Zoonosis Update

Cat scratch disease and other zoonotic *Bartonella* infections

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Since the early 1990s, there have been substantial advances in the understanding of the etiology, reservoir potential, vector transmission, and pathogenesis of bartonellosis in cats, dogs, and humans. *Bartonella* spp are fastidious, hemotropic, gram-negative organisms that have been recently identified in a wide range of domestic and wild mammals.[1] These organisms are considered to be emerging zoonotic agents. *Bartonella* spp are usually vector borne, and the vector varies with the *Bartonella* spp involved (eg, sandflies for *B bacilliformis* or human body lice for *B quintana*; **Appendix**). Fifty years ago, cat scratch disease was identified in France and described by Debré et al.[2] It is now known that this common zoonosis is caused by a bacterium of the genus *Bartonella* and not by *Afipia felis*.[3] Cats are the main reservoir of this bacterium, which is transmitted from cat to cat via the cat flea (*Ctenocephalides felis*).[4] Several new *Bartonella* spp or subspecies have been identified in domestic cats and dogs and free-ranging or captive wild felids or canids. Furthermore, many new species of *Bartonella* have been identified in a wide range of mammals, including rodents and ruminants. There is also an increasing number of reports of infections in humans and dogs caused by *Bartonella* spp associated with rodents.

Morphologic and Biological Features

Members of the genus *Bartonella* are short, pleomorphic, gram-negative rod bacteria; they are fastidious, aerobic, and oxidase-negative organisms. They belong to the α_2 subgroup of the class Proteobacteria and are closely related to the genera *Brucella*, *Agrobacterium,* and *Rhizobium*.[1] They are mainly hemotropic, intraerythrocytic bacteria. Isolation of the organisms is usually achieved via bacteriologic culture of blood after partial lysis of the erythrocytes. In culture, *Bartonella* organisms require specific axenic media (enriched with rabbit or horse blood), and for most of these bacteria, the culture must be performed at 35°C with an atmosphere containing 5% carbon dioxide. Growth of primary isolates occurs after several days (usually more than a week) to several weeks.[1,3] Identification of the bacteria is mainly based on results of **polymerase chain reaction (PCR)** assay and sometimes findings of partial sequencing of specific genes (eg, 16S rRNA, citrate synthase, and groEL). Via pulsed field gel electrophoresis, *B henselae* DNA has a wide range of profiles, compared with profiles of *B clarridgeiae*.

Four *Bartonella* spp have been isolated from domestic cats. Domestic cats appear to be the main reservoir of 3 of these 4 species: *B henselae*, the predominant agent of cat scratch disease; *B clarridgeiae*, another possible agent of cat scratch disease; and *B koehlerae*, isolated from 2 cats in northern California and more recently identified in cat fleas and a pet cat in France.[1,5-7] The fourth species, *B weissii* (now named *B bovis*[8]), was isolated from 4 domestic cats from Utah and Illinois.[a] Two main genotypes of *B henselae* have been identified in humans and cats (identified on the basis of partial sequencing of the 16S rRNA gene) and are presently designated as either genotype I and genotype II or genotype Houston I and genotype Marseille.[9-11]

In domestic dogs, *B vinsonii* subsp *berkhoffii* was first isolated from a dog with endocarditis.[12,13] Since then, this bacterium has been identified as an important cause of canine endocarditis[14] and was the cause of endocarditis in a human.[15] Similar to cats and humans, dogs can be infected with several other *Bartonella* spp. *Bartonella clarridgeiae* was isolated from a specimen of blood obtained from a dog with endocarditis[16] and detected in the liver by PCR assay in a dog with hepatic lymphocytic hepatitis.[17] *Bartonella henselae* DNA has been detected in a dog with peliosis hepatis[18] and more recently in a dog with granulomatous hepatitis.[17] *Bartonella henselae* DNA was amplified from blood samples obtained from 3 dogs with various clinical conditions.[19] *Bartonella elizabethae* DNA was also detected in a blood sample from a sick dog.[19] In addition, *B washoensis* (a rodent-borne zoonotic *Bartonella* sp) was isolated from a dog with mitral endocarditis.[20] It is becoming increasingly obvious that rodents and cats can serve as a potential reservoir for *Bartonella* infections in both humans and dogs.

Bartonella organisms have also been isolated from wild canids. Coyotes (*Canis latrans*) appear to be a major wildlife reservoir for *B vinsonii* subsp *berkhoffii* in the western United States.[21,22] Results of partial sequencing of the citrate synthase (*gltA*) and 16S rRNA genes indicated a 99.5% and a 100% homology

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between one of the coyote isolates and *B vinsonii* subsp *berkhoffii*, respectively. *Bartonella* organisms have also been isolated from gray foxes (*Urocyon cinereoargenteus*) and raccoons (*Procyon lotor*) in California by one of the authors.

In rodents, many *Bartonella* spp and subspecies have been identified, among which a few have been associated with diseases in humans, including neuroretinitis (*B grahamii*), neuromotor symptoms (*B vinsonii* subsp *arupensis*), and endocarditis and other cardiac diseases (*B elizabethae* and *B washoensis*).[1,23]

Epidemiology

Humans—Cat scratch disease, caused by *B henselae*, has a worldwide distribution. However, it is not a reportable disease in humans in most countries. Therefore, sufficient data to determine the exact incidence or prevalence of *Bartonella* infection are not available. In the United States, it was estimated that 22,000 to 24,000 humans developed cat scratch disease during 1992, of whom 2,000 were hospitalized.[24] The estimated annual health care cost of the disease was more than $12 million. In Connecticut, which is the only state where the disease is reportable in the United States, the incidence of cat scratch disease from 1992 to 1993 was estimated to be 3.7 cases/100,000 persons, whereas in The Netherlands, there was an estimated 2,000 cases/y or 12.5 cases/100,000 persons.[25] These observations suggest that several thousand cases of cat scratch disease may occur every year in many countries. Overall, cat scratch disease is more likely to occur in children and young adults. Transmission from cat to human mainly occurs via cat scratch or bite; less frequently, transmission could possibly be via a fleabite or a tick bite.[6,26,27]

Bacillary angiomatosis and bacillary peliosis are unusual vascular proliferative lesions observed in immunocompromised humans as a result of infection by *B henselae* or *B quintana*. In a recent study of *Bartonella* infection among HIV-infected patients with fever, 68 of 382 (18%) patients had evidence of *Bartonella* infection detected via bacteriologic culture, indirect **immunofluorescent antibody (IFA)** testing, or PCR assay.[28] Twelve patients (3%) had either *B henselae* or *B quintana* isolated from specimens of blood, tissue, or both or had *Bartonella* DNA detected in tissue.

Bartonella henselae and *B quintana* have also been associated with cases of endocarditis in immunocompetent and immunocompromised humans and were associated with 3% of the cases of endocarditis evaluated at 3 study centers.[29-31] The emergence of the popular, physically demanding, and nature-interactive sport of orienteering (cross-country running requiring navigational acuity with map and compass-reading skills) was marked in Sweden by sudden unexpected (apparently cardiac-related) deaths in young, premier competitors during the years 1979 through 1992. *Bartonella henselae* and *B quintana* DNA were detected in the cardiac tissue of 4 of those young orienteers who died suddenly and unexpectedly of cardiac-related conditions.[32]

In humans, antibodies against *B clarridgeiae* were detected in a suspected case of cat scratch disease and in a patient with a chest-wall abscess.[33,34] Anti-**flagella (FlaA)**-specific antibodies against *B clarridgeiae* have also been detected in 3.9% (28/724) of patients with lymphadenopathy.[35] Results of these serologic investigations suggest that *B clarridgeiae* could also be a possible causative agent of cat scratch disease.

To the authors' knowledge, there are few reports of human infection caused by other *Bartonella* spp or subspecies (mainly of rodent origin; Appendix). There are still numerous unknown risk factors associated with such infections (eg, mode of infection, the vectors involved, and source of infection). For instance, ticks have been suggested as a possible vector for *B henselae* infection in humans.[26,27,36] Among the rodent-borne *Bartonella* spp, infection with *B elizabethae* appears to be quite prevalent among homeless people and IV drug users in various parts of the United States and Sweden. Among IV drug users, seroprevalence for *B elizabethae* ranged from 33% in Baltimore[37] to 39% in Stockholm[38] and 46% in New York.[39] The seroprevalence was 12.5% among homeless people from Los Angeles.[40] Interestingly, 355 of 1,136 (31%) Swedish orienteers were seropositive against *B elizabethae*.[41]

Cats—Domestic cats are the main reservoir of *B henselae*. Seroepidemiologic studies have revealed worldwide distribution of *B henselae* infection in domestic cats, with 4% to 80% of cats having antibodies against *B henselae* (according to the geographic location).[3] Domestic cats can be bacteremic for several weeks to a few years.[42,43] Results of epidemiologic studies have indicated that the prevalence of bacteremia in cats ranges from 15% to 55% in Australia and many other countries in the Americas, Europe, Asia, and Africa. The prevalence of bacteremia in young cats (< 1 year old) is usually higher than it is in adult cats.[44] Major regional variations in the prevalence of *B henselae* type I (Houston I) and type II (Marseille) have been reported in domestic cat populations. For example, in a limited study performed in the United States by 2 of the authors of this report, the prevalence of *B henselae* type I in 20 cats from northern California reached only 18%, whereas this bacterium represented 21 (52%) of 40 isolates from cats from the southeastern United States. Similarly, in 271 young pet cats, prevalence of *B henselae*-associated bacteremia ranged from 33% in Florida and 28% in southern California to 12% in Washington, DC, and only 6% in Chicago.[45] In that study, most of the isolates (81%) in southern California were *B henselae* type II, whereas both *B henselae* types were evenly distributed in Florida. In most areas of Europe, *B henselae* type II is the dominant type,[46] whereas type I represents 70% to 80% of *B henselae* isolates detected in eastern Asia.[47-49] Direct transmission from cat to cat in a flea-free environment and vertical transmission from infected queens to their kittens have not been detected.[42,50] Warm and humid climates are strongly associated with the presence of antibodies against *B henselae* and ectoparasite infestation in cats, further supporting arthropod vector involvement in transmission.[51] The cat flea, *C felis*, plays a major role in cat-to-cat transmission of *B henselae*.[4,52]

Feline infection with *B clarridgeiae* has been reported in many parts of the world.[3] In western

Europe (ie, France and The Netherlands), 30% to 36% of cats with bacteremia were infected with *B clarridgeiae*.[25,53,54] However, *B clarridgeiae* was not isolated from bacteremic cats in Germany[55] or Denmark.[46] In Asia, 17% (13/76) to 32% (6/19) of bacteremic cats from Indonesia, Thailand, and the Philippines were infected with *B clarridgeiae*, but only 10% (5/49) of bacteremic cats were infected with *B clarridgeiae* in Japan.[47-49,56] Similarly, *B clarridgeiae* was isolated from only 10% (7/70) of cats evaluated in the southeastern United States.[57] Coinfection with *B clarridgeiae* and *B henselae* has been reported in cats from Europe, Asia, and the United States.[25,49,54,58,59] The mode of transmission of *B clarridgeiae* and *B koehlerae* in domestic cats has not been elucidated; however, cat fleas may be the main vector, as they are for transmission of *B henselae*. Identification of *B clarridgeiae* and *B koehlerae* DNA in cat fleas in France strongly supports flea-associated transmission of these bacteria.[6]

Dogs and wild canids—In California, coyotes (*C latrans*) are a major reservoir of *B vinsonii* subsp *berkhoffii* (35% of coyotes are seropositive against this bacterium, and 28% are bacteremic).[21,22] Coyotes with antibodies against *B vinsonii* subsp *berkhoffii* are more likely to be living in coastal counties than inland counties, and the clustered distribution of *Bartonella* infection among coyotes in California seems to coincide with the known geographic distribution in that state of tick species that are able to feed on carnivores.[21]

Compared with serologic findings in coyotes, only a small percentage (2.2% to 3.6%) of sick or healthy dogs in the United States had antibodies against *B vinsonii* subsp *berkhoffii* (detected via immunofluorescence techniques).[60,61] In a serologic evaluation of 1,875 US government-owned working dogs (mainly military-owned dogs), results of ELISAs indicated that seroprevalence of *B vinsonii* subsp *berkhoffi*i was 8.7%; 11% (13/118) of dogs from California and Arizona had antibodies against this bacterium.[62] In a study by Pappalardo et al,[60] domestic dogs that were seropositive against *Bartonella* were 14 times as likely to have a history of heavy tick exposure, 9 times as likely to have been exposed to cattle, 7 times as likely to be from a rural than an urban environment, and almost 6 times as likely to have a history of heavy flea exposure, compared with dogs that were seronegative against *B vinsonnii* subsp *berkhoffii*. Furthermore, 36% of the serum samples obtained from dogs that were known to be seropositive against *Ehrlichia canis* were also determined to be seroreactive to *B vinsonii* subsp *berkhoffii* antigens.[60] In Rhode Island, despite a low antibody prevalence, all but 1 of 6 dogs that had antibodies against *B vinsonii* subsp *berkhoffii* were also seropositive against more than 1 tick-borne agent.[61] Seroprevalence of *B vinsonii* subsp *berkhoffii* was also high in domestic dogs that were coinfected with multiple tick-borne pathogens. Of 27 sick Walker Hounds from a kennel in southeastern North Carolina (where dogs were heavily infested with ticks and commonly infected with *Ehrlichia* and *Babesia*), 25 (93%) had antibodies against *B vinsonii* subsp *berkhoffii*.[63] Similarly, in a retrospective survey performed in Israel, 10% (4/40) of dogs suspected to have tick-borne diseases were determined to be seroreactive to *B vinsonii* subsp *berkhoffii* antigens.[64] Such data are supportive of a tick vector for *B vinsonii* subsp *berkhoffii*. Infection of domestic dogs by *B vinsonii* subsp *berkhoffii* appears to be more frequent in tropical regions, with prevalence ranging from 19% (5/26) for dogs from French Guyana and Martinique to 65% (33/51) for native dogs from Sudan.[b] It was also reported that *B vinsonii* and *E canis* infections were more frequently found in the dogs infested with *Rhipicephalus sanguineus*.[b] Similarly, in 49 dogs from Thailand that had fever, anemia, or thrombocytopenia, the prevalence of antibodies against *B vinsonii* subsp *berkhoffii* was 38%; 52% (17/33) of the dogs that were seropositive against *E canis* were also seropositive against *B vinsonii* subsp *berkhoffii*.[65]

On the basis of indirect evidence, it is strongly suggested that *Amblyomma americanum* or ticks of the genus *Dermacentor* could also be involved in infection of dogs with *Bartonella* spp in the southeastern United States. *Amblyomma americanum* is also involved in the transmission of *E ewingii*.[60,66] *Rhipicephalus sanguineus*, which is the only confirmed tick vector for transmission of *E canis*, appears to be able to transmit *B vinsonii* subsp *berkhoffii*, particularly among dogs in kennels.[60,66,b] Furthermore, 29 of 151 (19%) individually examined adult questing *Ixodes pacificus* collected at 3 different sites in Santa Clara County, Calif (where *Bartonella* infection was found to be endemic in coyotes), yielded positive results for *Bartonella* via PCR assay.[67] One of the ticks was infected with a strain corresponding to *B vinsonii* subsp *berkhoffii* (confirmed by results of PCR-restriction fragment length polymorphism assay and partial sequencing of the citrate synthase gene).[67] Therefore, on the basis of indirect serologic and molecular evidence, several tick species may be able to transmit *B vinsonii* subsp *berkhoffii* in different regions and cotransmission with *Ehrlichia* spp or *Anaplasma* spp should be anticipated by veterinarians.

Limited data are available on the prevalence of *B henselae* in dogs. Demers et al[68] reported that 2 of 31 (6.5%) dogs in Hawaii were seropositive against *B henselae* (titers of 1:64 and 1:128, respectively); however, bacteria were not isolated from blood samples obtained from those dogs, and PCR assays were not performed. In the United Kingdom, results of 1 study[69] indicated that 3 of 100 (3%) dogs were seropositive against *B henselae*. However, it was not possible to determine in those 2 studies whether the serologic reactions were specifically directed against *B henselae*. In Japan, Tsukahara et al[70] performed IFA tests in 52 dogs and reported that 4 (7.7%) were seropositive against *B henselae*. Similarly, we have identified antibodies against *B henselae* (usually at low titers) in healthy dogs in North Carolina and California. The DNA of *B henselae* and *B elizabethae* have been detected in dogs with various clinical conditions, increasing the number of *Bartonella* spp that have been identified in infected dogs.[17-19] *Bartonella clarridgeiae* and *B washoensis* were isolated from blood samples obtained from dogs with endocarditis,[16,20] and *B clarridgeiae* DNA was detected via PCR assay in a dog with lymphocytic hepatitis.[17]

Rodents—Rats (*Rattus norvegicus*) are the main reservoir of *B elizabethae*.[1,71] This *Bartonella* sp has been isolated from urban rats from various parts of the United States (Louisiana and Maryland), Portugal, and Peru.[71,72] In China, rodents from the Yunnan Province, including various *Rattus* spp, are infected with a large number of *Bartonella* strains that are genetically related to *B elizabethae*.[73]

Bartonella grahamii has been mainly isolated from bank voles (*Clethrionomys glareolus*) in the United Kingdom[74] and Poland[75] and from yellow-necked mice (*Apodemus flavicollis*) in Sweden.[76] This bacterium has also been isolated from rats in the United States and a domestic mouse captured in California.[71] White-footed mice (*Peromyscus leucopus*) are the reservoir of *B vinsonii* subsp *arupensis*, which has been isolated from 5% (4/81) of mice captured in Minnesota and Wisconsin.[77,78] California ground squirrels (*Spermophilus beecheyi*) have recently been identified as the main reservoir of *B washoensis*[79]; in 41 California ground squirrels evaluated, *Bartonella* spp were isolated from 7 (17%), and all isolates were identical or closely related to *B washoensis*. Similarly, a previously unknown *Bartonella* sp has been identified in the western United States in prairie dogs (*Cynomys ludovicianus*) and in the fleas that they carried.[80] Coinfection of those fleas with *Yersinia pestis* and this newly identified *Bartonella* sp was detected. The epidemiologic importance of rodent-borne *Bartonella* spp as cause of disease in animals and humans is yet to be established.

Clinical Features

Humans—In immunocompetent patients, cat scratch disease caused by *B henselae* is mainly characterized by a benign regional lymphadenopathy. Seven to 12 days after receiving a cat scratch (or a bite), a papule and then a pustule develop at the inoculation site.[23,81,82] Regional lymphadenopathy develops 1 to 3 weeks after the inoculation and can persist for a few weeks to several months.[81] Atypical manifestations may develop in 5% to 15% of humans with cat scratch disease; these may include Parinaud's oculoglandular syndrome, encephalitis, endocarditis, hemolytic anemia, hepatosplenomegaly, glomerulonephritis, pneumonia, relapsing bacteremia, and osteomyelitis.[82] Cat scratch disease encephalopathy, which is possibly associated with immune-mediated symptoms caused by *B henselae*, is one of the most severe complications of cat scratch disease.[83] Patients with cat scratch disease encephalopathy usually completely recover within 1 year without any sequelae. *Bartonella henselae* was also recently identified as a frequent cause of prolonged fever and fever of unknown origin in children.[84,85] Rheumatic manifestations of *Bartonella* infection have also been described in children, including 1 case of myositis and 1 case of arthritis and skin nodules.[86] Arthritis has also been described in a limited number of cases.[81,87] Other rheumatic manifestations associated with *Bartonella* infection in humans include erythema nodosum,[81] leukocytoclastic vasculitis,[88] fever of unknown origin with myalgia,[84] and arthralgia.[81] A causative role for *B henselae* in Henoch-Schönlein purpura was recently suggested on the basis of serologic evidence; results of a study[89] indicated that 12 of 18 (67%) patients with Henoch-Schönlein purpura were seropositive against *B henselae* versus only 8 of 57 (14%) unaffected individuals. Henoch-Schönlein purpura is an immune-mediated vasculitis that is characterized by excessive IgA production. Monoclonal and biclonal gammopathies in 2 patients infected with *B henselae* have also been recently detected.[90] *Bartonella* spp have also been suggested as a cause of granuloma annulare[91] and glomerulonephritis.[92]

Bartonella spp were first described as a cause of endocarditis in humans in 3 reports in 1993: endocarditis was caused by *B quintana* in 1 immunocompromised individual,[93] caused by *B elizabethae* in an immunocompetent patient,[94] and caused by *B* (*Rochalimaea*) *henselae* in a third individual.[29] In humans, infection with *Bartonella* spp (mainly *B quintana* and *B henselae*) is the cause of approximately 3% of endocarditis cases, with > 100 cases reported in the international medical literature since 1993.[30,31,95,96] In most cases of *Bartonella*-associated endocarditis in humans, the vegetative lesions are preferentially located on the aortic valve,[31] and most patients have high antibody titers (eg, ≥ 1:800) detected via IFA testing.[95] Furthermore, blood samples from most humans with *B henselae*-associated endocarditis yield no growth of the organism in bacteriologic culture but yield positive results for *B henselae* via DNA amplification.[30] The DNA of *Bartonella henselae* and *B quintana* were also detected in the cardiac tissue of 4 young Swedish orienteers who died suddenly and unexpectedly as a result of cardiac conditions.[32]

In immunocompromised patients, bacillary angiomatosis is one of the most common clinical manifestations of *Bartonella* infections.[97] In affected individuals, chronic vascular proliferative lesions, which are clinically and histologically similar to those of verruga peruana caused by *B bacilliformis*, are observed. Persons infected with HIV that have CD4+ cell counts of < 50/mm^3 are likely to develop lesions of bacillary angiomatosis. Histologically, cutaneous bacillary angiomatosis is characterized by a tumor-like growth pattern with proliferation of capillaries that have protuberant epithelioid endothelial cells. These lesions are easily mistaken for pyogenic granuloma, Kaposi sarcoma, and angiosarcoma. A spectrum of pathologic changes (including bacillary angiomatosis and pulmonary nodules) has been described in transplant recipients.[98,99]

Cats—Because of the high prevalence of infection with *B henselae* in cats, it has been difficult to associate infection with specific clinical signs.[3,44] However, cats that were experimentally infected with *B henselae* (mainly type-II feline isolates) developed various clinical signs.[59,100,101] Fever was one of the most commonly observed clinical signs that usually developed within a few days of infection and persisted for 2 days to a few weeks. Local inflammation (erythema and swelling) at the site of inoculation and lymphadenopathy were also observed. Lethargy and anorexia have also been reported in experimentally infected cats. As reported for certain humans infected with *B henselae*, some cats also developed CNS disorders. Additionally, reproductive

disorders (eg, inability to become pregnant, pregnancy achieved only after repeated breedings, and stillbirths) have been observed in experimentally infected queens.[50] Variations in the pathogenicity of different strains of *B henselae* have been suggested for differences in clinical signs observed in experimental conditions.[101] On the basis of serologic findings, naturally infected cats were more likely to have lymphadenitis and gingivitis (especially those also infected with FIV) than were *Bartonella* seronegative cats.[102] A similar association between the presence of antibodies against *B henselae* and stomatitis or urologic diseases in cats has also been demonstrated.[103] *Bartonella henselae* has also been implicated as a potential cause of anterior uveitis in cats.[104] *Bartonella henselae*-associated endocarditis was recently confirmed via PCR assay in a cat from California.[105]

Dogs—*Bartonella vinsonii* subsp *berkhoffii* has been identified as an important cause of endocarditis in dogs[12,14] and was reported to be the cause of endocarditis in a human.[15] The known clinical spectrum of this infection in dogs continues to expand and includes cardiac arrhythmias, endocarditis, myocarditis,[14] granulomatous lymphadenitis, and granulomatous rhinitis.[106] In 12 dogs with cardiac arrhythmias, endocarditis, or myocarditis, 11 were seroreactive to *B vinsonii* subsp *berkhoffii*; in 3 of those 11 dogs, results of PCR assay and DNA sequencing confirmed that the lesions were caused by *B vinsonii* subsp *berkhoffii*.[14] In humans and dogs, *Bartonella*-associated endocarditis usually involves the aortic valve and is characterized by massive vegetative lesions.[107] Of the dogs diagnosed with endocarditis during a 2-year period at 1 veterinary teaching hospital, *Bartonella* infection was implicated as a causative agent in almost a third.[107] On the basis of serologic findings, infection with *B vinsonii* subsp *berkhoffii* may also cause polyarthritis, neutrophilic or granulomatous meningoencephalitis, immune-mediated anemia, thrombocytopenia, and eosinophilia in dogs.[108]

Nevertheless, *B vinsonii* subsp *berkhoffii* has also been isolated from clinically healthy dogs, which may be long-term carriers of the bacterium.[109] In 1 dog, *B vinsonii* subsp *berkhoffii* was isolated in 8 of 10 bacteriologic cultures of blood that were performed during a 16-month period.[109] Preliminary results of a case-control study performed by one of the authors to investigate clinical diagnoses in dogs that were seropositive against *Bartonella* spp suggest an association with lameness, vomiting, and lethargy.

Dogs may also be infected with several other *Bartonella* spp, including *B clarridgeiae* (which has been isolated from a blood sample obtained from a dog with endocarditis[16] and detected in a liver sample via PCR assay in a dog with lymphocytic hepatitis[17]). *Bartonella henselae* DNA has been detected in the liver from a dog with peliosis hepatis[18] and more recently in a dog with granulomatous hepatopathy.[17] The DNA of *Bartonella henselae* was amplified from blood samples obtained from 3 dogs with various clinical signs.[19] *Bartonella elizabethae* DNA was also detected in blood of a sick dog.[19] Furthermore, *B washoensis* (a rodent-borne zoonotic *Bartonella* sp) was isolated from a dog with mitral endocarditis.[20]

After experimental infection with *B vinsonii* subsp *berkhoffii*, dogs did not develop serious clinical signs other than transient pyrexia of 2 days' duration.[110] However, most of those experimentally infected dogs developed persistent bacteremia.[110,111] It appears that *B vinsonii* subsp *berkhoffii* establishes chronic infection in dogs, likely inducing immune suppression characterized by defects in monocytic phagocytosis, CD8+ T lymphopenia, and impaired B cell antigen presentation within lymph nodes.

Diagnosis

Clinical diagnosis—In humans, clinical diagnosis of cat scratch disease is made on the basis of detection of an enlarged lymph node and possibly the presence of a small vesicle or granuloma at the inoculation site that usually have developed following a cat scratch or bite. Confirmation of cat scratch disease is mainly established on the basis of results of serologic testing.[23,24] *Bartonella henselae*-associated endocarditis in humans is usually associated with high antibody titers (≥ 1:800) detected via IFA testing.[95] In cats, clinical diagnosis is not easy because many healthy cats are chronically infected.[3] In dogs, clinical diagnosis is problematic because the clinical spectrum of *Bartonella* infection is not fully elucidated.[1] *Bartonella* infection should be suspected in dogs with endocarditis or cardiac abnormalities (eg, arrhythmias or myocarditis), especially when the aortic valve appears to be affected. It also should be suspected in dogs with prolonged or intermittent fever, lethargy, unexplained lameness, or unexplained granulomatous disease. Similarly, veterinarians should consider performing a diagnostic test for *Bartonella* infection in clinically ill dogs when there is clinical or epidemiologic suspicion that tick exposure has occurred. Thrombocytopenia, anemia, neutrophilic leukocytosis, and eosinophilia are the most commonly detected hematologic abnormalities in dogs that are seropositive against *B vinsonii berkhoffii*.[108]

Serologic testing—In humans, serologic testing (mainly IFA testing) is the reference test for diagnosis of cat scratch disease.[23,95] An IgG anti-*B henselae* antibody titer ≥ 1:64 is considered as positive for infection when patients are tested at least 2 to 3 weeks after inoculation. Commercially prepared IFA slides for *B henselae* and *B quintana* antigens are available. At present, a limiting factor is the lack of commercial tests for most rodent-borne zoonotic *Bartonella* spp. Furthermore, serologic testing may not be useful for diagnosis of bacillary angiomatosis because patients with *Bartonella*-associated bacillary angiomatosis often do not mount a detectable antibody response to the organism.

In cats, serologic testing is of limited diagnostic value, as many cats (especially free-roaming felids) are likely to be seropositive against *B henselae*.[44] Testing is indicated in young cats or recently adopted cats because seronegative cats are more likely not to have bacteremia. However, bacteremia in seronegative cats has been reported in a few instances. An IFA test that detects antibodies against *B henselae* (and possibly also *B clarridgeiae*) should be performed on cats before

adoption by persons who may have immunocompromising conditions.

In dogs, serologic testing has mainly involved IFA tests for antibodies against *B vinsonii* subsp *berkhoffii*, but testing for other *Bartonella* spp that have been recently isolated or detected by PCR assay in dogs (especially *B henselae* and *B clarridgeiae*) should be performed. As for humans with endocarditis, *Bartonella*-associated endocarditis in dogs is usually characterized by high antibody titers; the antibodies usually cross-react with several *Bartonella* antigens.[107] Because of cross-reactivity, bacterial isolation or PCR assay is necessary to identify the infecting *Bartonella* spp.

Bacterial isolation or PCR assay—Isolation of *Bartonella* spp from cats is much easier than isolation of those organisms from other animal species. In humans with cat scratch disease or dogs with *Bartonella* infection, isolation of these bacteria is rarely successful. Isolation of *Bartonella* organisms from blood samples is performed by use of pediatric lysis-centrifugation tubes[c] or plastic tubes containing EDTA[d] (which are more convenient to use). Anticoagulated blood is plated (usually after freezing to induce RBC lysis) onto fresh rabbit blood agar and incubated for at least 4 weeks at 35°C with an atmosphere containing 5% carbon dioxide. Identification of the isolate is performed by use of PCR techniques and partial sequencing. Pulsed field gel electrophoresis (also known as fingertyping) of strains can be performed only on isolates.

Compared with bacteriologic culture, extraction of DNA from tissue samples and PCR testing has been more successful as a method of diagnosis of *Bartonella* infection in humans and dogs. Frozen tissue samples or fresh biopsy specimens can be easily tested. Polymerase chain reaction assay of paraffin-embedded tissues is more cumbersome, but possible. Testing should be performed by laboratory personnel who are familiar with processing these fastidious organisms; laboratories should be contacted for specific instructions for sample collection and submission.

Treatment

In humans with *B henselae* infection, treatment with antimicrobials for immunocompetent patients with cat scratch disease differs from that for immunocompromised patients with angiomatous proliferative diseases.[97] For immunocompetent patients, numerous antimicrobial agents have been advocated for the treatment of typical cases of cat scratch disease. However, in most instances, administration of antimicrobials does not appear to improve response to or shorten the duration of the infection. Azithromycin, rifampin, ciprofloxacin, and trimethoprim-sulfamethoxazole were effective in the improvement of clinical features associated with infection, but penicillins, cephalosporins, tetracyclines, and erythromycin had minimal or no clinical efficacy.[3] In humans with *Bartonella*-associated endocarditis, effective antimicrobial treatment should include an aminoglycoside administered for a minimum of 2 weeks.[96] In immunocompromised patients with bacillary angiomatosis or bacillary peliosis, the effectiveness of treatments with various antimicrobial agents has been evaluated.[97] Overall, tetracyclines, erythromycin, rifampin, doxycycline, or a combination of these antimicrobials are effective and should be administered to these patients for at least 6 weeks and continued for 4 to 6 months in those individuals who have relapses.

In cats, antimicrobial agents are not commonly used or recommended for treatment or prevention of infection with *B henselae*.[57] In a study of naturally infected cats,[52] *B henselae* was not isolated from 3 of 4 cats treated with doxycycline. However, in a later study,[112] the level of bacteremia in cats experimentally infected with *B henselae* and treated with enrofloxacin, erythromycin, or tetracycline was not significantly diminished, compared with a control group of cats that did not receive antimicrobial treatment. Finally, Kordick et al[57] reported that bacteriologic cultures of blood samples from cats experimentally infected with either *B henselae* or *B clarridgeiae* after administration of enrofloxacin or doxycycline yielded negative results transiently, but the antimicrobial effect was not long-lasting, and most of those cats developed bacteremia after completion of treatment. Thus, antimicrobial treatments evaluated in cats to date may reduce the level of bacteremia but do not eliminate the infection. Additionally, the minimal effectiveness of these antimicrobial agents could be explained by the fact that *Bartonella* spp are intracellular (especially intraerythrocytic) organisms.

In dogs, no experimental study has yet been performed to determine the efficacy of antimicrobials for treatment of *Bartonella* infection. On the basis of data from other species, it is likely that antimicrobials such as doxycycline (10 mg/kg/d [4.5 mg/lb/d]) or tetracycline could reduce the level of bacteremia during chronic infections with *Bartonella*, but should be administered for prolonged periods of time (4 to 6 weeks). Macrolides (eg, erythromycin or azithromycin) are most probably the antimicrobials of choice for oral administration in the treatment of *Bartonella* spp infections in dogs. Fluoroquinolones alone or in combination with amoxicillin have also elicited a positive therapeutic response in affected dogs.[108] When aminoglycosides are administered to dogs with endocarditis, renal function should be monitored carefully. Antimicrobial treatment may not be effective when the lesions of endocarditis are already well established. The use of antimicrobials that achieve high intracellular concentrations, such as doxycycline, fluoroquinolones, or azithromycin, would be required to eliminate intracellular infection.

Prevention

Among inhabitants of the most industrialized countries, cat ownership has been increasing during the last 2 decades and now surpasses dog ownership.[113] A large reservoir for *B henselae* exists among the more than 70 million pet cats that reside in more than a third of homes in the United States and among the more than 47 million pet cats that reside in homes in Europe. As the possibility of *B henselae* infection in humans becomes more widely recognized, negative publicity about the perceived hazards (especially for immuno-

compromised people) of cat ownership is likely. However, the company of cats can be very comforting to the chronically and terminally ill.[114] Selecting an appropriate companion animal is important. With regard to *B henselae* infection, seronegative cats are more likely not to have bacteremia and be less of a potential risk for ownership, compared with seropositive cats; however, at least 2% of seronegative cats have bacteremia.[45] Young kittens, especially impounded kittens and flea-infested kittens, are more likely to be bacteremic than other cats.[3,44,52] People who own kittens are 15 times as likely to develop cat scratch disease than are owners of older cats.[27] Therefore, people who want to acquire a cat as a companion animal, especially if they are immunocompromised, should perhaps seek a cat raised in a clean, flea-controlled cattery. If possible, the cat should be an adult and obtained from a flea-controlled environment.[54] Additionally, serologic testing could be performed and only seronegative cats adopted; however, there is no correlation between seropositivity and bacteremia.[44] Bacteremia can also be transient, and relapses may occur. Performance of onychectomy (declawing) in cats has also been suggested, but this procedure has a limited value because infection can be transmitted from cat to cat by fleas. Therefore, flea control appears to be one of the major control measures to prevent infection of cats with *B henselae*, its spread from cat to cat, and potentially the spread from cats to humans.[3] The most effective means of preventing *B henselae* infection are commonsense precautions, hygiene, and possibly modification of behavior of the cat owners themselves. For example, it is recommended that cat owners wash their hands after handling pets and clean any cuts, bites, or scratches promptly with soap and water. Development of a vaccine for cats to prevent the spread of infection in cat populations and reduce human risk of infection may be considered.

Infections with *Bartonella* spp in dogs are likely to be vector borne. A tick vector is strongly suspected for *B vinsonii* subsp *berkhoffii*.[60] Therefore, prevention of tick infestation should be one of the main control measures that are employed in a clinical setting. Use of tick repellents and cleaning of dogs after traversing high-risk terrain should be performed rigorously to prevent not only infection with *Bartonella* spp, but also other tick-borne infections. Flea-control measures are also important because dogs may become infected with *B henselae* when exposed to cat fleas (which are known to transmit the infection among cats).

Public Health Implications

Cat scratch disease is a somewhat common worldwide zoonosis associated with cat ownership. The disease is more commonly diagnosed in young children and teenagers who have contact with young kittens. Lymphadenopathy or prolonged fever of unknown origin in humans that develops subsequent to a cat scratch or bite should raise suspicion of cat scratch disease. Because *B henselae* is mainly transmitted via fleas from cat to cat, flea control is of utmost importance. It is clear that risk of infection increases with increased numbers of cats in a household.[54] To date, no direct contamination from dogs to humans has been identified. However, dogs may be infected by a wide range of *Bartonella* spp, and therefore canids may be excellent sentinels for potential human exposure. In dogs, transmission of *Bartonella* infection (at least transmission of *B vinsonii* subsp *berkhoffii*) appears to be associated to tick exposure; therefore, tick control appears to be essential for reduction of the risk of introducing infected ticks into the household and prevention of possible infection in dogs.

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[b]Davoust B, Drancourt M, Boni M, et al. Survey of seroprevalence of *Bartonella vinsonii*, *Ehrlichia canis* and *Coxiella burnetii* in dogs in southeast France, French Guyana, Martinique, Senegal, Ivory Coast and Sudan. Eur Work Group Rickettsia-Am Soc Rickettsiol Joint Meet 1999;232B.

[c]Wampole Isostat 1.5 mL, Wampole, Crambury, NJ.

[d]Vacutainer Plus, Becton-Dickinson, Franklin Lakes, NJ.

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Appendix

Epidemiologic features of *Bartonella* spp or subspecies

***Bartonella* sp**	**Reservoir**	**Accidental host**	**Vector or potential vector***	**Current geographic distribution**	**Present zoonotic status**
Bartonella bacilliformis	Humans	No	Pheblotomines (sand flies) (*Lutzomyia verrucarum*)	Andes (Peru, Ecuador, Colombia, Bolivia, Chile, Guatemala)	No
B quintana	Humans	No	Human body lice (*Pediculus humanis corporis*)	Worldwide†	No
B henselae	Cats (*Felis catus*)	Humans, dogs	Fleas (*Ctenocephalides felis*), Ticks?	Worldwide†	Yes
B clarridgeiae	Cats (*F catus*)	Humans, dogs	Fleas (*C felis*)	Cosmopolitan‡	Yes
B koehlerae	Cats (*F catus*)	Unknown	Fleas (*C felis*)	California, France	No
B vinsonii subsp *arupensis*	White-footed mice (*Peromyscus leucopus*)	Humans	Fleas? Ticks?	United States (Midwest)	Yes
B vinsonii subsp *berkhoffii*	Coyotes (*Canis latrans*)	Humans, dogs (*Canis familiaris*)	Ticks?	Cosmopolitan‡	Yes
B vinsonii subsp *vinsonii*	Meadow voles (*Microtus pennsylvanicus*)	No	Ear mites? (*Trombicula microti*)	Canada	No
B talpae	Moles (*Talpa europaea*)	No	Unknown	United Kingdom	No
B peromysci	Field mice (*Peromyscus* spp)	Unknown	Unknown	United States	No
B birtlesii	Wood mice (*Apodemus* spp)	Unknown	Unknown	France, United Kingdom	No
B grahamii	Bank voles (*Clethrionomys glareolus*)	Humans	Fleas?	United Kingdom	Yes
B taylorii	Wood mice (*Apodemus* spp)	Unknown	Fleas?	United Kingdom	No
B doshiae	Meadow voles (*M agrestis*)	Unknown	Unknown	United Kingdom	No
B elizabethae	Rats (*Rattus norvegicus*)	Humans, dogs	Fleas	Worldwide	Yes
B tribocorum	Rats (*R norvegicus*)	Unknown	Unknown	Cosmopolitan‡	No
B alsatica	Rabbits (*Oryctolagus cuniculus*)	Unknown	Fleas? Ticks?	France	No
B washoensis	Ground squirrels (*Spermophilus beecheyi*)	Humans, dogs	Fleas? Ticks?	United States (Western)	Yes
Bartonella sp Unknown	Prairie dogs (*Cynomys ludovicianus*)	Unknown	Fleas?	United States (Western)	No
B bovis	Domestic cattle (*Bos taurus*)	Unknown	Biting flies? Ticks?	Cosmopolitan‡	No
B capreoli	Roe deer (*Capreolus capreolus*)	Unknown	Biting flies? Ticks?	Europe	No
B schoenbuchensis	Roe deer (*C capreolus*)	Unknown	Biting flies? Ticks?	Europe	No
B chomelii	Domestic cattle (*B taurus*)	Unknown	Biting flies? Ticks?	France	No

*Potential vectors are organisms that have been suggested as vectors but for which there is no experimental proof. †Worldwide distribution (ie, reported from several continents). ‡Cosmopolitan (ie, detected where the organism was looked for).