegative cats with laboratory evidence of *Bartonella* spp or hemoplasma infection with no other obvious cause of fever detected on physical examination or the diagnostic workup. As both drugs induced similar response rates in *Bartonella* spp or hemoplasma test positive cats, whether to chose one or the other drug class for primary therapy will be based on other factors like cost, likelihood of being tolerated by cats, side-effects (strictures with doxycycline; retinal degeneration with some fluoroquinolones), and efficacy against other differential diagnoses.[30]

For example, orbifloxacin is now available as a palatable liquid for use in cats that when administered at the label dose in rarely associated with side-effects.[c] However, the dosing recommendations for the oral suspension formulation differ from those of the orbifloxacin tablets used in the present study. Further data will be needed to determine the effect of orbifloxacin suspension on *Bartonella* spp and hemoplasmas at the label dose of 2.5 mg/kg, as the current study evaluated the empirical dose of approximately 5 mg/kg. In contrast, doxycycline also is effective for the treatment of ehrlichiosis and anaplasmosis in cats, but has to administered as a liquid or otherwise manipulated to avoid esophageal strictures and has been associated with other side-effects in cats including fever.[3,4,25,31]

As *Bartonella* spp and some hemoplasmas can be associated with human illness, the high prevalence rates documented in this study support the recommendations of a variety of human health and veterinary health organization to prescribe flea control for all cats.[5,32,g]

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FOOTNOTES

[a]Lappin MR. Infectious causes of fever in cats. J Vet Int Med 2002;16:366 (abstract).

[b]www.catvets.com

[c]Orbifloxacin, Intervet/Schering-Plough

Animal Health, Summit, NJ

[d]FeLV/FIV SNAP® Combo, IDEXX Laboratories, Portland, ME.

[e]Center for Companion Animal Studies at Colorado State University, Fort Collins, Colorado USA (http://csuvth.colostate.edu/veterinarians/research/companion_animals/)

[f]Griffin B, Beard DM, Klopfenstein KA. Use of butter to facilitate the passage of tablets through the esophagus in cats. Proceedings of the ACVIM Forum, 2003 (abstract).

[g]www.capcvet.org

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