

## REVIEW ARTICLE

**Bartonellosis, an increasingly recognized zoonosis**

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**Summary**

Cat scratch disease is the most common zoonotic infection caused by *Bartonella* bacteria. Among the many mammals infected with *Bartonella* spp., cats represent a large reservoir for human infection, as they are the main reservoir for *Bartonella henselae*, *Bartonella clarridgeiae* and *Bartonella koehlerae*. *Bartonella* spp. are vector-borne bacteria, and transmission of *B. henselae* by cat fleas occurs mainly through infected flea faeces, although new potential vectors (ticks and biting flies) have been identified. Dogs are also infected with various *Bartonella* species and share with humans many of the clinical signs induced by these infections. Although the role of dogs as source of human infection is not yet clearly established, they represent epidemiological sentinels for human exposure. Present knowledge on the aetiology, clinical features and epidemiological characteristics of bartonellosis is presented.

**Introduction**

*Bartonella* spp. are fastidious haemotropic Gram-negative bacteria which are mainly transmitted by vectors (Chomel *et al.* 2009a). Since the last 20 years, the number of *Bartonella* species or subspecies identified from a wide range of mammals has increased considerably (Chomel *et al.* 2009a). Among the 13 species or subspecies known or suspected to be pathogenic for humans, four have been isolated from cats (Table 1). Domestic cats are the principal reservoir for *Bartonella henselae*, the main agent of cat scratch disease (CSD), *Bartonella clarridgeiae*, which has been suspected in a few cases of CSD and *Bartonella koehlerae*, reported as the cause of human and dog endocarditis (Avidor *et al.* 2004; Chomel *et al.* 2004; Ohad *et al.* 2009). Recently, *Bartonella quintana* was isolated from a pet cat and its owner (Breitschwerdt *et al.* 2007b). Fleas play a major role in the transmission of feline *Bartonella* (Chomel *et al.* 1996), but other potential vectors, such as ticks and biting flies, have been recently identified to harbour *Bartonella* DNA, including *B. henselae* (Sanogo *et al.* 2003; Chung *et al.* 2004). Domestic dogs have been shown to be infected with a broad range of *Bartonella* species, such as *Bartonella vinsonii berkhoffii*, *B. henselae*, *B. clarridgeiae*, *Bartonella rochalimae*, *B. quintana*, *B. koehlerae*, *Bartonella washoensis* and *Bartonella elizabethae* (Chomel *et al.* 2009a). They display a broad range of

clinical signs similar to those observed in humans. Our manuscript is an update on the aetiological agents, new clinical features and evolving epidemiological characteristics of these emerging zoonoses.

**Feline *Bartonella* species*****Bartonella henselae***

Since the first isolation of *B. henselae* from a domestic cat in the early 1990s, several studies have been conducted worldwide to determine the importance of cats as reservoir of this bacterium (Boulouis *et al.* 2005; Chomel *et al.* 2006). Prevalence of infection varies considerably among cat populations (stray or pets) with an increasing gradient from cold climates (0% in Norway) to warm and humid climates (68% in the Philippines) (Boulouis *et al.* 2005). Several genotypes have been identified, especially two main genotypes designated Houston-1 (type I) and Marseille (previously BATF) (type II) (Chomel *et al.* 2004; Boulouis *et al.* 2005). The respective prevalence of these two genotypes varies considerably among cat populations from different geographical areas. *Bartonella henselae* type Marseille is the dominant type in cat populations from the western USA, western Europe (France, Germany, Italy, The Netherlands and United Kingdom) and Australia, whereas type Houston-1 is dominant in Asia (Japan

**Table 1** Species and subspecies of *Bartonella* that are confirmed or potential human pathogens, primary hosts and vectors and known accidental hosts

<i>Bartonella</i>	Primary reservoir	Vector	Accidental host(s)
<i>Bartonella alsatica</i>	Rabbit ( <i>Oryctolagus cuniculus</i> )	Rabbit flea? ( <i>Spilopsyllus cuniculi</i> )	Human
<i>Bartonella bacilliformis</i>	Human	Sandfly ( <i>Lutzomia verrucarum</i> )	None
<i>Bartonella clarridgeiae</i>	Cat ( <i>Felis catus</i> )	Cat flea ( <i>Ctenocephalides felis</i> )	Human, Dog
<i>Bartonella elizabethae</i>	Rat ( <i>Rattus norvegicus</i> )	Oriental rat flea ( <i>Xenopsylla cheopis</i> )	Human, Dog
<i>Bartonella grahamii</i>	Wild mice ( <i>Clethrionomys glareolus</i> , <i>Microtus agrestis</i> , <i>Apodemus flavicollis</i> )	Rodent fleas	Human
<i>Bartonella henselae</i>	Cat ( <i>Felis catus</i> )	Cat flea ( <i>Ctenocephalides felis</i> )	Human, Dog, Horse, Marine animals
<i>Bartonella koehlerae</i>	Cat	Cat flea	Human, Dog
<i>Bartonella melophagi</i>	Sheep ( <i>Ovis aries</i> )	Sheep ked ( <i>Melophagus ovinus</i> )	Human
<i>Bartonella quintana</i>	Human	Body louse ( <i>Pediculus humanis</i> )	Cat, Dog
<i>Bartonella rochalimae</i>	Canids	Fleas? ( <i>Pulex irritans</i> , <i>Pulex simulans</i> )	Human, dog
<i>Bartonella tamiae</i>	Unknown (Rat?)	Mites? Ticks?	Humans
<i>Bartonella vinsonii arupensis</i>	White-footed mouse ( <i>Peromyscus leucopus</i> )	Unknown (Fleas? ticks?)	Human
<i>Bartonella vinsonii berkhoffii</i>	Coyote ( <i>Canis latrans</i> ) Dog ( <i>Canis familiaris</i> )	Unknown (Ticks?)	Human, cat
<i>Bartonella washoensis</i>	Californian ground squirrel ( <i>Spermophilus beecheyii</i> )	Fleas ( <i>Oropsylla montana</i> )	Human, Dog

and the Philippines) (Boulouis *et al.* 2005). A few studies in western Europe and Australia have reported that most human cases of CSD were caused by *B. henselae* type Houston-1, despite the fact that type Marseille was found to be the dominant type in the cat population, suggesting that type Houston-1 strains could be more virulent to humans (Boulouis *et al.* 2005). Clustering of human cases was recently confirmed by multiple locus variable number tandem repeat analysis (Bouchouicha *et al.* 2009). Cats are usually bacteraemic for weeks to months, but some cats have been reported to be bacteraemic for more than a year (Abbott *et al.* 1997). Young cats ( $\leq 1$  year) are more likely than older cats to be bacteraemic (Chomel *et al.* 1995), and stray cats are more likely to be bacteraemic than pet cats (Chomel *et al.* 2004).

The clinical description of CSD was first reported in France by Debré *et al.* 1950; but the identification of the aetiological agent occurred only in 1993 (Dolan *et al.* 1993). The annual number of human cases in the USA has been estimated to be between 22 000 and 24 000, with about 2000 cases requiring hospitalization and thousands of cases may occur yearly in Europe (Boulouis *et al.*

2005). In various studies, the seroprevalence of antibodies to *B. henselae* in healthy people has ranged from 3.6 to 6% and could be higher in some specific population groups, such as veterinarians, children or elite orienteers (Boulouis *et al.* 2005; Chomel *et al.* 2006). *Bartonella henselae* seroprevalence data for cat and healthy human populations suggest that seroprevalence is low in both cats and humans at northern latitudes and increases in warmer climates (Chomel *et al.* 2006). Despite the fact that *B. henselae* infection can cause meningitis and encephalitis, there have been a very limited number of case reports of fatal infection in immunocompetent people (Boulouis *et al.* 2005). CSD is more frequently observed in persons who are less than 20-years-old and in people who own a young cat ( $< 1$  year old, especially if this cat is infested with fleas) or in people who have been scratched or bitten by a cat (Chomel *et al.* 2006).

In immunocompetent people, CSD is mainly characterized by a benign regional lymphadenopathy (Boulouis *et al.* 2005). Usually after a cat scratch, a papule and then a pustule develops within 7–12 days at the inoculation site followed one to 3 weeks after the inoculation by a

regional lymphadenopathy (usually involving a single lymph node) that can persist a few weeks to several months (Chomel *et al.* 2004). Low-grade fever, malaise and aching are often reported. In some instances, headache, anorexia and splenomegaly can occur. Abscessed lymph nodes are reported occasionally. From 5 to 9% of CSD cases may develop atypical manifestations, including Parinaud's oculo-glandular syndrome, encephalitis, endocarditis, haemolytic anaemia, hepatosplenomegaly, glomerulonephritis, pneumonia, relapsing bacteraemia and osteomyelitis (Boulouis *et al.* 2005). Based on serology or PCR testing, several recent publications have associated *B. henselae* with uveitis, focal retinal phlebitis, neuroretinitis, retinal and optical nerve neovascularization, retinal artery and vein occlusions (Boulouis *et al.* 2005). Neurological forms are rare, and patients usually completely recover within 1 year without any sequelae. Hepatosplenomegaly and osteolytic bone lesions have been described in people seropositive for *B. henselae*. Pseudotumoral lesions involving the mammary gland, the liver or the spleen, glomerulonephritis and cases of monoclonal and biclonal gammopathy have also been associated with the presence of *B. henselae* antibodies (Chomel *et al.* 2006). Cases of prolonged fever without adenopathy, chronic fatigue, haemolytic anaemia, thrombocytopenic purpura, Henoch-Schonlein purpura syndrome, pleuritis, pneumonia and even paronychia have been reported in patients who were seropositive for *B. henselae* (Chomel *et al.* 2006). Usually, these clinical manifestations disappear in a few weeks to a few months. Bacteraemia is rarely detected in immunocompetent persons (Zangwill *et al.* 1993). Several cases of endocarditis have been associated with *B. henselae* infection, most frequently in individuals with pre-existing valvular lesions (Fournier *et al.* 2001).

Bacillary angiomatosis or peliosis is usually observed in highly immunocompromised individuals (low CD4 count), often infected with the human immunodeficiency virus (HIV). Several severe infections have also been reported in organ transplant recipients (Boulouis *et al.* 2005).

The clinical spectrum of the infection in cats has not been fully investigated, but naturally infected cats mainly seem to be healthy carriers of the bacterium (Chomel *et al.* 2009a). However, cases of uveitis and rare cases of endocarditis have been associated by molecular tests with infection caused by *B. henselae* (Chomel *et al.* 2009b). Bartonella-seropositive cats were also more likely to have kidney disease and urinary tract infections, stomatitis and lymphadenopathy (Boulouis *et al.* 2005). An association between bacteraemia and presence of oral lesions (stomatitis) in sick pet cats was recently documented (J.E. Sykes *et al.* unpublished data). In experimentally infected cats,

fever, lymphadenopathy, mild neurological signs and reproductive disorders have been reported (Guptill *et al.* 1997, 1998).

### *Bartonella clarridgeiae*

*Bartonella clarridgeiae* was first isolated in the USA from the pet cat of a HIV-positive patient (Clarridge *et al.* 1995). This *Bartonella* species has been less frequently isolated from domestic cats than *B. henselae*, as it appears to be more difficult to isolate on conventional 5% blood agar plates and is unevenly distributed in cat populations worldwide (Chomel *et al.* 2004). A *B. clarridgeiae* prevalence of 17 to 36% among all *Bartonella* isolates was reported in studies conducted in France, the Netherlands, the Philippines and Thailand (Maruyama *et al.* 2001; Boulouis *et al.* 2005). However, *B. clarridgeiae* represented 10% or less of all isolates from domestic cats in some studies conducted in the south-eastern USA, Japan or Taiwan and was never isolated in other studies conducted in Europe, Australia and North America (Boulouis *et al.* 2005). No specific pathology has been associated with natural infection in cats. However, in experimentally co-infected cats (*B. henselae* type II and *B. clarridgeiae*), clinical signs were minimal, and gross necropsy results were unremarkable, but histopathology revealed peripheral lymph node hyperplasia, splenic follicular hyperplasia, lymphocytic cholangitis/pericholangitis, lymphocytic hepatitis, lymphoplasmacytic myocarditis and interstitial lymphocytic nephritis (Kordick *et al.* 1999). In humans, *B. clarridgeiae* has never been isolated or detected by molecular methods. However, *B. clarridgeiae* was suggested to be a minor causative agent of CSD, as the presence of *B. clarridgeiae* antibodies was reported in a suspect case of CSD and in a patient with a chest-wall abscess (Chomel *et al.* 2006). Furthermore, anti-flagella (FlaA)-specific antibodies against *B. clarridgeiae* were detected by immunoblotting in 3.9% of 724 patients with lymphadenopathy but not in 100 healthy controls (Sander *et al.* 2000). However, significant cross-reactivity between *B. henselae* and *B. clarridgeiae* detected by indirect fluorescence antibody assay was noted in human sera in a study from Japan (Boulouis *et al.* 2005). The recent identification of a human infection with *B. rochalimae*, a new *Bartonella* species closely related to *B. clarridgeiae* (Eremeva *et al.* 2007), could explain the seropositivity of human patients to *B. clarridgeiae*.

### *Bartonella koehlerae*

*Bartonella koehlerae* is a *Bartonella* species that has rarely been isolated from domestic cats worldwide, as it is a very fastidious bacterium to grow (Droz *et al.* 1999; Avidor

*et al.* 2004). Until recently, it had been isolated only from two cats in California (Droz *et al.* 1999) and one cat in France (Rolain *et al.* 2003a). However, the first human case of *B. koehlerae* endocarditis was reported from Israel in 2004 (Avidor *et al.* 2004). Furthermore, these authors were able to isolate *B. koehlerae* from a bacteraemic stray cat from that country. More recently, the first case of canine endocarditis caused by *B. koehlerae* was also reported from Israel in a 5·5-year-old boxer dog with severe subaortic stenosis aortic (Ohad *et al.* 2009). Experimental infection of cats was not associated with any clinical symptoms (Yamamoto *et al.* 2002).

#### *Bartonella quintana*, *Bartonella bovis* and *Bartonella vinsonii berkhoffii*

A few suspect cases of CSD and cases of bacillary angiomatosis or endocarditis have been associated with *B. quintana*, for which the only risk factor identified was a contact with cats or cat fleas (La *et al.* 2005). Furthermore, the identification of *B. quintana* DNA in cat fleas (Rolain *et al.* 2003b), in the dental pulp of a cat (La *et al.* 2005) and more recently its isolation from a patient and her cat (Breitschwerdt *et al.* 2007b) has raised the question as to whether cats might be a possible source of human infection. However, *B. quintana* has only ever been an exceptional isolate from naturally infected cats. Two cats inoculated with a human strain of *B. quintana* did not become bacteraemic, but seroconverted (Regnery *et al.* 1996). Subsequently, both cats became bacteraemic when challenged with *B. henselae*.

A few cases of *B. bovis* (formerly *Bartonella weissii*) infections were reported in cats from Illinois and Utah in the United States (Chomel *et al.* 2004). The epidemiological role of cats for this organism is still unknown. Recently, *B. vinsonii ssp. berkhoffii* was isolated from a cat with osteomyelitis in the carpal joint that developed 18 months after amputation of an osteomyelitis digit in the rear leg. Organism-specific DNA sequences were retrospectively amplified from a paraffin block containing the original osteomyelitis lesion (Varanat *et al.* 2009).

#### **Bartonella vectors**

The primary mode of transmission of *B. henselae* to humans is through a cutaneous trauma caused mainly by the scratch of a cat, less likely a cat bite, as shedding of *B. henselae* in cat saliva has not been clearly documented (Chomel *et al.* 2006). The possibility of direct transmission of *B. henselae* to humans by the cat flea has not been proven experimentally and is mainly hypothetical. However, the presence of cat fleas (*Ctenocephalides felis*) is essential for the maintenance of the infection within the

cat population (Chomel *et al.* 1996). It has been shown that *B. henselae* can multiply in the digestive system of the cat flea and survive several days in the flea faeces (reviewed in Chomel *et al.* 2009a). Experimentally, only cats inoculated with flea faeces compared to those on which fleas were deposited in retention boxes or which were fed fleas became bacteraemic (Foil *et al.* 1998). Therefore, the main source of infection appears to be the flea faeces that are inoculated by contaminated cat claws.

Beside the cat flea, new possible vectors have been suggested. *Bartonella* DNA, including *B. henselae*, has been detected in *Ixodes ricinus* ticks collected on humans (Sanojo *et al.* 2003) and in *Ixodes scapularis* ticks collected in households of persons co-infected with *B. henselae* and *Borrelia burgdorferi* (Eskow *et al.* 2001). *Bartonella quintana*, *B. henselae* and *B. vinsonii ssp. berkhoffii* DNA were also detected in questing *Ixodes pacificus* ticks in California, and a few human cases of *B. henselae* infection were temporally related to a tick exposure in the USA (reviewed in Chomel *et al.* 2009a). Tick exposure was reported as a risk factor associated with CSD in humans (Zangwill *et al.* 1993). Similarly, tick exposure was determined to be a risk factor associated with *B. v. berkhoffii* seropositivity in dogs (Billeter *et al.* 2008). The specific role of ticks in *Bartonella* transmission requires additional studies. However, several recent publications have reported a high prevalence of *Bartonella* spp. infection in ticks from various parts of the world (Chomel *et al.* 2009a). Experimental transmission of infective material from *I. ricinus* ticks to cats was recently demonstrated (Cotté *et al.* 2008). Finally, *B. henselae* type Marseille DNA was detected in a stable fly (Chung *et al.* 2004).

#### **Pathogenesis**

In the mammalian reservoir, bartonellae initially infect a yet unrecognized primary niche, which seeds organisms into the blood stream leading to the establishment of a long-lasting intra-erythrocytic bacteraemia as the hallmark of infection (Chomel *et al.* 2009a). Bacterial type IV secretion systems, which are supra-molecular transporters ancestrally related to bacterial conjugation systems, represent crucial pathogenicity factors that have contributed to a radial expansion of the *Bartonella* lineage in nature by facilitating adaptation to unique mammalian hosts (Schülein *et al.* 2001). On the molecular level, the type IV secretion system, VirB/VirD4, is known to translocate a cocktail of different effector proteins into host cells, which subvert multiple cellular functions to the benefit of the infecting pathogen (Dehio 2001). Furthermore, bacterial adhesins mediate a critical, early step in the pathogenesis of the bartonellae by binding to extracellular matrix components of host cells, which leads to firm



bacterial adhesion to the cell surface as a prerequisite for the efficient translocation of type IV secretion effector proteins (Zhang *et al.* 2004). The best-studied adhesins in bartonellae are the orthologous trimeric autotransporter adhesins, BadA in *B. henselae* and the Vomp family in *B. quintana* (Zhang *et al.* 2004). Genetic diversity and strain variability also appear to enhance the ability of bartonellae to invade not only specific reservoir hosts, but also accidental hosts, as shown for *B. henselae* (Dehio 2008). Bartonellae have been identified in many different blood-sucking arthropods in which they are typically found to cause extracellular infections of the mid-gut epithelium (Chomel *et al.* 2009a). Adaptation to specific vectors and reservoirs seems to be a common strategy of bartonellae for transmission and host diversity (Dehio 2008).

### Diagnosis

The diagnosis of *Bartonella* infection should be confirmed by culturing the organism from blood or tissues such as lymph node or heart valve (endocarditis) or by amplifying *Bartonella*-specific DNA sequences from tissues using PCR (Chomel *et al.* 2006). Cell lysis by freezing the blood sample prior to plating facilitates bacterial isolation from blood. Although organisms within the genus *Bartonella* are fastidious and slow growing, they can be cultured successfully with agar plates containing 5% defibrinated rabbit or sheep blood that are maintained at 35°C in a high-humidity chamber with a 5% CO<sub>2</sub> concentration. As cats maintain a higher level of bacteraemia, culturing *B. henselae* or *B. clarridgeiae* from aseptically obtained blood samples is much more likely to be successful than culturing *B. henselae* from a dog or human blood sample. However, the use of a novel chemically modified liquid medium has enhanced considerably the ability to detect and/or isolate *Bartonella* species from various animal species, including humans, dogs, horses and wildlife (Maggi *et al.* 2005, 2008, 2009; Breitschwerdt *et al.* 2007a, 2008; Diniz *et al.* 2009). PCR assays targeting several *Bartonella*-specific gene sequences have been described and should be used to detect *Bartonella* species infection in tissues or blood (Fenollar and Raoult 2004).

### Treatment and prevention in humans and cats

Because of disparate results among studies and an overall lack of microbiological data in clinical therapeutic trials, numerous issues related to treatment of *Bartonella* infection remain controversial (Breitschwerdt 2008). In contrast to the apparent lack of response to antimicrobial treatment in human patients with CSD, bacillary angiomatosis, parenchymal bacillary peliosis and acute

*Bartonella* bacteraemia appear to respond to antimicrobial treatment, even in immunocompromised (predominantly HIV-infected) individuals (Breitschwerdt 2008). Doxycycline, erythromycin and rifampin are recommended antibiotics, but clinical improvement has also been reported following the use of penicillin, gentamicin, ceftriaxone, ciprofloxacin and azithromycin (Breitschwerdt 2008). Treatment for 2 weeks in immunocompetent individuals and 6 weeks in immunocompromised people is generally recommended (Rolain *et al.* 2004). Relapses, associated with bacteraemia, have been reported in immunocompromised people despite treatment for 6 weeks (Rolain *et al.* 2004). Antimicrobial efficacy has not been established for any antibiotic for elimination of *B. henselae* bacteraemia in cats. Results from various laboratories indicate incomplete treatment responses in cats treated for 2 or 4 weeks with doxycycline or enrofloxacin (Breitschwerdt 2008).

Prevention of infection in cats relies on flea control. A recent study showed that monthly topical imidacloprid and moxidectin prevented flea transmission of *B. henselae* in six treated cats, whereas all six untreated cats became bacteraemic (Bradbury and Lappin 2009). In humans, avoiding being scratched or bitten by cats as well as a thorough disinfection of a scratch is a main preventative measure to be taken to reduce the risk of developing CSD.

### New developments: new zoonotic bartonellae

Several new zoonotic *Bartonella* species have been identified recently, including *Bartonella alsatica* initially isolated from wild rabbits in France and shown to cause endocarditis and lymphadenitis in humans (Raoult *et al.* 2006; Angelakis *et al.* 2008; Jeanclaude *et al.* 2009). *Bartonella tamiae* has been isolated from humans in Thailand, and its vector and reservoir are being investigated (Kosoy *et al.* 2008). It is suggested that mites could be one of the main vectors (M. Kosoy, personal communication). 'Candidatus *Bartonella melophagi*' initially isolated from sheep keds (*Melophagus ovinus*) and from sheep blood was recently detected in the blood of two sick women in the USA (Maggi *et al.* 2009). Finally, the presence of *B. rochalimae* (previously described as *B. clarridgeiae*-like) in dogs, grey and red foxes, raccoons and coyotes, as well as fleas collected on grey foxes, indicates that wild carnivores may be the natural reservoir of this zoonotic *Bartonella* species and with fleas being the main vector (Henn *et al.* 2007, 2009a,b; Gabriel *et al.* 2009). The spectrum of *Bartonella* species causing endocarditis in mammals is also widening with the first report of endocarditis caused by a *Bartonella* species in free-ranging sea otters from Alaska (Chomel *et al.* 2009b).

## Conclusion

The number of zoonotic *Bartonella* species identified in the last 20 years has increased considerably. Cats have been identified as an important reservoir of *Bartonella* species and play an important role as source for human infection. Enhanced isolation techniques have allowed to better detect human and canine infections and to document the presence of new *Bartonella* species in these infections. A better understanding of the modes of transmission and vectors involved in these zoonotic infections is a priority to implement appropriate parasite control measures.

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