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CLINICAL REVIEW

BARTONELLA SPECIES INFECTION IN CATS
ABCD guidelines on prevention and management

Maria Grazia Pennisi, Fulvio Marsilio, Katrin Hartmann, Albert Lloret, Diane Addie, Sándor Belák, Corine Boucraut-Baralon, Herman Egberink, Tadeusz Frymus, Tim Gruffydd-Jones, Margaret J Hosie, Hans Lutz, Karin Möstl, Alan D Radford, Etienne Thiry, Uwe Truyen and Marian C Horzinek

Overview: Over 22 *Bartonella* species have been described in mammals, and *Bartonella henselae* is most common worldwide. Cats are the main reservoir for this bacterium. *B henselae* is the causative agent of cat scratch disease in man, a self-limiting regional lymphadenopathy, but also of other potentially fatal disorders in immunocompromised people.
Infection: *B henselae* is naturally transmitted among cats by the flea *Ctenocephalides felis felis*, or by flea faeces. A cat scratch is the common mode of transmission of the organism to other animals, including humans. Blood transfusion also represents a risk.
Disease signs: Most cats naturally infected by *B henselae* do not show clinical signs but cardiac (endocarditis, myocarditis) or ocular (uveitis) signs may be found in sporadic cases. *B vinsonii* subspecies *berkhoffii* infection has reportedly caused lameness in a cat affected by recurrent osteomyelitis and polyarthritis.
Diagnosis: Isolation of the bacterium is the gold standard, but because of the high prevalence of infection in healthy cats in endemic areas, a positive culture (or polymerase chain reaction) is not confirmatory. Other compatible diagnoses must be ruled out and response to therapy gives a definitive diagnosis. Serology (IFAT or ELISA) is more useful for exclusion of the infection because of the low positive predictive value (39–46%) compared with the good negative predictive value (87–97%). Laboratory testing is required for blood donors.
Disease management: Treatment is recommended in the rare cases where *Bartonella* actually causes disease.

Bacterial properties

Bartonella (previously named *Rochalimaea*) species are small, vector-transmitted Gram-negative intracellular bacteria that are well adapted to one or more mammalian reservoir hosts.

To date, over 22 *Bartonella* species have been described, but their role as pathogens of humans and domestic animals is the subject of ongoing investigations (Table 1).[1] The most common species in both cats and humans is *B henselae*, the agent of cat scratch disease as well as of other potentially fatal disorders in immunocompromised people.

B henselae is naturally transmitted among cats by the flea *Ctenocephalides felis felis*, or by flea faeces. In the infected cat, *Bartonella* inhabits red blood cells, which are ingested by the flea, and the bacterium survives in the flea's gut. Contaminated flea faeces deposited on the skin of the cat end up under the cat's claws due to self-scratching. A cat scratch is the common mode of transmission of the organism to other animals, including humans.[2]

European Advisory Board on Cat Diseases
The European Advisory Board on Cat Diseases (ABCD) is a body of experts in immunology, vaccinology and clinical feline medicine that issues guidelines on prevention and management of feline infectious diseases in Europe, for the benefit of the health and welfare of cats. The guidelines are based on current scientific knowledge of the diseases and available vaccines concerned.

The latest version of the *Bartonella* species infection in cats guidelines is available at www.abcd-vets.org

B henselae has been experimentally transmitted among cats by transferring fleas fed on naturally infected cats to specific pathogen-free (SPF) cats, and by intradermal inoculation of excrement collected from fleas fed on *B henselae*-infected cats.[2] This has demonstrated that both the vector and the cat – through scratches – may transmit the organism. Infection is amplified in the flea hindgut, and *B henselae* can persist in the environment in flea faeces for at least 9 days.[3] Blood transfusion also represents a risk: cats have been experimentally infected with *B henselae* and *B clarridgeiae* by intravenous or intramuscular inoculation with infected cat blood.[4]

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Table 1 Species and subspecies of *Bartonella* that are confirmed or potential human pathogens[1]

Bartonella species	Primary reservoir	Vector	Accidental host
B bacilliformis	Human	*Lutzomyia verrucarum*	None
*B quintana**	Human	*Pediculus humanus*	Cat, dog, monkey
B elizabethae	*Rattus norvegicus*	*Xenopsylla cheopis*	Human, dog
B grahamii	Several species of wild mice	Rodent fleas	Human
*B henselae**	Cat	*Ctenocephalides felis felis (C felis)* Other vectors?	Human, dog
*B clarridgeiae**	Cat	*C felis*	Human, dog
*B koehlerae**	*Cat*	*C felis*	Human
B vinsonii subspecies *berkhoffii**	Coyote, dog	Ticks?	Human, cat
B vinsonii subspecies *arupensis*	*Peromyscus leucopus*	Ticks? Fleas?	Human
B washoensis	*Spermophilus beecheyii*	Fleas?	Human, dog
B asiatica	Rabbit	Fleas?	Human

*Zoonotic species

B henselae can persist in the environment in flea faeces for at least 9 days.

B henselae transmission did not occur when infected cats lived together with uninfected cats in a flea-free environment. Transmission consequently does not occur through bites, scratches (in the absence of fleas), grooming, or sharing of litter boxes and food dishes. Furthermore, transmission could not be demonstrated between bacteraemic female cats and uninfected males during mating, or to the kittens of infected females either during gestation or in the neonatal period, again in flea-free environments.[5]

Ticks may also act as vectors for transmission among cats, human beings, dogs and other mammalian hosts: trans-stadial transmission of *B henselae* was demonstrated in *Ixodes ricinus*.[6]

Epidemiological evidence and experimental studies have demonstrated the important role of fleas in the transmission of *B henselae* and *B clarridgeiae* among cats. Three other species, *B koehlerae*, *B bovis* and *B quintana*, have been isolated from cat blood, but the modes of transmission and the reservoir potential of these species in felids have not been established. In addition, *B vinsonii* subspecies *berkhoffii* DNA was detected in the blood of a cat.[7]

Epidemiology

Bartonella species have a worldwide distribution, with highest prevalences in areas where conditions are most favourable for arthropod vectors, mainly fleas. In Europe, many studies have been carried out and the antibody prevalence in cats has ranged from 8–53% (Table 2).

Pathogenesis

Chronic bacteraemia mainly occurs in young cats, under the age of 2 years.[20] Young experimentally infected cats maintained relapsing *B henselae* or *B clarridgeiae* bacteraemia for as long as 454 days.[21] Immune system avoidance via intracellular location, frequent genetic rearrangements and alteration of outer membrane proteins are considered important factors for the maintenance of persistent bacteraemia. The location within erythrocytes and vascular endothelial cells is believed to protect *Bartonella* also from antimicrobial agents.

As the host-adapted reservoir of *B henselae*, cats display minimal pathogenic effects after experimental infection. Gross necropsy findings were unremarkable in experimentally infected cats but some histopathological changes emerged: follicular hyperplasia of lymph nodes and spleen, lymphocyte and plasma cell infiltrates in liver, heart, kidney and eye, and pyogranulomatous inflammation in liver, spleen, kidney, heart and lymph nodes.[5,21]

Immunity

The antibody response to *B henselae* has been investigated for the identification of vaccine candidates. The kinetics in response to *B henselae* antigens in chronically infected experimen-

Table 2 Antibody prevalence of *Bartonella* infection in the feline population in European countries

Country	Number of cats	Prevalence (%)	Reference
Netherlands	163 (stray)	52	Bergmans et al (1997)[8]
Austria	96	33	Allerberger et al (1995)[9]
Switzerland	728	8	Glaus et al (1997)[10]
Germany	713 245	15 37.1	Haimerl et al (1999)[11] Morgenthal et al (2012)[12]
France	64 94 179	36 53 41	Chomel et al (1995)[13] Heller et al (1997)[14] Gurfield et al (2001)[15]
Spain	680	23.8	Ayllon et al (2012)[16]
Italy	540 1300 (stray)	38 23.1	Fabbi et al (2004)[17] Brunetti et al (2013)[18]
Scotland	78	15.3	Bennett et al (2011)[19]

tal cats is highly variable in degree and duration.[2,21,22] Reinfection by a different strain of *B henselae* is possible, as supported by the isolation of unrelated bacterial clones from the same cat at different times.[23] Antibodies are, therefore, considered not protective, and *Bartonella* species antibody positive cats may be infected.[17] A cell-mediated response was not evident in investigated experimentally infected cats.[21]

Clinical signs

Cats naturally infected with *Bartonella* species usually do not show clinical signs. Both experimental and natural infection studies have tried to establish an association between clinical signs and infection, but a link has not been unequivocally proven.

Experimental infection

Exposure to infected fleas does not result in clinical signs [EBM grade II].[2,24] In some cases of experimental inoculation, a self-limiting febrile disease, transient mild anaemia, localised or generalised lymphadenopathy, mild neurological signs and reproductive failure have been reported [EBM grade III].[21]

Natural infection

The role of *Bartonella* as a cause of clinical signs is even more unclear after natural infection despite a plethora of studies. Studies based on antibody detection are of limited value because antibody only proves exposure, and not necessarily an active infection. Moreover, there is cross-reactivity between different *Bartonella* species and strains that may or may not cause clinical signs. Because of the high percentage of infected healthy cats in endemic areas an association between clinical signs and *B henselae* infection is not easy to demonstrate.

It has been suggested that *Bartonella* infection could play a role in chronic gingivostomatitis, but the prevalence of antibodies or organisms was not higher in diseased cats than in control populations [EBM grade II].[10,25–30]

Cats positive for both feline immunodeficiency virus (FIV) and *Bartonella* antibodies had in one study an increased risk of lymphadenopathy [EBM grade III].[25]

An association between *Bartonella* antibodies and urinary tract disease or haematuria was found in two studies [EBM grade III].[10,31]

Pearce et al did not find any difference in antibody prevalence between healthy cats and cats with seizures or other neurological conditions.[32] A non-controlled retrospective study reported *Bartonella* DNA and antibodies in cerebrospinal fluid from cats with CNS disease [EBM grade III].[33]

No difference in *Bartonella* antibody prevalence was found between healthy cats and those affected by uveitis, but in some cases evidence of *Bartonella* species exposure was reported in cats with uveitis responsive to drugs considered effective against *Bartonella* [EBM grade IV].[34–36]

No difference in *Bartonella* antibody prevalence was found in cats affected by anaemia, but in cats positive for *Bartonella* antibodies a significant association with hyperglobulinaemia was seen [EBM grade I].[37,38] Lappin et al demonstrated no association between fever and positivity to *Bartonella* antibodies or DNA.[39]

A study based on serology and culture did not find an association between *Bartonella* infection and chronic rhinosinusitis.[40] Also no link was reported between *Bartonella* infection and pancreatitis, based on the finding that cats with normal feline pancreatic lipase immunoreactivity values and cats with elevated values did not show any difference in *Bartonella* antibody prevalence.[41]

A few case reports concern *B henselae*-associated endocarditis or myocarditis. Fatal aortic and mitral valve *B henselae*-associated endocarditis was reported in two cats in the USA.[42,43] Moreover, *B henselae* anterior mitral valve leaflet vegetative endocarditis was successfully treated in a cat presenting with a grade III/IV systolic heart murmur and signs of aortic embolisation (lethargy and weakness in the hind limbs, weak femoral pulses, pelvic pain, increased serum creatine kinase activity).[44] This case report confirms that *Bartonella* species may be a cause of blood culture-negative endocarditis, as suspected.[45] *Bartonella*-associated myocarditis was suspected in a cat presenting with supraventricular tachycardia responsive to antibiotic therapy.[46]

Because of the high percentage of infected healthy cats in endemic areas, an association between clinical signs and *B henselae* infection is not easy to demonstrate.

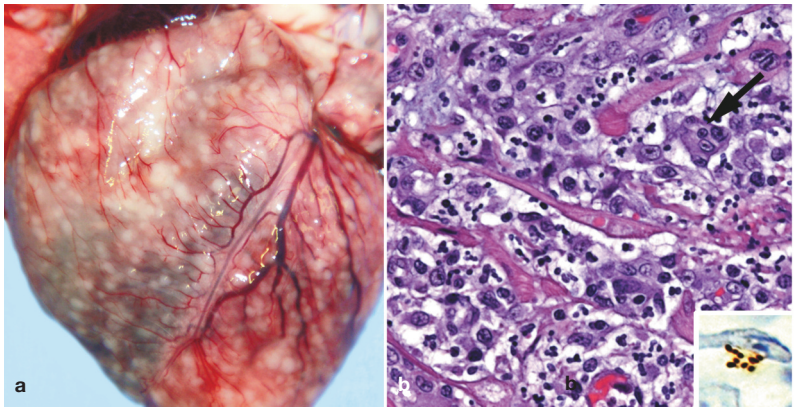

Figure 1 **Gross and histological findings in two cats from a North Carolina shelter that died after a litter of flea-infested kittens was introduced to the shelter. (a) Coalescing granulomas distributed throughout the myocardium of an approximately 9-week-old female kitten. (b) Pyogranulomatous myocarditis in an 8-month-old castrated male cat, which had been co-housed with the flea-infested kittens. Macrophages, with a rare multinucleated giant cell (arrow), are particularly numerous towards the upper left of the image; haematoxylin and eosin stain. Inset: Cluster of short bacilli in an inflammatory focus are immunoreactive (brown) for *B henselae*-specific monoclonal antibody; immunohistochemistry with diaminobenzidine chromogen and haematoxylin counterstain.** *Reproduced, with permission, from Varanat et al (2012)*[47]

Disease in humans

B henselae is the causative agent of cat scratch disease (Figure 2). This is a usually self-limiting regional lymphadenopathy that develops after a primary papular lesion and lasts for a few weeks to several months.[48] Abscessation of the lymph node and systemic signs are occasionally reported. Atypical forms and an expanding spectrum of clinical conditions are being associated with *B henselae* infection, such as neuroretinitis, uveitis, endocarditis and neurological disorders.[48–52] An unusual case of cat scratch disease has been reported in a veterinarian affected by persistent fever and back pain after an accidental needle puncture.[53] The occupational risk of exposure to arthropod vectors, as well as the reservoir host, should be also considered by veterinarians for this vector-borne disease.[54] Immunocompetent individuals may even experience subclinical *Bartonella* infection; conversely, immunocompromised persons suffer from clinical forms of a disseminated infection that may be fatal if untreated.[55,56]

Zoonosis

B henselae is the causative agent of cat scratch disease.

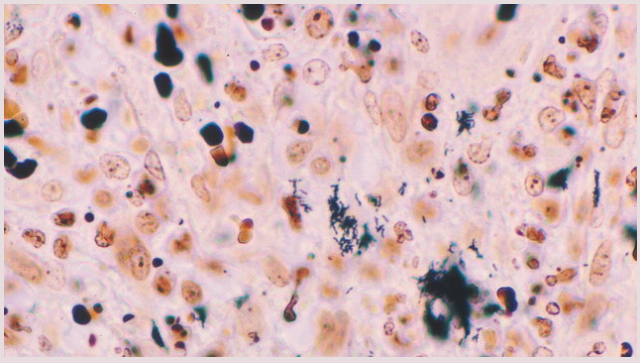

Figure 2 Immunohistochemical identification of *B henselae* in a case of cat scratch disease. With Warthin-Starry silver stain, these coccobacillary pathogens can be seen singly, in small clumps or in chains in necrotic foci. *Courtesy of Dharam Ramnani, Webpathology.com*

Post mortem evidence of pyogranulomatous myocarditis and diaphragmatic myositis associated with *B henselae* infection was also obtained in two cats (Figure 1).[47]

Lameness and pain during limb palpation were observed in a cat affected by recurrent osteomyelitis and polyarthritis associated with *B vinsonii* subspecies *berkhoffii* infection and bacteraemia.[7]

In conclusion, most cats naturally infected by *B henselae* do not show clinical signs. The identification of *Bartonella* infection in cats with disease should prompt a critical assessment of the role of the infection in the causation of the clinical signs and the exclusion of other compatible diagnoses.

Diagnosis

Bartonella laboratory testing is required for feline blood donors, for pet cats belonging to immunosuppressed persons, or when a human *Bartonella*-related disease is diagnosed in a cat's home.

Isolation of the bacterium is the gold standard, but because of the high prevalence of infection in healthy cats in endemic areas, a positive culture is not confirmatory, and other compatible diagnoses must be ruled out.

The disease is, therefore, diagnosed on the basis of exclusion, and by assessing the response to therapy. The ex juvantibus inference about disease causation from the observed response to a treatment may apply to uveitis, endocarditis, myocarditis, osteoarthritis and multifocal central nervous system (CNS) disease, which are considered compatible with feline bartonellosis.

PCR may be used on samples of blood, aqueous humour, cerebrospinal fluid or tissues, and several gene targets have been studied. To reduce false-negative test results, repeated blood cultures are required or PCR performed on more than one kind of biological sample (blood, lymph node, oral swab).

Serology (IFAT or ELISA) is more useful for exclusion than for confirmation of the infection because of the low positive predictive value (39–46%) compared with the good negative predictive value (87–97%) [EBM grade III].[13,15,17,20] *Bartonella* IgM antibodies are found in experimentally and naturally infected cats but their occurrence seems not to be related to bacteraemia [EBM grade II].[57]

EBM grades

The ranking system for grading the level of evidence of various statements within this article is described on page 533 of this Special Issue.

Treatment

Treatment is recommended in the rare cases where *Bartonella* has actually caused disease (eg, endocarditis).

Table 3 Suggested treatment for bartonellosis in cats

Drug	Dose	Duration	Reference(s)	EBM grade
Doxycycline	10 mg/kg PO q12–24 h	2–4 weeks	Lappin and Black (1999)[35]	IV
Azithromycin	10 mg/kg PO q24h (q48h)	For 7 days followed by every other day for 6–12 weeks	Ketring et al (2004)[36] Varanat et al (2009)[7]	IV
Marbofloxacin	5 mg/kg PO q24h	6 weeks	Perez et al (2010)[44]	IV
Amoxicillin–clavulanate (with azithromycin)	62.5 mg PO q12h	2 months	Varanat et al (2009)[7]	IV

Public health considerations

Cats are the main reservoir for *B henselae*, the agent of cat scratch disease and more severe human diseases observed in severely immunosuppressed persons such as bacillary angiomatosis and peliosis hepatis. Recognised risk factors for bacteraemia in cats are young age, infestation with fleas, outdoor lifestyle and a multicat environment.[13,15,20,48]

There is no evidence of benefit to cats or their owners from routine testing of the pet for *Bartonella* infection or from antibiotic treatment of healthy antibody positive cats [EBM grade IV].[61] Infection does not always lead to clinical signs in healthy persons and many of them have antibodies.[55]

Owner education by practitioners about *Bartonella* transmission is essential to reduce the zoonotic risk, and the presence of immunosuppressed persons in the cat family should be specifically considered. It is recommended that immunosuppressed persons are allowed to keep their pet cat or to adopt a new one and a few simple tips summarised on the right can minimise their exposure risk.[61,62]

Recommendations for prevention of *B henselae* infection in immunocompromised persons[61,62]

- Immunocompromised owners should adopt cats that are older than 1 year, flea-free, in good health, not from shelters or multicat households, and have no history of contact with cats of unknown health status
- Strict flea control should be exercised under veterinary supervision
- Rough play should be avoided, and the cat's claws kept trimmed
- Any wound should promptly be cleaned with soap and water, and medical advice sought
- Cats should be kept indoors to avoid exposure to fleas and other possible vectors, and also to prevent other zoonotic risks

Current therapeutic strategies in cats (Table 3) are based on in vitro studies and human bartonellosis. Data from controlled efficacy studies in cats are lacking. A cat affected by recurrent osteomyelitis and polyarthritis associated with *B vinsonii* subspecies *berkhoffii* genotype II infection and bacteraemia recovered after therapy with azithromycin (10 mg/kg PO q48h for 3 months) and amoxicillin–clavulanate (62.5 mg PO q12 for 2 months) [EBM grade IV].[7]

After natural or experimental infection with *B henselae* or *B clarridgeiae*, healthy cats have been treated to eliminate bacteraemia and many drugs have been evaluated: doxycycline, amoxicillin, amoxicillin-clavulanate, enrofloxacin, erythromycin and rifampicin [EBM grade II].[58–60] Based on these results, clearance of bacteraemia cannot be guaranteed and, in the case of failure, there is the risk of inducing antimicrobial resistance. Treatment of healthy carriers, therefore, cannot be considered an effective measure for eliminating the zoonotic risk, as is sometimes requested in human cases of cat scratch disease or where other *Bartonella*-related disease occurs in a family member.

Prevention

Based on transmission studies to date, strict flea (and tick) control is the only successful preventive measure. There is no vaccine available against *Bartonella* infection.

KEY POINTS

- ***B henselae*** **is the most common *Bartonella* species infecting cats, which are the main reservoir for this bacterium.**
- ***B henselae*** **is the causative agent of cat scratch disease in man, a self-limiting regional lymphadenopathy.**
- ***B henselae*** **is naturally transmitted among cats by the faeces of *Ctenocephalides felis felis* fleas; contact infections do not occur. Blood transfusion also represents a risk.**
- **Most cats naturally infected by *B henselae* do not show clinical signs but sporadic cases of endocardial, myocardial or ocular feline disease have been reported.**
- **Other *Bartonella* species, for which cats are accidental hosts, may have more pathogenic potential.**
- **Antibodies are not protective, and seropositive cats may be reinfected.**
- **Bartonellosis is diagnosed on the basis of exclusion, and by assessing the response to antibiotic therapy.**
- **Testing healthy cats or people is of no benefit.**
- **Treatment of healthy carriers is no measure for eliminating the zoonotic risk.**
- **Strict flea and tick control is the only effective preventive measure.**

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Conflict of interest

The authors do not have any potential conflicts of interest to declare.

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