

Bartonella spp. in cats

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Bartonella spp. are gram-negative, haemotropic bacteria infecting both a wide range of animals and humans. The currently known vectors of *Bartonella* spp. are fleas, ticks, lice, and sand flies. Domestic cats are the main reservoir for *B. henselae*, *B. clarridgeiae*, and *B. koehlerae*. *Bartonella* infections in cats vary from mild to deadly and, since they usually have no specific symptoms, they are often underestimated. This review provides information on *Bartonella* infections in cats, their biology, and pathogenicity.

Keywords: bartonella, cats, vector-borne zoonotic diseases, pathogenesis

INTRODUCTION

Most of the human diseases are zoonoses, which are usually vector-borne (VBDs) (Ehlers et al., 2020). These diseases, especially companion animal VBDs, have a major impact on the welfare of pets and humans due to the close association among them (Latrofa et al., 2020; Maggi, Krämer, 2019). Cats are considered less susceptible to vector-borne diseases than dogs, therefore there is less data and studies regarding feline vector-borne diseases (FeVBDs). Despite the growing distribution areas of feline vector-borne pathogens, especially *Bartonella* spp., they are underestimated and frequently unsuspected by clinicians (Latrofa et al., 2020; Morelli et al., 2019). Such factors as globalization, increased travel, climate change, and international trade of goods favour the spread of vectors and pathogens they transmit (Ehlers et al., 2020; Maggi, Krämer, 2019; Morelli et al., 2019). Effective control of vector-borne diseases, including bartonellosis, can only be

achieved by a thorough knowledge of the infectious agents, their vectors, and major hosts. As no obvious agreement has been reached among veterinary practitioners regarding many issues concerning *Bartonella* infections in cats (Brown et al., 2005), it is necessary to study and spread information about these pathogens in cats. This review provides an overview of cat-infecting *Bartonella* species, their biology, pathogenicity, treatment, and prevention.

Bartonella vectors and hosts

Bartonella spp. are relatively diverse and have a global distribution. They infect a wide range of wild and domestic animals, including bats, birds, canids, cattle, deer, felids, horses, marine mammals, rodents, sheep, and reptiles. *Bartonella* spp. is also found in humans (Corduneanu et al., 2018; Diaz et al., 2012) (Table). These bacteria are adapted and co-evolved with specific reservoir hosts and, possibly, arthropod vectors. Although this ability is one of the ways to ensure successful transmission, accidental hosts are also possible (Álvarez-Fernández et al., 2018; Kosoy,

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Table. Domestic cat-infecting *Bartonella* species, their known and suspected vectors, other hosts, and diseases they cause to humans

<i>Bartonella</i> species	Vectors	Other hosts	Diseases in humans	References
<i>Bartonella henselae</i>	Cat and dog fleas, biting flies, ticks (<i>Ixodes</i> spp., <i>Rhipicephalus</i> spp., <i>Dermacentor</i> spp.), lice	Humans, guinea pigs, rabbits, dogs, birds, squirrels	CSD, Parinaud's oculoglandular syndrome, endocarditis, bacillary peliosis, bacillary angiomatosis, neuroretinitis	Billeter et al., 2008; Chang et al., 2001; Chung et al., 2004; Guptill, 2003; Mascarelli et al., 2014; Mazur-Melewska et al., 2015; Sanogo et al., 2003; Tsai et al., 2011; Wikswo et al., 2007
<i>Bartonella clarridgeiae</i>	Cat and dog fleas, cattle tick	Humans, dogs, cattle, voles, cotton rats	CSD, aortic root abscess, endocarditis	Guptill, 2003; Logan et al., 2019; Mosbacher et al., 2011; Tsai et al., 2011
<i>Bartonella koehlerae</i>	Cat flea	Humans, dogs, birds	CSD, endocarditis, neuropathy	Breitschwerdt et al., 2010; Cheslock, Embers, 2019; Chomel et al., 2006; Mascarelli et al., 2014
<i>Bartonella bovis</i>	Cattle tick, flies	Cattle	–	Guptill, 2010; Kho et al., 2015
<i>Bartonella quintana</i>	Cat and squirrel fleas, head and body lice, ticks (<i>Ixodes</i> spp., <i>Dermacentor</i> spp.)	Humans, squirrels, monkeys	Bacillary angiomatosis, trench fever, endocarditis, lymphadenopathy	Billeter et al., 2008; Chang et al., 2001; Mosbacher et al., 2011; Raoult, Roux, 1999; Sasaki et al., 2006; Tsai et al., 2011

Goodrich, 2019; Tay et al., 2018). Domestic cats (*Felis catus*) are the main reservoir for *B. henselae*, *B. clarridgeiae*, and *B. koehlerae*, the causal agents of human cat scratch disease (CSD). Other cat infecting *Bartonella* species include *B. bovis* and *B. quintana*, (Lappin, 2018). *Bartonella* spp. are mainly transmitted by fleas. The main *Bartonella henselae* vector is the cat flea *Ctenocephalides felis*. *Ctenocephalides felis* is also suspected to transmit *Bartonella quintana* (Iannino, 2018). However, other arthropods, such as sand flies, ticks, or lice have also been shown to transmit these pathogens (Diaz et al., 2012). Several species of ticks of the genera *Ixodes* and *Dermacentor* have been shown to harbour *Bartonella* DNA (Billeter et al., 2008; Chomel, Kasten, 2010). As the main vectors are fleas, *Bartonella* infections are seasonal and depend on the location just as the flea infesta-

tion rates. Prevalence of the diseases caused by *Bartonella* is higher in warm geographical areas with high humidity (Abdullah et al., 2019; Hobson et al., 2017). Alternative transmission types may involve cat scratches and bites (particularly important in developing CSD) or blood transfusion and transmission through needle stick injury (Almeida et al., 2019). After a cat scratch, the wound becomes infected with cat flea faeces containing *Bartonella* spp. bacteria. *Bartonella henselae* can remain viable in flea faeces for over 72 hours (Klotz et al., 2011; Kosoy, Goodrich, 2019).

Pathogenesis of *Bartonella* infection

Bartonella spp. are small, gram-negative, haemotropic bacteria, members of the class Alphaproteobacteria. These bacteria are slow-growing

intracellular and facultative (Donovan et al., 2018; Hobson et al., 2017). There are numerous factors that determine the level of infection by *Bartonella* spp. Some of them include the cat's immune status, living conditions, *Bartonella* strain virulence, and the infection phase (Álvarez-Fernández et al., 2018; Mazurek et al., 2020). Successful *Bartonella* spp. persistence in the environment is mainly a result of arthropods having access to reservoir animals that are bacteraemic for a long enough time to become infected (Kosoy, Goodrich, 2019). The long-term bacteraemia in cats can last for months or even years. It is achieved by a relapsing infection without any particular symptoms, damaging the organs in a harmful way instead (Chomel et al., 2009; Donovan et al., 2018; Ianino et al., 2018).

The main stages of infection with *Bartonella* bacteria include transmission by the vector and infection of the reservoir host (Harms, Dehio, 2012). When a blood-sucking arthropod vector feeds on an infected cat, *Bartonella* bacteria enter the vector gut and form biofilms for protection from the toxic environment (Okaro et al., 2017). They reproduce in the gut and are later released to the salivary glands. From the glands, *Bartonella* spp. can infect new cats or humans during blood-sucking vector feeding (Liu, Bonnet, 2014). After infecting cats, *Bartonella* bacteria must cope with an opposite environment as there is a deprivation of heme and iron in the mammalian host (Okaro et al., 2017). Hemin is required for *Bartonella* spp. growth, especially for *B. quintana* and *B. henselae*, as it is an important source of iron and porphyrin (Alsmark et al., 2004; Chomel et al., 2009). Hemin-binding proteins (Hbps) and hemin-uptake genes are necessary not only to acquire hemin but also to combat toxic concentrations of heme in the cat flea vector (Tu et al., 2017).

Bartonella bacteria usually infect erythrocytes or endothelial cells by conventional phagocytosis or invasome-mediated mechanism using type IV or type V secretion systems (Almeida et al., 2019; Alsmark et al., 2004; Tamarit et al., 2018). Non-haemolytic persistence in blood cells enables the transmission of the bac-

teria by the blood-sucking arthropods (Kosoy, Goodrich, 2019). If the bacteria are cleared from the bloodstream, they can grow in endothelial cells, seed into the blood, and invade erythrocytes again (Chomel et al., 2009; Okaro et al., 2017). To infect endothelial cells, *Bartonella* spp. use phage-like gene transfer agents. α -proteobacteria usually have RcGTA that are broadly distributed between species. However, *Bartonella* spp. have specific and highly conserved gene transfer agents (BaGTA) (Tamarit et al., 2018; Tay et al., 2018; Québatte, Dehio, 2019). In cats, a chronic invasion of erythrocytes is more likely to happen than an invasion of endothelial cells (Álvarez-Fernández et al., 2018).

Phagocytes are the first line of immune defence against *Bartonella* infection. However, antibodies are usually evaded as they cannot reach the intracellular bacteria and rarely target infected erythrocytes, which have a similar lifespan to the uninfected ones (Chomel et al., 2009). Another line of defence is pattern-recognition receptors – TLRs. *Bartonella* spp. pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharides, flagella and adhesins, have an unusual structure and their expression can be suppressed. This is the reason they are weakly recognized by TLRs and do not induce production of pro-inflammatory cytokines (Okaro et al., 2017). Infection with one *Bartonella* species has not been shown to provide immunity to another species. Co-infection in cats with two *Bartonella* species or genotypes, as well as co-infection with other pathogens, is also possible (Boulouis et al., 2005).

***Bartonella* species infecting cats**

Bartonella henselae

Bartonella henselae is grouped into Genotype I and Genotype II based on *16S-rDNA* sequences (Duscher et al., 2018). These strains have different point mutations, protein profiles, host specificity, prevalence, and pathogenicity (Castel et al., 2019; Chomel et al., 2009; Diaz et al., 2012; Iredell et al., 2003; Mietze et al., 2011). Genotype I (Houston) is more often found in humans and is prevalent in Asia. Genotype II (Marseille) is mostly found

in cats and is prevalent in Europe, Australia, and the United States (Bouchouicha et al., 2009; Mazurek et al., 2020). It is also considered to be less pathogenic as Genotype I is more likely to cause human CSD (Maggi et al., 2013). In the US, 30–60% of domestic cats are infected with *B. henselae* (Alsmark et al., 2004). In Europe, prevalence of *Bartonella henselae* in cats ranges from 0% to 71.4% (Álvarez-Fernández et al., 2018).

Bartonella clarridgeiae

Bartonella clarridgeiae is second most commonly detected *Bartonella* species responsible for CSD (Kordick et al., 1997). It is also one of the few *Bartonella* species possessing flagella (Minnick, Anderson, 2015). An extremely high number of these bacteria is found in the domestic cat population. Infection is also possible between other members of the Felidae family, e.g., puma. Bacterium is also found in members of the canine family (Boulouis et al., 2005). It was first isolated in 1995 by the researcher Jill Clarridge and colleagues from cat blood, which was linked to human infection with CSD caused by *B. henselae*. Both species of this bacterial genus are widespread, with recorded cases in domestic cats in North America, Europe, Asia, and Australia (Clarridge et al., 1995). Studies in cats with bacteraemia in Western Europe – France and the Netherlands have shown 30 to 36% infection with *B. larridgeiae* (Gurfield, 2001).

Bartonella koehlerae* and *Bartonella bovis

As mentioned above, *Bartonella koehlerae* and *Bartonella bovis* have been detected in cats several times. Cats are considered to be the main reservoir of *B. koehlerae*, which has been reported to cause human endocarditis (Avidor et al., 2004). Domestic cats are also principal reservoir hosts for *B. koehlerae*. Infected cats are thought to rarely develop clinical signs. Although chronic relapsing bacteraemia can frequently be detected in infected cats, potential long-term consequences of relapsing bacteraemia are unknown (Álvarez-Fernández et al., 2018). As for *B. bovis*, it is mainly associated with cattle (Breitschwerdt et al., 2010; Cher-

ry et al., 2009). The effect of *Bartonella* infections in cattle, if any, is unknown. Because *B. bovis* is very common in some herds, it is difficult to attribute clinical signs to this organism. In one study, *B. bovis* was suggested as the cause of endocarditis in two older cows. The role of domestic cats in the epidemiology of *B. bovis* (formerly *B. weissii*) has not been clearly established, as only a limited number of isolates have been obtained from cats in Illinois and Utah (Regnery et al., 2000). There is a relatively low amount of studies on the manifestations of these *Bartonella* species in cats and humans.

Bartonella quintana

Bartonella quintana is the causative agent of trench fever in humans (Stützer, Hartmann, 2012). This disease is not necessarily fatal. However, it results in a fever that lasts a few days (Sander et al., 1997). Cats are only an accidental host of this *Bartonella* species, as the main reservoir hosts are humans (Iannino et al., 2018). *B. quintana* is often associated with homelessness, alcoholism, and poverty (Chang et al., 2001; Billeter et al., 2008).

Clinical manifestations of cat-associated *Bartonella* infection and treatment

The severity of the diseases caused by *Bartonella* spp. may range from asymptomatic to fatal depending on the host's immune status (Amer, Tugal-Tutkun, 2017). In cats, *Bartonella* spp. infection usually causes no particular symptoms. Clinical symptoms are more likely to develop in young kittens (Abreu-Yanes et al., 2020). In more severe cases, the infection can result in lymphadenopathy, endocarditis, myocarditis, hyperglobulinemia, chronic relapsing bacteraemia, or even severe haemolytic anaemia. The bacteraemia is more frequently observed in stray cats. (Abdullah et al., 2019; Álvarez-Fernández et al., 2018; Chomel et al., 2009). Most of the clinical symptoms are caused by *B. quintana* and *B. henselae* (Almeida et al., 2019). Treatment of sick cats usually consists of administering one or few antibiotics for

a certain amount of time. Most often recommended antibiotics include doxycycline, fluoroquinolones, enrofloxacin, oribifloxacin, or pradofloxacin. Enrofloxacin is known to be useful for fever treatment (Lappin, 2018; Lappin et al., 2020). Fluoroquinolones are usually used in combination with other antibiotics (Biswas, Rolain, 2010). It is not recommended to use rifampicin or azithromycin for cat treatment (Álvarez-Fernández et al., 2018; Lappin, 2018).

Cat-scratch disease usually develops in immunocompetent humans and more commonly affects children and teenagers (Amer, Tugal-Tutkun, 2017). The symptoms include erythematous papule at the site of inoculation, swelling of lymph nodes, fever, aching, malaise, or anorexia (Canneti et al., 2019; Hobson et al., 2017; Klotz et al., 2011). Other less common symptoms may include myalgia, arthralgia, and hepatosplenomegaly (Johnson, 2020). Ocular bartonellosis, such as Parinaud oculoglandular syndrome and neuroretinitis, can also occur (Amer, Tugal-Tutkun, 2017; Klotz et al., 2011). Other diseases that *B. henselae*, *B. clarridgeiae*, and *B. koehlerae* may cause involve bacillary peliosis and angiomas, endocarditis, pneumonia, osteomyelitis, encephalitis, meningitis, and neuropathy (Cheslock, Embers, 2019; Deng et al., 2018; Johnson, 2020; Klotz et al., 2011; Ksiaz et al., 2019). Since CSD is considered to be a self-limiting disease, the use of antibiotics is not recommended in patients with mild symptoms. Patients that develop complications such as endocarditis or hepatic peliosis are usually treated with gentamicin, doxycycline, rifampicin, or erythromycin as the bacteria are susceptible to beta-lactams, aminoglycosides, macrolides, and tetracyclines (Almeida et al., 2019; Hobson et al., 2017).

Diagnosics and prevention

Diagnostic methods for *Bartonella* spp. in cats include PCR, culture, and serology methods (Lappin et al., 2020). Formerly, *Bartonella* spp. isolation from blood was considered to be

the golden standard (Breitschwerdt et al., 2010). However, culturing these bacteria is a challenge. Bacteria growth takes a long time, and they require a specific media and an environment rich in CO₂ (Agan, Dolan, 2002). Currently, PCR is more often used than culture methods. PCR methods target genes, such as *gltA*, *groEL*, *pap31*, *ftsZ*, *16rRNA*, and 16S-23S ITS region (Billeter et al., 2008; Urdapilleta et al., 2020). Serological methods include ELISA, immunofluorescent antibody assays. However, cross-reactions can occur and these methods are questionable in diagnosing active infections (Bergmans et al., 1997; Maurin et al., 1997).

The most important preventive measure of *Bartonella* spp. infections in cats is ectoparasitic treatment and control (Pennisi et al., 2013). Animal lifestyle, grooming, and behavioural prophylaxis also have a huge impact on the occurrence of *Bartonella* spp. infections (Amer, Tugal-Tutkun, 2017; Duscher et al., 2018; Ksiaz et al., 2019; Maggi, Krämer, 2019). To minimize the risk of these infections, adopting healthy seronegative adult cats rather than kittens should also be considered (Boulouis et al., 2005).

CONCLUSIONS

Vector-borne diseases, especially feline vector-borne diseases, are emerging due to climate change and other ecological factors. *Bartonella* spp., one of the most abundant and diverse zoonotic vector-borne pathogens, is often underestimated because of the non-specific symptoms. Domestic cats are the natural reservoir of *Bartonella henselae* and *Bartonella clarridgeiae*. To prevent the spread of such pathogens, it is important to establish ectoparasitic treatment, animal grooming, behavioural prophylaxis, and to study factors involved in keeping the bacteria persistent in the environment.

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KATĖS APTINKAMŲ BARTONELLA SPP. PATOGENŲ APŽVALGA

Santrauka

Bartonella spp. yra gramneigiamos hemotropinės bakterijos, infekuojančios daugelį gyvūnų ir žmones. Šiuo metu žinomi *Bartonella* spp. pernešėjai yra blusos, erkės, utėlės ir smėlio musės. Naminės katės yra pagrindiniai *B. henselae*, *B. clarridgeiae* ir *B. koehlerae* rezervuariniai šeimininkai. *Bartonella* kačių infekcijos gali pasireikšti įvairiomis formomis – nuo lengvos iki sunkios, gyvybei pavojingos ligos, tačiau dažniausiai specifinių simptomų nesukelia. Tai lemia, jog šie patogenai yra dažnai nuvertinami ar neįtariami. Šioje apžvalgoje pateikiama informacija apie *Bartonella* bakterijų biologiją, patogeniškumą bei jų sukiamas kačių infekcijas.

Raktažodžiai: *Bartonella*, katės, pernešėjų platinamos zoonozės, patogenezė