

GUIDELINE for Feline bartonellosis

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The *Bartonella* species infection in cats guidelines were first published in the J Feline Med Surg 2013, 15: 563-569 by [Maria Grazia Pennisi](#) et al. and updated by Fulvio Marsilio in 2015 and by Maria Grazia Pennisi and Fulvio Marsilio in 2018. The present guidelines were updated by Maria Grazia Pennisi and Fulvio Marsilio.

Key points

- *Bartonella* (*B.*) spp. infect humans and domestic animals and some species and subspecies are confirmed or suspected pathogens.
- *B.* spp. have a worldwide distribution with higher prevalences in areas where most favorable conditions for arthropod vectors (particularly fleas) exist.
- *B. henselae* is the causative agent of cat scratch disease (CSD) in humans, a self-limiting regional lymphadenopathy.
- Cats are main reservoir host of *B. henselae* and accidental hosts of other species.
- The primary role of fleas in the transmission of *B. henselae* among cats has been demonstrated.
- Most cats naturally infected by *B. henselae* do not show clinical signs, but some individuals may develop life-threatening cardiovascular diseases and possibly other pathologies associated with generalized lymphadenopathy.
- Other *B.* spp. may have pathogenic properties in cats as seen in dogs and humans.
- Antibodies are not protective and antibody-positive cats may be reinfected.
- Bartonellosis is diagnosed in symptomatic *Bartonella* positive cats based on exclusion of other compatible diagnoses, and by assessing the response to antibiotic therapy.
- No benefit derives from testing healthy cats and humans, except in cases of immunosuppressed people in the home.
- Strict flea and tick control is the only effective preventive measure.

Agent properties

Bartonella are small (2.0 by 0.5 μm), vector-transmitted Gram-negative intracellular bacteria that are well adapted to one or more mammalian reservoir hosts. Until now, 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).

Table 1: Species and subspecies of *Bartonella* that are confirmed or potential human pathogens (Chomel et al., 2006; Molia et al., 2016)

<i>Bartonella</i> spp.	Primary reservoir	Vector	Accidental host
<i>B. bacilliformis</i>	Humans	<i>Lutzomia verrucarum</i>	None

<i>Bartonella</i> spp.	Primary reservoir	Vector	Accidental host
<i>B. quintana</i>	Humans	<i>Pediculus humanus</i>	Cat, dog, monkey
<i>B. elizabethae</i>	<i>Rattus norvegicus</i>	<i>Xenopsylla cheopis</i>	Human, dog
<i>B. grahamii</i>	Several species of wild mice	Rodent fleas	Humans
<i>B. henselae</i>	Cat	<i>Ctenocephalides felis felis</i>	Humans, dog
<i>B. clarridgeiae</i>	Cat	<i>C. felis</i>	Humans, dog
<i>B. koehlerae</i> subsp. <i>koehlertae</i>	Cat, lion	<i>C. felis</i>	Humans
<i>B. koehlerae</i> subsp. <i>boulouisii</i>	Mountain lion	Fleas?	Unknow
<i>B. koehlerae</i> subsp. <i>bothieri</i>	Bobcat, cheetah	Fleas?	Unknow
<i>B. vinsonii</i> subsp. <i>berkhoffii</i>	Coyote, dog	Ticks?	Humans
<i>B. vinsonii</i> subsp. <i>arupensis</i>	<i>Peromyscus leucopus</i>	Ticks? Fleas?	Humans
<i>B. washoensis</i>	<i>Spermophilus beecheyii</i>	Fleas?	Humans, dog
<i>B. asiatica</i>	Rabbit	Fleas?	Humans
<i>B. rochalimae</i>	Wild carnivores	Fleas	Humans

The most common species in both cats and humans is *B. henselae*, which causes cat scratch disease (CSD) in the latter, as well as other potentially fatal disorders affecting immunocompromised people. Cats naturally infected with *Bartonella* usually do not show clinical signs. Given the long-lasting association of *B. henselae* and domestic cats, there have been adaptations between host and bacterium to facilitate co-existence and minimise pathogenic effects on the mammalian host (Guptill, 2010).

Epidemiology

Prevalence

Bartonella spp. 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 ranged from 8 to 53% (Table 2).

Table 2: Antibody prevalence of *Bartonella* infection in the feline populations sampled in European countries

Country	Number of cats	Prevalence (%)	Reference
The Netherlands	163 (stray)	52	Bergmans et al., 1997
Austria	96	33	Allerberger et al., 1995
Switzerland	728	8	Glaus et al., 1997
Germany	713	15	Haimerl et al., 1999
	245	37.1	Morgenthal et al., 2012
France	64	36	Chomel et al., 1995

Country	Number of cats	Prevalence (%)	Reference
	94	53	Heller et al., 1997
	179	41	Gurfield et al., 2001
Spain	680	23.8	Ayllon et al., 2012
	118	78	Álvarez-Fernández et al., 2021
Italy	540	38	Fabbi et al., 2004
	1300 (stray)	23.1	Brunetti et al., 2013
	197	45.7	Persichetti et al., 2018
	167	18.0	Morelli et al., 2019
	95	29.47	Ebani et al., 2021
Scotland	78	15.3	Bennett et al., 2011
Greece	452	35.4	Kokkinaki et al., 2022

Mazurek et al. (2019) reported the frequency of the occurrence of *Bartonella* spp. DNA in dogs from households where cats with clinical bartonellosis were kept. The presence of DNA with 99–100% compliance of the nucleotide sequence with the sequence of the *Bartonella* DNA isolated from cats was demonstrated in the body of 10% of tested dogs. The results indicated that cats serve as a *Bartonella* reservoir for dogs, and the dogs can play the same role with regard to humans. Furthermore, Mazurek et al. (2020) reported the occurrence of *Bartonella* spp. by PCR on 672 cats randomly selected from the largest clinics in eastern Poland and a prevalence of 40.48% was found. Interestingly, only the *B. henselae* DNA was detected.

Razgūnaitė et al. (2021) found the *Bartonella* spp. DNA from 4.9% of lithuanian cat blood samples (8/163) and from 29.4% (30/102) of fleas collected from the same cats. *B. henselae* and *B. clarridgeiae*, were identified in the cats and fleas, and *B. henselae* was found to be more common than *B. clarridgeiae*.

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* subsp. *berkhoffii* DNA was detected in the blood of a cat (Varanat et al., 2009).

Transmission

Epidemiological evidence and experimental studies have demonstrated the important role of fleas in the transmission of *B. henselae* and *B. clarridgeiae* between cats. *B. henselae* is naturally transmitted among cats by the flea *Ctenocephalides felis felis*, or by flea faeces. Using a quantitative real-time PCR, *B. henselae* DNA was detected in both fleas and their faeces for the entire 12-day life span of the arthropod, starting at 24 hours after the blood meal (Bouhsira et al., 2013). The possible role of several bat fly species (Nycteribiidae) as *Bartonella* vectors has been studied. It remains a subject of debate, but a reservoir function should be considered in addition to pathogenic, parasitic, or mutualistic interactions (Morse et al., 2012).

Bartonella henselae was experimentally transmitted among cats by transferring fleas fed on naturally infected cats to SPF cats, and by intradermal inoculation of excrement collected from fleas fed on *B. henselae*-infected cats (Chomel et al., 1996). 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 nine days (Finkelstein et al., 2002).

Ticks may also act as vectors for transmission among cats, human beings, dogs, and other mammalian hosts: transstadial transmission of *B. henselae* was demonstrated in *Ixodes ricinus* (Cottè et al., 2008). Persichetti et al. (2016) evaluated PCR positivity to vector-borne pathogens in cats and their ectoparasites and they sequenced *B. clarridgeiae* in PCR products amplified from DNA extracted from two ticks (one *Ixodes ventralloii* and one *Rhipicephalus sanguineus*) specimen but not in the blood of the two cats carrying each of them. Similarly, Regier et al. (2017) found *B. henselae* in *Ixodes ricinus* ticks collected from one PCR negative cat that was however positive for anti-*B. henselae* antibodies. Whether this observation implies a role for ticks in the transmission of both *Bartonella* spp. to cats needs

to be resolved.

Blood transfusion represents a risk: cats have been experimentally infected with *B. henselae* and *B. clarridgeiae* by intravenous or intramuscular inoculation with infected cat blood (Abbott et al., 1997).

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 (Guptill et al., 1997).

Pathogenesis

A cat scratch is the common mode of transmission of the organism to other animals, including humans (Chomel et al., 1996). *Bartonella*, ingested by the flea, survives in its gut. Contaminated flea faeces deposited on the skin end up under the cat's claws due to grooming. In the infected cat, *Bartonella* inhabits red blood cells.

Chronic bacteraemia mainly occurs in cats under the age of 2 years (Guptill et al., 2004). Young experimentally infected cats maintained relapsing *B. henselae* or *B. clarridgeiae* bacteraemia for as long as 454 days (Kordick et al., 1999). Immune system avoidance due to its intracellular location, frequent genetic rearrangements and alteration of outer membrane proteins are considered important for the maintenance of persistent bacteraemia. The location within erythrocytes and vascular endothelial cells is believed to protect *Bartonellae* from antimicrobial agents. Cats can be re-infected by different strains of *Bartonella* (Guptill, 2010).

Clinical signs

Cats naturally infected with *Bartonella* spp. 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. Exposure to infected fleas does not result in clinical signs (Chomel et al., 1996; Bradbury and Lappin, 2009). In some cases of experimental inoculation, a self-limiting febrile disease, transient mild anaemia, localized or generalized lymphadenopathy, mild neurologic signs and reproductive failure have been reported (Kordick et al., 1999). In these animals, pyogranulomatous inflammation was seen in the lung, liver, spleen, kidney, heart (Figure 1) and lymphoid tissue at necropsy (Guptill et al., 1997; Kordick et al., 1999).

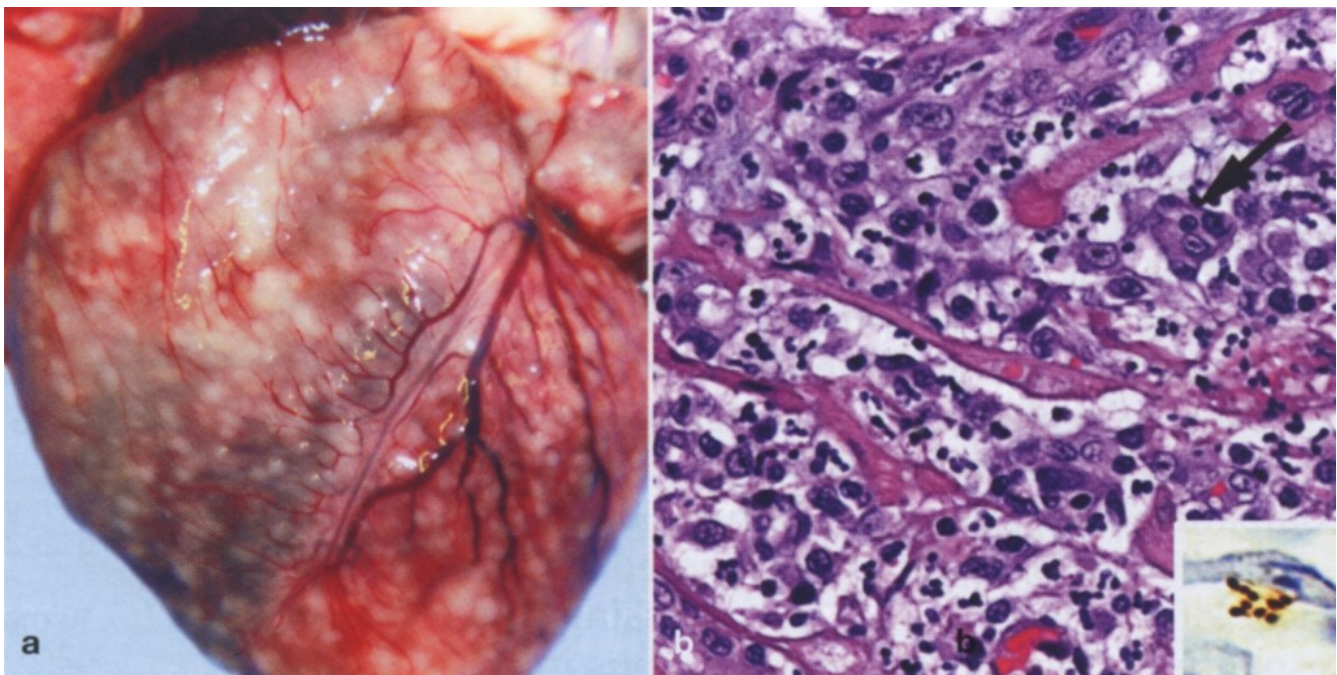


Fig. 1. Gross and histological findings in two cats from North Carolina shelter that had died after a litter of flea-infested kittens was introduced to the shelter. (a) Coalescent granulomas distributed throughout the myocardium (b) Pyogranulomatous myocarditis in an 8-month-old castrated male cat, which had been co-housed with the flea-infested kittens. Macrophages, with a rare multinucleated giant cell (arrow) are particularly numerous at the upper left of the image. Hematoxylin/eosin stain. Inset: cluster of short bacilli in an inflammatory focus are immunoreactive (brown) for *B. henselae*-specific monoclonal antibody.

Reproduced with permission from Varanat et al. (2012).

The role of *Bartonella* in causing clinical signs in cats after natural infection is even more unclear. Studies based on antibody detection are of limited value because antibody only proves exposure, but not necessarily active infection. Moreover, there is cross reactivity between different *Bartonella* species 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, (Ueno et al., 1996; Glaus et al., 1997), but the prevalence of antibodies or organisms was not higher in diseased cats than in control populations (Quimby et al., 2008; Dowers et al., 2010; Pennisi et al., 2010; Belgard et al., 2010; Namekata et al., 2010).

Cats positive for both FIV and *Bartonella* antibodies had an increased risk of lymphadenopathy (Ueno et al., 1996). An association between anti-*Bartonella* antibodies and urinary tract disease or haematuria has been suggested (Glaus et al., 1997; Breitschwerdt et al., 2005). Pearce et al. (2006) did not find any difference in antibody prevalence between healthy cats and cats with seizures or other neurological conditions. However, a non-controlled retrospective study reported *Bartonella* DNA in cerebrospinal fluid and confirmed specific antibody production in the CNS of cats with CNS disease (Leibovitz et al., 2008). Despite the EBM grade III of this observation, *Bartonella* spp. infection should be considered when other compatible diagnosis of CNS disease are excluded in symptomatic cats.

Castel et al. (2019) reported co-infection with *B. henselae* and *Sarcocystis* sp. in a 6-year-old male neutered domestic longhair cat with chronic waxing and waning neurologic mild signs and presenting an acute progressive multifocal neuromuscular syndrome and chorioretinitis. The contribution of each agent and the influence of the co-infection on the pathogenesis of the neuromuscular and ocular lesions was not possible and treatment with fluoroquinolones, trimethoprim sulfadiazine and pyrimethamine were directed at both organisms. After an initial worsening of clinical signs, a progressive improvement followed by full recovery was observed. As *Sarcocystis* sp. clinical infection in cats has been associated with immunosuppression, Authors hypothesized that relapsing *B. henselae* bacteraemia may have decreased the cat's immune competence and caused a normally quiescent protozoal infection to induce intermittent clinical signs (Castel et al., 2019).

No difference in *Bartonella* antibody prevalence was found between healthy cats and cats affected by uveitis (Fontenelle et al., 2008), but some had reported evidence of *Bartonella* spp. exposure in cats with uveitis responsive to drugs considered effective against *Bartonella* (Lappin and Black, 1999; Ketring et al., 2004). No difference in the prevalence of positive *Bartonella* PCR was found in cats affected by anaemia compared to control cats (Ishak et al., 2007). Prevalence of anti-*Bartonella* antibodies was lower in cats with fever compared to afebrile controls, but the former had a higher blood DNA positivity approaching statistical significance (Lappin et al., 2009). Moreover, a unique, identical *B. henselae* genotype was cultured from blood of three kittens and it was recognised as the causative agent of their cyclic relapsing fever associated with anaemia and neutropenia by excluding other infections and clinical cure with azithromycin treatment (Breitschwerdt et al., 2015).

A study based on serology and culture did not find an association between *Bartonella* infection and chronic rhinosinusitis (Berryessa et al., 2008). There was also no association found between *Bartonella* infection and pancreatitis, because cats with normal fPLI values and cats with elevated fPLI values did not show any difference in *Bartonella* prevalence (Bayliss et al., 2009).

Since 1993, many *Bartonella* species have been associated with endocarditis in humans and dogs (Breitschwerdt et al., 1995; La Scola and Raoult, 1999; Mc Donald et al., 2004). Some research groups have looked for *Bartonella* in cats with endocarditis, an uncommon problem in cats. Aortic and fatal mitral valve *B. henselae*-associated endocarditis was reported in two cats in the USA (Chomel et al., 2003; Chomel et al., 2009). Also, *B. henselae* anterior mitral valve leaflet vegetative endocarditis associated with a grade III to IV systolic heart murmur and signs of aortic embolization (lethargy and weakness in the hind limbs, weak femoral pulses, pelvic pain, increased serum creatine kinase activity) was successfully treated in a cat (Perez et al., 2010), suggesting that *Bartonella* species may be a cause of blood culture-negative endocarditis, as previously suspected (Malik et al., 1999).

Myocarditis caused by *B. henselae* was diagnosed at *post-mortem* examination in two cats (Varanat et al., 2012) and Joseph et al. (2018) described a clinical case of congestive heart failure with acute onset in a 3 year-old cat from a household fostering stray cats. Echocardiography and electrocardiography respectively evidenced ventricular asymmetrical myocardial thickening with a diffusely mottled hypochoic echotexture and a left bundle branch block. After a positive blood PCR test for *B. henselae*, azithromycin treatment was given for a month and a complete resolution of clinical, ultrasound and electrocardiographic abnormalities were documented.

Lameness and pain during limb palpation were observed in a cat affected by recurrent osteomyelitis and polyarthritis associated with *B. vinsonii* subsp. *berkhoffii* infection and bacteraemia (Varanat et al., 2009). Aggressive osteomyelitis causing an incomplete fracture of

radial metaphysis was recently associated with *B. henselae* bacteraemia in a young cat with generalized peripheral and abdominal lymphadenopathy (Hui et al., 2022). The cat was treated with doxycycline and pradofloxacin in combination for 6 weeks and clinical and radiographic healing was documented. A negative blood culture was also obtained as well as seroreversion one year later (Hui et al., 2022).

In conclusion, most cats naturally infected by *B. henselae* do not show clinical signs, but some individuals may develop life-threatening cardiovascular diseases and possibly other pathologies associated with generalized lymphadenopathy. Moreover, other *Bartonella* species, for which cats are accidental hosts, may have pathogenic properties.

Immunity

Passive immunity

Data concerning passive immunity are lacking.

Active 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 experimental cats is highly variable in degree and duration (Chomel et al., 1996; Kordick et al., 1999; Yamamoto et al., 2002). The extent of serologic cross-reactivity to other *Bartonella* species needs to be clarified. 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 (Arvand et al., 2008). Antibodies are therefore considered not protective, and *Bartonella* spp.-seropositive cats may be infected (Fabbi et al., 2004).

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 person that lives with cats or has contact with cats.

Cultivation of the bacterium is the gold standard method of diagnosis of *Bartonella* infection, but because of the high prevalence of infection in healthy cats in endemic areas, a positive culture is not confirmatory of disease, 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. This 'ex juvantibus'-inference about disease causation from the observed response to a treatment may apply to uveitis, endocarditis, and multifocal CNS disease, which can all be compatible with feline bartonellosis.

PCR may be used in blood, aqueous humour, cerebrospinal fluid or tissues, and several gene targets have been studied. For rapid laboratory diagnosis, a real-time PCR and pyrosequencing-based algorithm was described that allowed rapid differentiation of at least 11 medically relevant *Bartonella* spp. within five hours from receipt of the specimens (Buss et al., 2012). A real-time PCR for *Bartonella* spp. detection was proposed to improve PCR sensitivity and to identify species not previously described (Parra et al., 2017). Moreover, in order to detect and classify new *Bartonella* species from fleas a Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDITOF-MS) has been proposed (El Hamzaoui et al., 2018).

Serology (IFAT or ELISA) is more useful for exclusion than for confirmation, because of the low positive predictive value (39-46%) compared to the good negative predictive value (87-97%; Chomel et al., 1995; Gurfield et al., 2001; Fabbi et al., 2004; Guptill et al., 2004).

Repeated blood cultures are required, or PCR performed on more than one kind of biological sample (blood, lymph node, oral swab; Pennisi et al., 2010; Drummond et al., 2018). A combinational approach with pre-enrichment culture and PCR increases sensitivity (Breitschwerdt et al., 2007).

Treatment

Treatment is recommended for cats living with immunosuppressed persons or in the rare cases where *Bartonella* has actually caused disease, e.g endocarditis or myocarditis. Current therapeutic strategies in cats (Table 3) are based on *in vitro* studies and human bartonellosis.

Table 3: Suggested treatment for Bartonellosis in cats

Drug	Dose	Duration	Reference
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Doxycycline	50 mg/cat, PO, q12-24h	14-28 days	Guptill-Yoran, 2012
Azithromycin	10 mg/kg PO q24h (or q48h)	7 days followed by every other day for 6-12 weeks or daily for 3 weeks	Ketring et al., 2004; Varanat et al., 2009; Breitschwerdt et al., 2015; Joseph et al., 2018
Marbofloxacin	5 mg/kg PO q24h	6 weeks	Perez et al., 2010
Amoxicillin-clavulanate (with azithromycin)	62.5 mg PO q12h	2 months	Varanat et al., 2009
Ciprofloxacin	25 mg/kg PO q24h	15 days	Castel et al., 2019
Pradofloxacin (with doxycycline)	7.5 mg/kg PO q24h	6 weeks	Hui et al., 2022

Data from controlled efficacy studies in cats are lacking. A cat affected by recurrent osteomyelitis and polyarthritis associated with *B. vinsonii* subsp. *berkhoffii* genotype II infection and bacteraemia recovered after therapy with azithromycin (10 mg/kg PO q48h for three months) and amoxicillin-clavulanate (62.5 mg PO q12 for two months; Varanat et al., 2009).

After natural or experimental infection with *B. henselae* or *B. clarridgeiae*, healthy cats have been treated to eliminate bacteraemia (Greene et al., 1996; Regnery et al., 1996; Kordick et al., 1997), and many drugs have been evaluated: doxycycline, amoxicillin, amoxicillin-clavulanate, enrofloxacin, erythromycin, rifampin. Based on these results, clearance of bacteraemia cannot be guaranteed and, in the case of treatment 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; it is sometimes requested, in human cases of CSD or other *Bartonella*-related disease in a family member.

Prevention

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

Zoonotic risk

Cats are the main reservoir for *B. henselae*, the agent of CSD and other human diseases mainly observed in immunosuppressed persons. Recognised risk factors for bacteraemia in cats are young age, infestation with fleas, outdoor lifestyle and a multicat environment (Chomel et al., 1995; Foley et al., 1998; Gurfield et al., 2001; Guptill et al., 2004; Boulouis et al., 2005).

Clinical signs in humans

Bartonella henselae is the causative agent of CSD (Fig. 2). This is a self-limiting regional lymphadenopathy developing after a primary papular lesion and lasting for a few weeks to several months (Boulouis et al., 2005). 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 (Boulouis et al., 2005), such as neuroretinitis, uveitis (Fonollosa et al., 2011), endocarditis (Tsuneoka et al., 2010) and encephalopathy (Samarkos et al., 2018). An unusual CSD case has been reported in a veterinarian affected by persistent fever and back pain after an accidental needle puncture (Lin et al., 2011). Bacillary angiomatosis (Lange et al., 2009) is one of the most common clinical manifestations in immunocompromised individuals that may be fatal if untreated, whereas immunocompetent persons may experience subclinical *Bartonella* infection (Massei et al., 2004).

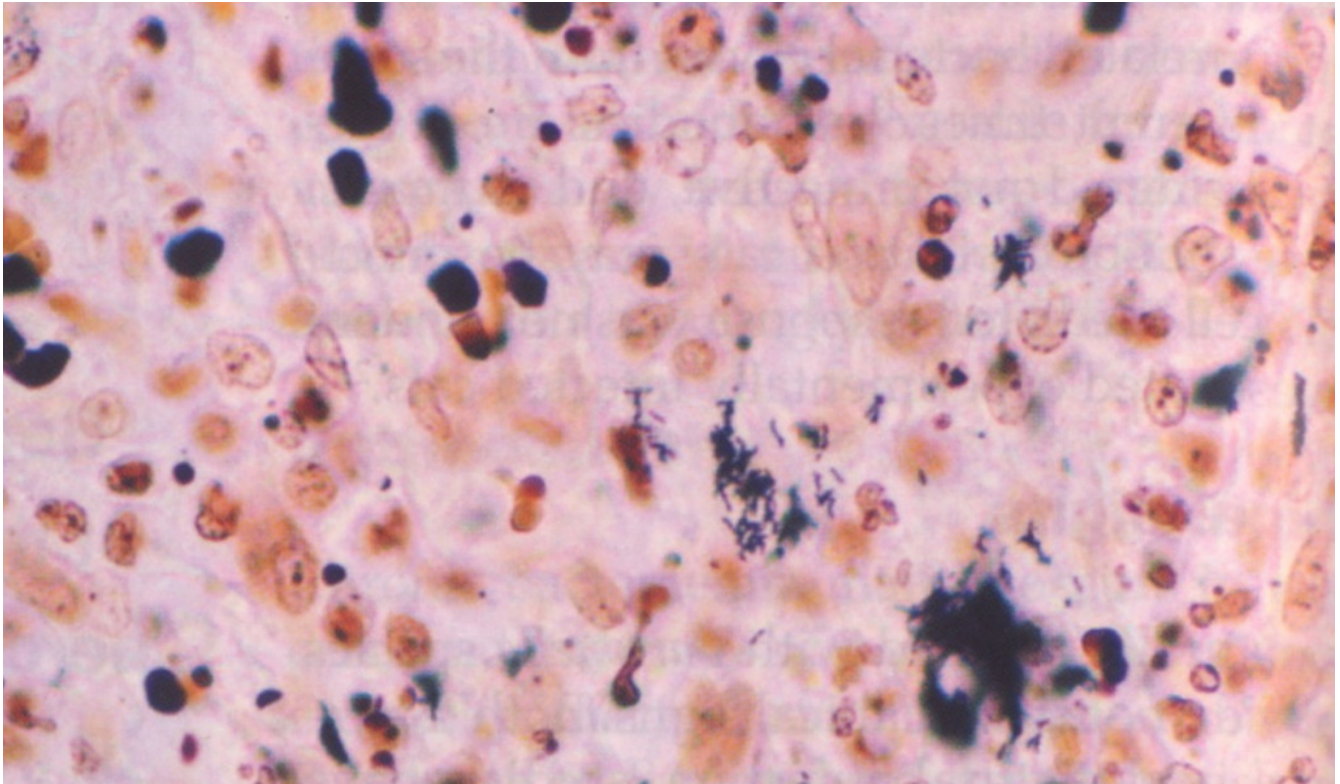


Fig. 2. Immunohistochemical identification of *B. henselae* in a case of cat scratch disease. Courtesy of Dharam Ramnani, Webpathology.com

There is no benefit of testing asymptomatic cats or people, except in cases of immunosuppressed persons in the home. Infection does not always lead to clinical signs in healthy persons, and many have antibodies (Massei et al., 2004; Mc Gill et al., 2005). Owner education about *Bartonella* transmission is essential to reduce the zoonotic risk; it is crucial to allow immunosuppressed people to keep their pet cat or to adopt a new one.

Key points to minimise the zoonotic risk (Kaplan et al., 2002; Brunt et al., 2006):

- Immunosuppressed owners should preferably adopt cats older than 1 year, flea-free, in good health, not from shelters or multicat households, and without contact with cats of unknown health status.
- A strict flea and tick control should be exercised.
- 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, but also to prevent other zoonotic risks.

Disease control in Specific Situations

Strict flea and tick control is the only effective preventive measure.

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