Supplement - *Bartonella* Infections in Animals: Clinical Signs

This document is a supplement to the CFSPH "Cat Scratch Disease and Other Zoonotic *Bartonella* Infections" factsheet providing further details on studies in cats, dogs, cattle, horses and rodents.

Bartonella Infections in Animals: Clinical Signs

The importance of *Bartonella* spp. as pathogens in animals is still unclear. Most infections appear to be asymptomatic. Some experimental infections, case reports and studies have suggested possible links to disease, but other studies have been unable to substantiate a role for *Bartonella*. Investigations are complicated by the high prevalence of infections in healthy animals, the uncertainties in diagnostic testing for these organisms, and the possibility of co-infection with other microorganisms.

Cats

Naturally-infected bacteremic cats are usually asymptomatic. Some studies have suggested that *B. henselae* might be pathogenic under some circumstances, but at present, definitive evidence is lacking.

In experimental studies, most cats inoculated with *B. henselae* remained asymptomatic or had only mild clinical signs. In one experiment, cats developed inflammatory swellings or pustules at the inoculation site. Other clinical signs reported in experimentally infected cats were lymphadenopathy, myalgia and transient fever with lethargy and anorexia during febrile periods. Transient mild behavioral or neurological dysfunction, consisting of disorientation, nystagmus, hypersensitivity to stimuli, decreased responsiveness to environmental stimuli, or increased aggressiveness, as well as mild transient anemia, eosinophilia, and reproductive disorders have also been reported. In a recent study, no cats inoculated intravenously with *B. henselae* became ill, although bacteremia was detected in all cats. However, 3 of 6 cats exposed to *B. henselae*-infected fleas developed fever and inappetence. One of these cats was euthanized, as it became severely ill, and myocarditis was found at necropsy. There was some evidence that this cat may have failed to mount an adequate immune response: it had the lowest IgM titer to *Bartonella*, and was the only cat that did not have detectable IgG to this organism.

No clinical signs have been reported in cats inoculated with *B koehlerae* or *B. rochalimae.* Two cats inoculated with *B. quintana* seroconverted with no evidence of bacteremia.

A limited number of case reports and case series in naturally infected cats suggest that *B. henselae* or other *Bartonella* species might cause disease. Other studies have found no link to illness.

A few case reports have attributed cardiac conditions, especially endocarditis, to *Bartonella*. *B. henselae* DNA was detected by PCR in the diseased heart valves of two cats that died of endocarditis. *B. henselae* was also isolated from the blood of a young cat with aortic valve endocarditis, and antibiotic treatment resulted in total resolution of the heart murmur and valvular lesion.

B. henselae infections were reported in two cats with fatal pyogranulomatous myocarditis and diaphragmatic myositis at an animal shelter. Ten cats at this shelter developed fever, lethargy and diarrhea after a litter of flea-infested cats entered the facility. Feline leukemia virus (FeLV), feline panleukopenia virus, and feline immunodeficiency virus (FIV) were ruled out. One kitten died after developing acute respiratory distress, and an 8-month-old cat, which had been in contact with the litter, died acutely 2 weeks later. Bacteria were found in inflammatory foci in the heart of both cats, as well as the diaphragm of one cat. These bacteria were identified as *B. henselae* by immunohistochemistry. PCR detected *B. henselae* DNA in the heart of one cat, and in multiple tissues including heart and diaphragm of the other cat.

B. vinsonii subsp. *berkhoffii* was detected in lesions from a cat with recurrent osteomyelitis. *Salmonella enterica* subsp. *enterica* was also isolated from a bone marrow aspirate. The condition responded to treatment with azithromycin and amoxicillin-clavulanate.

A number of studies have investigated whether *B. henselae* might be associated with stomatitis or gingivitis. In a study from Japan, the incidence of lymphadenopathy and gingivitis was significantly increased in cats seropositive for both FIV and *B. henselae*, compared to cats with antibodies only to FIV. A Swiss study reported a correlation between seropositivity to *B. henselae* and stomatitis. In a recent study that examined sick cats presented to a U.S. referral hospital, *Bartonella* was cultured more often from the blood of cats with gingivostomatitis than cats without this condition, although there was no correlation with seropositivity for *B. henselae or B. clarridgeiae*. However, one study reported no statistically significant relationship between gingivostomatitis and the prevalence of *Bartonella* DNA in blood samples, while another found no correlation with DNA in oral swabs. Similarly, a study of healthy shelter cats found no significant correlation between stomatitis and the prevalence of either antibodies to *Bartonella* spp. or DNA, when pair-matched samples were analyzed.

One study reported that the presence of antibodies to *B. henselae* was correlated with an increased incidence of various unspecified urinary tract diseases. A newer study found a weak association between seropositivity, but not bacteremia, and idiopathic lower urinary tract disease. In this study, there was no correlation with urolithiasis or chronic kidney disease.

A possible association between *B. henselae* and uveitis was proposed, after antibodies to this organism were found in the serum and aqueous humor of an immunocompetent cat with uveitis, which responded clinically to doxycycline. In a follow-up study, anti-*Bartonella* IgG was found in the aqueous humor of 7 of 49 client-owned cats with uveitis, and 0 of 49 healthy shelter cats. Four of 9 experimentally infected cats also had IgG antibodies in the aqueous humor. Uveitis was not correlated with antibodies in the serum. Two newer studies were unable to substantiate a link between uveitis and either seroprevalence or bacteremia. Unexplained cataracts were reported in SPF cats from a commercial vendor within a year after the cats became naturally infected with *Bartonella*. The relationship between the cataracts and the infection (if any) is not known, and this association may be coincidental.

One study found no correlation between neurological signs and *B. henselae* or *B. clarridgeiae* bacteremia. There was also no correlation with antibodies to these organisms. Another study detected no difference in seroprevalence or the magnitude of antibody titers to *B. henselae*, in a comparison of cats with neurological disease, cats with non-neurological illnesses and healthy cats, when age and flea exposure were controlled. However, one retrospective study reported evidence of local anti-*Bartonella* antibody production in the central nervous system (CNS). These antibodies were detected in 31% of cats that had neurological signs together with serological or DNA evidence of *Bartonella* infection. A small number of cats had both *B. henselae* DNA in the CSF and *Bartonella*-specific IgG in the cerebrospinal fluid. The findings are not conclusive, as *Bartonella* DNA can also be found in the brain of healthy cats; however, the authors suggest that further studies might be warranted.

Studies reported no evidence for *B. henselae* in the lesions from 26 cats with peliosis hepatis, or 14 cats with plasmacytic pododermatitis. One study reported no evidence for *Bartonella* as a cause of chronic rhinosinusitis in cats.

Dogs

No clinical signs other than transient fever were reported in dogs inoculated with *B. vinsonii* subsp. *berkhoffii*. Two dogs inoculated with *B. rochalimae* also remained asymptomatic, with the exception of inflammation at the inoculation site. However, *Bartonella* spp. have been suggested as possible etiologic agents in some case reports. As with cats, it is difficult to establish a causative role, especially for organisms maintained in dogs, such as *B. vinsonii* subsp. *berkhoffii*.

Bartonella spp. have been detected, by PCR or culture, in a few cases of endocarditis in dogs. Reported organisms include *B. vinsonii* subsp. *berkhoffii*, *B. henselae*, *B. clarridgeiae*, *B. washoensis*, *B. quintana* and *B. rochalimae*. *B. koehlerae* DNA was found in the aortic valve of another dog that died of endocarditis; however, *E. coli* was also cultured from aortic valve tissue. Additional cases of *Bartonella*-associated endocarditis have been suggested based on serology alone. *B. vinsonii* subsp. *berkhoffii* was implicated in a case of myocarditis.

One dog infected with *B. vinsonii* subsp. *berkhoffii* developed clinical signs resembling human bacillary angiomatosis, after treatment with immunosuppressive drugs for pancytopenia. The condition was characterized by widespread, round to oval, erythematous, angioproliferative skin nodules. *B. vinsonii* subsp. *berkhoffii* DNA was found in the skin lesions, as well as in the blood. Bacteria consistent with *Bartonella* were also detected in the lesions, although some bacteria were either close to or within the endothelial cells. Azithromycin treatment was effective, with clinical resolution beginning within 2 days of starting the antibiotic.

Bartonella spp. DNA was detected in the enlarged submandibular lymph node from a dog that developed fever, facial and cervical edema, and granulomatous lymphadenitis of the left regional lymph nodes, soon after a tick bite to the ear. Bacteria consistent with *Bartonella* were also detected in the node by Warthin–Starry silver staining. The dog did not have antibodies to *Ehrlichia canis*, *Babesia canis*, *Rickettsia rickettsii* or various fungi, but it was seropositive for *B. vinsonii* subsp. *berkhoffii*. Treatment with enrofloxacin for three weeks resulted in resolution of the fever and edema, and decreased lymph node size.

Bartonella spp. were detected in a few case reports of liver disease. *B. henselae* DNA was found in the liver of one dog with peliosis hepatis (blood-filled cysts and cavities in the liver). DNA from this organism was also identified in two dogs with granulomatous hepatitis. Both dogs were treated with antibiotics for bartonellosis. One dog progressed to hepatic cirrhosis in spite of treatment. The other dog improved clinically, although the clinical signs appeared to recur when it was taken off azithromycin. It was apparently stable on this drug for approximately a year, then deteriorated and was euthanized. Other drugs and vitamins had also been administered by the owner. Limited necropsy results suggested death might have been caused by a toxic insult to the liver. *B. clarridgeiae* DNA

was found in the liver of a dog with lymphocytic hepatopathy. This dog responded to treatment with azithromycin (for bartonellosis), prednisone and other drugs, and remained well for a year, but then developed signs consistent with liver failure before being lost to follow-up.

In a dog with pyogranulomatous lymphadenitis, arthritis consistent with immune-mediated polyarthropathy, protein-losing nephropathy and conjunctivitis, *B. henselae* DNA was found in blood samples and in an affected lymph node. The dog had no antibodies to *Bartonella* or to several other organisms (*Anaplasma phagocytophilum, Borrelia burgdorferi, Dirofilaria immitis, Ehrlichia canis* and *Rickettsia rickettsii*), and culture of the joints was negative. The conjunctivitis in one eye initially worsened despite treatment with carprofen, doxycycline, enalapril and an ophthalmic solution containing neomycin, polymyxin, and dexamethasone. However, all clinical signs later resolved after a 6-week course of doxycycline. Another case of pyogranulomatous lymphadenitis attributed to *Bartonella* was based on positive serology and the detection of *B. henselae* DNA in blood and lymph nodes, together with negative bacterial and fungal cultures and the exclusion of seroreactivity to various fungi and *Anaplasma phagocytophilum, Borrelia burgdorferi, E. canis,* and *R rickettsii*. The dog was treated with a number of antibiotics over the course of the illness. Initial treatment with enrofloxacin, metronidazole and carprofen was unsuccessful; however, the clinical signs later resolved with a 7-day course of enrofloxacin and carprofen. When signs recurred 4 months later, the dog was treated for *Bartonella* with azithromycin and doxycycline. This resulted in limited improvement, but the clinical signs resolved with the addition of an immunosuppressive dose of prednisone.

B. henselae and *B. vinsonii* subsp. *berkhoffii* were both isolated from the blood of a 4-year-old dog with a 2-year history of joint pain progressing to pelvic limb ataxia and refusal to walk. *B. vinsonii* subsp. *berkhoffii* was isolated from joint fluid. The condition was partially responsive to non-steroidal anti-inflammatory medications, and became progressively worse despite treatment with antibiotics for bartonellosis, including two 7-week courses of azithromycin. *Bartonella* spp. were still isolated from the blood and synovial fluid after treatment.

Other case reports in the literature describe the isolation of *B. vinsonii* subsp. *berkhoffii,* or its detection by PCR, in syndromes as diverse as neoplasia, seroma after a traumatic injury, and panniculitis.

One retrospective survey reported the diagnostic findings in sick dogs that also had antibodies to *B. vinsonii* subsp. *berkhoffii*. The diagnoses encompassed a diverse group of conditions, with most syndromes reported in only one to a few dogs. They included endocarditis, myocarditis, lymphadenitis, polyarthritis, cutaneous vasculitis, meningoencephalitis and other neurological syndromes, immune-mediated hemolytic anemia/immune thrombocytopenia, and ocular signs (anterior uveitis, chorioretinitis, ocular hemorrhage, and retinal detachment associated with hypertension). Thrombocytopenia was detected in approximately half of the dogs, and anemia in a third. A wide variety of antibiotics were used, and most but not all cases responded to treatment. After treatment, titers to *Bartonella* were no longer detected in the subset of cases where titers were measured. Whether *Bartonella* had a role in any of the cases was not established.

In one case report, *B. vinsonii* subsp. *berkhoffii* DNA was found in a granulomatous nasal mass from an afebrile dog with rhinitis and protein-losing nephropathy. No bacteria could be identified in the lesion by any technique, including Warthin–Starry silver staining. The dog had antibodies to both *B. vinsonii* subsp. *berkhoffii* and *Ehrlichia canis*, and *E. canis* DNA was detected in the blood 9 months after the mass was removed. The clinical signs resolved after removal of the mass and treatment with doxycycline for 30 days. In a recent case control study of dogs with idiopathic rhinitis, no dogs had antibodies to *B. henselae* or *B. vinsonii* subsp *berkhoffii*, and there was no evidence for these organisms by PCR. This study does not rule out the possibility that some cases of rhinitis are caused by *Bartonella*, but suggests that it is not a common etiology.

Cattle

The effect of *Bartonella* infections in cattle, if any, is unknown. Because *B. bovis* is very common in some herds, it is difficult to attribute clinical signs to this organism. *B. bovis* was suggested as the cause of endocarditis in two older cows. These animals had high antibody titers to this organism, and DNA was detected in the lesions. One study of a dairy herd suggested that adverse effects on health and reproductive success are uncommon. In this herd, there was no correlation between bacteremia and milk yield, milk cell count or various parameters of reproductive success. Fewer bacteremic cows retained the placenta, and the interval from calving to first artificial insemination was shorter.

Horses

Four horses inoculated intradermally with an equine isolate of *B. henselae* developed injection site reactions (mild edema, sensitivity and pruritus, sometimes accompanied by purulent drainage), and had mild, nonpainful, unilateral enlargement of the regional lymph node, without fever. Three of the horses also had mild to moderate

limb edema. One of these horses had evidence of concurrent infection with *B. vinsonii* subsp. *berkhoffii*, apparently acquired during the experiment. In the same experiment, four horses inoculated intradermally with a bovine isolate of *B. bovis* had milder injection site reactions consisting of sensitivity and mild edema. Two horses developed mild, unilateral, nonpainful regional enlargement of the regional lymph node, two horses had nonpruritic urticaria, and one horse had mild colic and mild hind limb edema. However, only one horse had evidence of infection with *B. bovis* (transient low titers to this organism).

Possible involvement of *B. henselae* was suggested in a few case reports:

B. henselae DNA was detected in the tissues of an aborted equine fetus that had necrosis and vasculitis in multiple tissues. Gram-negative bacteria, which stained with Warthin-Starry silver stain and labeled with a monoclonal antibody to *B. henselae*, were found in many of the inflammatory lesions. No known agents of equine abortion could be detected in this fetus. The mare had no history of clinical signs or prior abortions. Other mares on the same farm successfully carried foals to term.

In one report, *B. henselae* was detected in blood samples from a horse with chronic arthropathy and another horse with vasculitis. Whether *Bartonella* had any role in these conditions is unclear. The horse with vasculitis had a high antibody titer to *Streptococcus equi*, and was diagnosed as having purpura hemorrhagica. In the horse with chronic arthropathy, the clinical signs did not resolve after treatment with antibiotics effective against *Bartonella*.

Rodents

Experimentally infected rodents have remained asymptomatic in some studies. Granulomatous hepatitis was the only necropsy lesion in rodents inoculated with large numbers of bacteria. However, the incidence of fetal death and placental vasculitis was increased in mice infected with *B. birtlesii*. Inoculation of mice with two *B. tamiae* isolates from humans resulted in axillary and inguinal lymphadenopathy, ulcerative skin lesions and subcutaneous masses on the thorax. Myocarditis, lymphadenitis with vascular necrosis, and granulomatous hepatitis and nephritis were reported at necropsy. Mice inoculated with another human isolate of *B. tamiae* (from a patient with less severe symptoms) developed dermatitis and granulomas in the kidneys, but did not have lymphadenitis.

Non-human primates

In one experiment, simian immunodeficiency virus (SIV)-infected macaques inoculated with *B. henselae* remained asymptomatic. These monkeys did not become bacteremic or seroconvert. In another experiment, two macaques became febrile and developed subcutaneous purple-red spots at the inoculation site. The significance of this finding is unclear, as *B. henselae* was not recovered from the regional lymph nodes and the animals did not seroconvert.