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

between one of the coyote isolates and *B vinsonii* subsp *berkhoffii*, respectively. *Bartonella*

Europe (ie, France and The Netherlands), 30% to 36% of cats with bacteremia were infected with

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.

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

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 w[(with f728l tr)iate is per-with f728l trgda974.2962 128.954-0.001 T77i Twaiques a

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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