This document is a supplement to the CFSPH "Cat Scratch Disease and Other Zoonotic *Bartonella* Infections" factsheet providing further details on human cases, and cat scratch disease-related complications.

Bartonella Infections in Humans: Clinical Signs

B. henselae appears to infect some immunocompetent people without causing clinical signs. Most others develop a self-limiting condition called cat scratch disease. Immunocompromised individuals infected with *B. henselae* may develop a more severe form of cat scratch disease, as well as bacillary angiomatosis and peliosis hepatis.

Cat scratch disease

In many cases, the first sign of cat scratch disease is the development of one or more small, reddish-brown, erythematous papules, pustules, macules, vesicles or ulcers at the inoculation site. These lesions disappear in 1-3 weeks, and may be mistaken for insect bites; however, they are not usually pruritic. The characteristic solitary lymphadenopathy or (less frequent) regional lymphadenopathy usually develops within a few weeks of exposure. Affected lymph nodes are often painful or tender, and the skin over the nodes can be warm, reddened and indurated. Cellulitis is, however, rare. Occasionally, the nodes may suppurate, especially when they are large. Lymphadenopathy usually lasts for a few weeks to a few months, and occasionally up to a year. Rarely, enlarged lymph nodes may persist longer. Cat scratch disease without lymphadenopathy is possible, but appears to be unusual in young, healthy patients. It is reported to be more common in elderly individuals and transplant patients. Other common symptoms are a low grade fever, malaise and fatigue. The fever usually disappears within 1-2 weeks but fatigue may persist for weeks or months. Less often, there may be other nonspecific signs such as headache, anorexia, vomiting, nausea, weight loss, generalized pain or a sore throat.

Complications, systemic signs and atypical presentations are reported to occur in at least 5% and possibly up to 25% of patients, with an increased incidence in the elderly and people who are immunocompromised.

- Parinaud oculoglandular syndrome is the most common atypical presentation. It is thought to result from inoculation of the organism into the eye. This syndrome is characterized by nonpurulent unilateral conjunctivitis and/or conjunctival granuloma, together with preauricular, submandibular, or cervical lymphadenopathy. It usually resolves in several weeks without permanent damage.
- Neurological complications are uncommon. Encephalitis, the most common syndrome, has been reported in as many as 4-5% of patients in some series. It typically occurs 1-6 weeks after the classic symptoms, but cases without lymph node involvement, as well as cases preceding lymphadenopathy, have been reported. This condition may progress rapidly to seizures, coma with respiratory depression and other severe signs, but patients usually recover completely without permanent damage. Cranial or peripheral nerve involvement is less common than encephalitis. A wide variety of syndromes, such as transverse myelitis, transient facial nerve paresis, sensory loss, alterations in reflexes and motor deficits may be seen. Some neurological syndromes appear to be rare, and have been documented in only a few case reports in the literature.
- Ocular complications: Neuroretinitis is an uncommon but well-recognized condition in cat scratch disease. It is characterized by the sudden onset of painless visual loss, usually unilateral. Although the condition is temporary and resolves in months, some patients may have residual defects such as mildly decreased visual acuity, or abnormal color vision or contrast sensitivity. Various other ocular conditions such as anterior uveitis have also been attributed to *B. henselae*. Subretinal masses have been reported in HIV-positive patients.
- *B. henselae* bacteremia can result in endocarditis, most often in people with existing heart valve abnormalities.
- Disseminated disease with granulomatous hepatitis and/or splenitis has been reported in some patients. The usual signs are a persistent spiking fever and abdominal pain. Chills, weight loss, headache and myalgia may be seen. Lymphadenopathy may or may not be present. In most cases, the lesions and symptoms resolve within 6 months.
- Arthropathy has been reported in patients infected with *Bartonella.* The knee, wrist, ankle and elbow joints are most often involved. Arthropathy can persist for weeks after the lymphadenopathy has resolved.

- Osteomyelitis has been reported rarely. The osteolytic lesions are usually localized to one area, although cases of multifocal disease have been reported. The vertebrae and pelvic girdle are involved most often. The main symptoms are fever with pain and tenderness over the affected bone. Patients with bone involvement have usually recovered completely, although antibiotics were given in most cases.
- Various nonspecific rashes are reported infrequently. They are usually nonpruritic and resolve in days to weeks.
- Pulmonary involvement is rare. In most cases, it was characterized by pneumonia or pleural thickening and/or effusion. Patients have usually recovered completely, with a mean recovery time of 2 months.
- Other complications or syndromes have also been attributed to *B. henselae*, based on diagnosis by serology and/or PCR. They include fever of unknown origin, thrombocytopenic purpura (usually transient), hemolytic anemia, vasculitis, monoclonal gammopathy, biclonal gammopathy and glomerulonephritis, as well as soft tissue masses in the mammary gland, the liver or the spleen that may mimic neoplasia. Septic shock was reported in a transplant patient. Some of these complications seem to be rare, and have been documented in only a few case reports.

Immunocompetent individuals with cat scratch disease usually recover without antibiotic treatment, and even complications generally resolve without sequelae. Although residual deficits have been reported, this is uncommon. Deaths are very rare. Endocarditis is usually the most serious concern; however, fatal encephalitis was reported in one child. In immunocompromised individuals, the clinical signs may be more severe; complications, bacteremia and atypical presentations are more common; and most cases are treated with antibiotics.

Recurrent illness has been described in a few people with severe signs, including a transplant patient. The clinical signs recurred at 4-20 month intervals, and consisted of lymphadenopathy in one patient, lymphadenopathy and fever in another patient, and fever, headache, malaise and weight loss in two others.

Bacillary angiomatosis and bacillary peliosis

B. henselae can also cause bacillary angiomatosis (epithelioid angiomatosis) and peliosis hepatis. Although rare cases have been reported in immunocompetent individuals, these conditions occur mainly in those who are immunocompromised.

Bacillary angiomatosis is a vascular proliferative disease of the skin and/or internal organs. It is most often an AIDS-related disease in people with a very low CD4 count. The most apparent symptoms are one to hundreds of cutaneous papules and nodules, which may resemble granulomas, Kaposi's sarcoma (violaceous nodules), or lichenoid violaceous plaques. They vary in size from pinhead-sized to 10 cm in diameter. Subcutaneous nodules resembling a common abscess may also be seen. In addition, bacillary angiomatosis can involve the internal organs including the heart, brain, liver, spleen, bone, larynx, lymph nodes and gastrointestinal tract. The symptoms vary with the organ(s) affected, and may include neurological signs, bone pain, weight loss or symptoms related to massive visceral lymphadenopathy.

Peliosis hepatis is a rare condition, caused by *B. henselae* as well as other pathogens, drugs and toxins. It is characterized by vascular proliferation in the liver, which can result in multiple blood-filled cysts and sinusoidal dilatation. The symptoms of peliosis hepatis may include fever, weight loss, abdominal pain, nausea, vomiting, diarrhea and hepatosplenomegaly. In some cases, this condition may be an incidental finding at necropsy. Peliosis hepatis can be seen in some patients with bacillary angiomatosis.

Other zoonotic Bartonella

Additional zoonotic *Bartonella* spp. have been reported in people with various illnesses. A number of these case reports are described below. The type of evidence presented for the involvement of *Bartonella* in the condition, as well as the strength of the evidence, varies between cases.

- Endocarditis has been attributed to several species of *Bartonella*, and might also be caused by others. This condition occurs most often in people with pre-existing abnormalities of the heart valves. Most cases have been caused by *B. henselae* or the human pathogen *B. quintana*, but culture or PCR evidence has linked *B. elizabethae, B. koehlerae, B. vinsonii* subsp. *berkhoffii, B. vinsonii* subsp. *arupensis, B. washoensis* and *B. alsatica* to a few cases. Additional cases have been diagnosed based on serology alone.
- A *B. vinsonii* subsp. *berkhoffii* infection was reported in a veterinarian who sustained a needlestick injury while aspirating a neoplastic mass from a dog. There was no evidence of infection 5 days after exposure, but DNA from the organism was detected in the veterinarian's blood at 34 days, after he reported frequent

headaches, fatigue and intermittent paresthesia. *B. vinsonii* subsp. *berkhoffii* was also isolated from his blood, and seroconversion occurred. The symptoms resolved after treatment with doxycycline and rifampin. While the evidence suggests that the dog was the source of the infection, this could not be proved. Only one tissue sample was available for testing from the dog, and although *B. vinsonii* subsp. *berkhoffii* DNA was detected, it was of a different genotype. Antibodies to *B. vinsonii* (subspecies not identified) were also found in a child with fever and regional lymphadenopathy, who had been bitten by a dog (of unknown *Bartonella* status) 3 weeks earlier.

- *B. clarridgeiae* was suggested as the cause of cat scratch disease symptoms in at least three people, based on serology alone. The signs consisted of papules at the inoculation site, fever and regional lymphadenopathy. The organism was not cultured or detected by PCR.
- Regional lymphadenopathy was associated with *B. alsatica* infection in an elderly woman who had been scratched while butchering a wild rabbit. Bacteria consistent with *Bartonella* were identified by Warthin-Starry silver staining in the enlarged lymph node, and these bacteria stained for *B. alsatica* by immunohistochemistry. PCR on the lymph node was also positive for this organism. Her condition responded to doxycycline.
- *B. rochalimae* was isolated from the blood of a person who developed an acute febrile illness with a diffuse macular rash, mild anemia and splenomegaly, soon after returning to the U.S. from a trip to South America. The infection responded to a short course of levofloxacin. A macaque that was inoculated with this organism had bacteremia and a decreased hematocrit.
- *B. washoensis* was isolated from the blood of a woman with fever, chills, headache, nausea, joint pain, an episode of vomiting, epigastric and lower left sided abdominal pain, and signs of meningitis. The symptoms improved after treatment with moxifloxacin, but persistent body aches and bone pain were still reported after 2 months.
- Both *B. melophagi* and *B. henselae* were isolated from the blood of a person who developed a relatively large ("hand-sized"), nonpruritic, red, cutaneous plaque, followed by a febrile illness with neutropenia, myalgia, neurological signs and joint pain. The illness waxed and waned at 3-4 week intervals. A heart murmur with mild aortic insufficiency and mild mitral regurgitation were also identified. *Babesia microti*, *Anaplasma phagocytophilum* and *Borrelia burgdorferi* were ruled out. Some improvement was seen with drugs effective for *Bartonella* (rifampin and azithromycin), but the symptoms did not resolve until cefuroxime was also added. In another case reported in the same paper, *B. melophagi* was isolated from the blood of a woman who had residual fatigue and muscle weakness, 6 months after an episode of pericarditis of uncertain etiology. No further information was given for the second case.
- *B. tamiae* was cultured from the blood of three patients enrolled in a prospective study to determine the etiology of febrile illnesses in Thailand. The clinical signs consisted of fever and nonspecific signs such as fatigue and headache, as well as anemia and mild liver function abnormalities. One patient had a maculopapular rash that had lasted 22 days, while another had a transient petechial rash. The report did not indicate whether the patients responded to antibiotics, or what other agents were ruled out. However, the organisms isolated from all three patients caused illness when inoculated into mice, and DNA was detected in the lesions in these animals. PCR assays detected DNA from *B. vinsonii* subsp. *arupensis*, *B. elizabethae*, *B. rattimassiliensis* and *B. tribocorum* in other febrile patients in this study. Further investigations of the latter cases have not been published.
- *B. vinsonii* subsp. *arupensi* was isolated from the blood of a U.S. cattle rancher who had high fever, headache, myalgia and neurological signs. The condition responded to treatment with ceftriaxone and prednisone. The rancher had a history of a relapsing rheumatologic syndrome with vasculitis and neurological signs, which was responsive to corticosteroids. The authors of this study concluded that his symptoms were consistent with his previously diagnosed condition, and the contribution of the *Bartonella* to the symptoms was uncertain.