



## HUMAN *BARTONELLA* INFECTION: A REVIEW OF LITERATURE

Bistra Blagova, Nikolay Yanev

Maxillofacial Surgery Division, University Multiprofile Hospital for Active Treatment and Emergency Medicine N. I. Pirogov, Sofia, Bulgaria.

### ABSTRACT

Cat scratch disease has been reported in the literature for more than half a century as a syndrome of regional lymphadenopathy and fever. However, only a quarter of a century has passed since *Bartonella henselae* was identified as an etiological agent. As diagnostic techniques have improved, *Bartonella* has been found to be responsible for a wide range of clinical syndromes. This review summarizes current knowledge about microbiology, clinical manifestations, diagnostic techniques and treatment of *Bartonella henselae* infection.

**Keywords:** *Bartonella henselae*, bartonellosis, cat scratch disease (CSD), cat scratch fever, felinosis,

### BACKGROUND

Members of the genus *Bartonella* are bred in many domestic hosts and wild animals [1]. In immunocompetent humans, *Bartonella henselae* causes cat scratch disease (CSD), which is most often a relatively benign and self-limiting disease [2]. In contrast, *Bartonella henselae* infections in immunocompromised individuals are often severe and can be fatal without antibiotic treatment [3, 4]. Other *Bartonella* species are also sometimes associated with human diseases, with varying levels of evidence for a causal role. There is no extensive prevalence study to clarify the revalent data. The true incidence of *Bartonella* infection is also difficult to determine, as no disease has been reported in most countries [3]. This finding probably underestimates the true frequency, as most cases of *Bartonella* infection are not recognized or treated on an outpatient basis [5]. It can present with a wide variety of clinical symptoms [6] and can be difficult to diagnose. Thus, the **purpose** of this article is to review the available literature, human and veterinary, and to acquaint practitioners with this condition, as it must be taken into account in the differential diagnosis of pathological conditions of unknown origin.

### REVIEW RESULTS

#### Historical notes

The clinical syndrome of Cat scratch disease (CSD) was first reported in 1950 by Debre et al. [7]. Despite numerous reports and studies of CSD, the causative agent was not recognized until 1983. At that time, Wear et al. [8] found a small, pleomorphic Gram-negative bacillus using a Warthin-Starry silver stain in infected lymph nodes in CSD

patients. It was originally known simply as the “cat scratch disease bacillus”. Only five years later, this organism was successfully isolated and cultivated [9]. In 1991, Brenner et al. [10] called the CSD bacillus *Afipia felis* of the Institute of Pathology of the Armed Forces, where the organism was found. In 1992, *Rochalimaea henselae* was isolated from HIV-infected patients with bacillary angiomatosis, peliosis hepatis and fever syndromes [11]. In that report, Regnery et al. [11] note that the majority of their patients with clinically suspected CSD have high serum titers to the *Rochalimaea henselae* antigen. Further research in the 1990s refuted the role of *Afipia felis* in CSD in favor of *Rochalimaea* species [12]. In 1993, the genera *Bartonella* and *Rochalimaea* were merged, with *Bartonella* having nomenclature priority over *Rochalimaea* [13]. Thus, *Bartonella henselae* is now recognized as a causative agent of CSD.

#### Microbiology and pathogenesis

The genus *Bartonella* includes 25 different species, of which at least 6 are responsible for human diseases (*Bartonella henselae*, *Bartonella bacilliformis*, *Bartonella quintana*, *Bartonella elizabethae*, *Bartonella vinsonii*, *Bartonella koehlerae*) [3]. These species are small, fastidious, intracellular (intraerythrocyte) Gram-negative chemotropic bacilli that are aerobic and oxidase-negative [13].

*Bartonella* infection in humans leads to prolonged bacteremia in the blood [14]. Once transmitted to humans through cat saliva or cat scratch, *Bartonella henselae* invades CD 34 hematopoietic progenitor cells instead of human erythrocytes directly [15]. Bacterial infection does not affect the erythroid differentiation of hematopoietic progenitor cells; therefore, infection of these progenitor cells results in intracellular presence and replication of *Bartonella henselae* in erythroid cell differentiated cells [15]. In infected patients, the organisms are most often found in vessel walls, in macrophages lining the lymph nodes sinuses, in nodal germ centers, in necrotic areas of inflammation and in areas of expanding and suppurative necrosis [6].

The response to *Bartonella henselae* infection depends on the immune status of the infected host. In immunocompetent individuals, the response is granulomatous and purulent, compared to a vasoproliferative response in immunocompromised patients [6]. Lymphoid hyperplasia, arteriolar proliferation and dilated arteriolar walls in biopsied lymph nodes are observed in immunocompetent patients at the onset of infection. This progresses to granu-

lomatous disease, with central areas of necrosis and multinucleated giant cells. *Bartonella* infection causes an interferon- $\gamma$ -mediated T-helper-cellular response, which leads to the recruitment and stimulation of macrophages, which ultimately leads to granulomatous disease. [16] At the end of the disease, stellar microabscesses form with suppuration of the affected lymph nodes [6]. In individuals with an intact immune system, the infection usually remains in the lymphatic system, with a symptomatic immune response lasting 2 to 4 months [17].

#### Transmission of zoonotic *Bartonella* to humans

*Bartonella spp.* infect humans and a number of domestic and wild mammals such as cats, cheetahs, African lions, cougars, mice, dogs, foxes, livestock, rodents, rabbits, horses, cattle, wild boars, seals, whales, guinea pigs, kangaroos, wild badgers, bats, etc. [1]. Direct horizontal transmission of *Bartonella henselae* does not occur, but rather the spread of infection between cats depends on the arthropod vector *Ctenocephalides felis* or cat flea [18]. Although some details of the transmission are not fully understood, humans appear to acquire *Bartonella henselae* from scratches and cat bites. It has not yet been proven whether the bacteria in cat saliva come from the cat's blood or from the feces of fleas ingested during maintenance. [1] The possibility of transmission directly from fleas to humans has also been proposed (e.g. through flea bites), but there is no evidence that this is possible [1]. It is possible that some wounds were contaminated later by *Bartonella henselae*, i.e. after exposure to inanimate objects [19]. There is no evidence that zoonotic *Bartonella* can be transmitted from person to person through accidental contact. How-

ever, *Bartonella henselae* was cultured from human units of red blood cells that had been inoculated with this organism and stored at 4 °C for 35 days, suggesting the possibility of transfusion transmission [1].

#### Epidemiology

*Bartonella henselae* is worldwide distributed. There appears to be a seasonal distribution, with most cases occurring between July and January. [20] Some authors attribute this seasonal variation to temporal breeding patterns of domestic cats, the acquisition of kittens as family pets and the peak temporal presence of the cat flea, the main mode of transmission of *Bartonella* among cats [21]. Seroprevalence of antibodies in humans to *Bartonella henselae* and *Bartonella henselae* bacteremia has been found to be highest in regions with warm, humid climates [22].

*Bartonella* infection was thought to be largely a childhood disease, with studies reporting between 54 % and 87 % of CSD cases in patients under the age of 18 [20]. Recent studies, though, suggest that CSD may be more common in adults than previously recognized, with some studies reporting that 40 % of their patients are over the age of 20 [23].

#### Clinical presentation

The clinical manifestations of *Bartonella henselae* infection are enhanced by the improved ability to recognize the presence of the organism. Some forms of infection appear to be regional, but maybe in a spectrum with a more severe systemic [24] or even recurrent forms [9]. A list of different clinical forms of *Bartonella henselae* infection is given in Table 1. [3]

**Table 1.** Clinical manifestation of human *Bartonella* infection.

more common:	less common:
<ul style="list-style-type: none"> <li>· typical CSD;</li> <li>· localized lymphadenopathy only;</li> <li>· prolonged fever of unknown origin;</li> <li>· hepatosplenic disease;</li> </ul>	<ul style="list-style-type: none"> <li>· <b>ocular manifestations</b> – Parinaud oculoglandular syndrome, neuroretinitis, posterior segment ocular disease;</li> <li>· <b>neurological manifestations</b> – encephalopathy, status epilepticus, facial nerve palsy, <i>Guillain-Barre</i> syndrome, epilepsy partialis continua, radiculopathy;</li> <li>· <b>vascular manifestations</b> – bacillary angiomatosis, cerebral arteritis;</li> <li>· <b>cardiac manifestations</b>;</li> <li>· <b>renal manifestations</b>;</li> <li>· <b>pulmonary manifestations</b>;</li> <li>· <b>hematologic manifestations</b> – thrombocytopenic purpura;</li> <li>· <b>orthopedic manifestations</b> – osteomyelitis, arthritis/arthralgia;</li> <li>· <b>pseudomalignancy</b>;</li> </ul>

**Typical Cat Scratch Disease (dermatologic manifestations combined with benign regional lymphadenopathy):** This is the most common manifestation of *Bartonella henselae* infection [3, 20]. It begins with an erythematous papule (single or in groups) at the site of inoculation [14]. The papule appears 3 to 10 days after inoculation and progresses through the erythematous, vesicular and papular cortical stages. The lesion lasts for a period of 1 to 3 weeks. [25] Regional lymphadenopathy occurs 1 to 3 weeks after

inoculation. Lymphadenopathy is observed in all patients with typical CSD and is most common in the axillary and epitrochlear nodes (46 %), head and neck (26 %) and groin (17.5 %). [20] On ultrasound, the nodules are multiple, hypoechoic and highly vascularized with increased echogenicity of the surrounding soft tissues [26]. Approximately 10 % of the nodules suppurate, thus requiring drainage [27]. Systemic symptoms are mild in most patients and may include fever, generalized pain, malaise, anorexia,

nausea and abdominal pain [3]. It should be noted that 10 % of patients have a body temperature higher than 39 °C, but one-third of patients have no temperature [20].

Skin lesions other than papules observed at the site of inoculation are rare and occur in 5 % of patients infected with *Bartonella henselae*. They consist of maculopapular and urticarial eruptions, ring-shaped granuloma, *erythema nodosum*, *erythema marginatum* and leukocytoclastic vasculitis. [28]

**Prolonged fever of unknown origin:** Although there are several definitions of fever of unknown origin, the common definition is a fever that lasts 2 weeks without diagnostic signs or symptoms of obvious clinical disease. With improvements in diagnostic methods for detecting *Bartonella henselae*, this agent is increasingly recognized as the cause of chronic fever of unknown origin, especially in children [29]. Approximately 30 % of cases of fever of unknown origin caused by *Bartonella henselae* had hepatosplenic involvement [3]. Thus, *Bartonella henselae* infection should always be considered as a diagnostic option in patients with fever of unknown origin and in patients with fever and abdominal pain.

**Pseudomalignancy:** There is an increasing number of reports of *Bartonella henselae* infections mimicking various malignancies [30]. Infection disease resembling lymphoma is commonly reported, especially when lymphadenopathy of the neck and abdomen is involved [31]. The clinical symptoms are even more confusing when splenomegaly occurs together with “B symptoms” – weight loss, night sweats and prolonged fever [32]. Another unusual presentation involves a patient with a single soft tissue mass covering a lytic cranial lesion suggesting *Histocytosis X* [33]. In adults, *Bartonella henselae* has presented with imitatorial characteristics to pharyngeal cancer [34] and vascular neoplasms [35].

**Orthopedic manifestations:** Bone lesions are a rare complication of *Bartonella henselae* infection. Often these lesions are osteolytic and occur as osteomyelitis. Clinical manifestations of the bone disease include pain and tenderness over the affected bone combined with lymphadenopathy. [5] Lytic lesions often occur in the context of systemic manifestations of *Bartonella* infection. Lymphadenopathy, on the other hand, often occurs distant from the site of osteomyelitis, suggesting that the bone infection occurs by hematogenous or lymphatic spread [36]. Radiographic findings include lytic lesions with sporadic sclerosis or periosteal reaction. In most patients, the osteolytic disease is isolated to one bone. [36 - 38] Despite the tendency of *Bartonella henselae* to cause isolated bone disease, recent series reported two cases of multifocal bone marrow *Bartonella* infection with foci of increased T 2 signal intensity on magnetic resonance imaging of the sacrum, ilium and femur, with accompanying lesions in the hepatic parenchyma [37]. Biopsy revealed necrotizing bone granulomas [38]. Bone lesions have been associated with adjacent abscesses [39].

### Diagnosis

**Patient history and examination:** Diagnosis is facilitated by information about cat scratching in the patient’s

history or signs of typical skin erosions caused by cats [40].

**Diagnostic tests:** An early approach for detection of *Bartonella henselae* infection was the intradermal *Hanger-Rose* skin test [41], which relies on a delayed-type hypersensitivity reaction within 48 to 96 hours after inoculation with *Bartonella henselae* antigen. The test has a specificity of 99 % and minimal cross-reactivity with other organisms [20]. Other *Bartonella* tests or laboratory examinations of *Bartonella* infection are often nonspecific [28]. The infection could be associated with normal or slightly increased white blood cell count and a normal increased or decreased platelet count. The erythrocyte sedimentation rate may be normal or increased. [24]

Isolation of *Bartonella* species in culture was found to be more difficult, especially if patients do not have any systemic disease [21]. Other diagnostic methods include histopathological examination of affected lymph nodes [23]. The pathology suggestive of *Bartonella henselae* infection includes specific granuloma formation with microabscesses and follicular hyperplasia [20, 21]. An example of angioproliferation in immunocompromised individuals infected with *Bartonella henselae* is shown by the accumulation of rounded blood vessels on biopsy, with fluffy epithelial cells and a mixed inflammatory infiltrate in predominance [25].

Later on, more advanced diagnostic techniques such as serology or polymerase chain reaction (PCR) have been introduced to detect *Bartonella* [42]. And although the specificity of the PCR test is excellent, it lacks sensitivity – ranging from 43 % to 76 % [43]. Hence the serology for *Bartonella henselae* antibodies has become the test of preference, as it avoids invasive sampling, use of specialized equipment and long incubation period techniques [21]. The two main serological diagnostic methods used are: indirect fluorescence analysis (IFA) and enzyme immunoassay (EIA) [3]. Disadvantages of serological tests include variable sensitivity and specificity, difficulties to distinguish between acute or past infection due to *Ig G* antibodies persisting for up to one year and lack of antibody-specific *Bartonella* response – leading to cross-reactivity [21]. However, serology remains the most useful diagnostic tool in the laboratory detection of *Bartonella henselae* infection.

**Diagnostic criteria.** Ultimately, no diagnostic criterion should be considered as a gold standard, and the diagnosis of *Bartonella henselae* infection is based on a combination of epidemiological, serological, clinical, histological and bacteriological criteria. There are 4 main diagnostic criteria: cat contact, regional lymphadenopathy, inoculation site and a positive skin test [20]. Carithers [20] developed the “*Rule of Five*” as a diagnostic tool in their original series. Points are given for each of the 4 criteria: Lymphadenopathy – 1 point, Exposure to cats – 2 points, Presence of an inoculation site – 2 points, and Positive skin test – 2 points. The accumulation of 5 points strongly recommends CSD, and 7 points make the diagnosis definitive. The diagnosis of *Bartonella henselae* infection is still considered mainly clinical, and laboratory evaluation is used to support the initial suspicion. The updated CSD criteria by Margileth are summarized in Table 2 [4].

**Table 2.** Diagnosis criteria for cat scratch disease. [4]

<b>3 of 4 of the following:</b>
1. Cat or flea contact regardless of presence of inoculation site.
2. Negative serology for other causes of adenopathy, sterile pus aspirated from a node, a positive PCR assay, and/or liver/spleen lesions seen on computed tomographic scan.
3. Positive enzyme immunoassay or IFA assay with a titer ratio of 1:64.
4. Biopsy showing granulomatous inflammation consistent with CSD or a positive Warthin-Starry silver stain.

### Treatment

The therapeutic approach to *Bartonella* infection varies depending on the clinical manifestation and the patient's immune status. Typical CSD is a self-limiting disease that resolves within 2 to 6 months and usually does not respond to therapy [2, 42]. Due to the natural progression of uncomplicated CSD and the risk of adverse effects in regular antibiotic use, alongside the development of resistant flora, antibiotics are not usually recommended for localized CSDs [23]. In mild to moderate infections in immunocompetent patients, suggested treatment consists of adequate monitoring and analgesia [4]. In patients with significant lymphadenopathy, treatment with azithromycin at

10 mg/kg doses during day 1 and 5 mg/kg per day between days 2 – 5 may be considered. Other antibiotics suggested include rifampin (20 mg/kg per day divided into 2 doses for 2 – 3 weeks), ciprofloxacin (20 – 30 mg/kg per day in 2 daily doses for 2 – 3 weeks) or trimethoprim-sulfamethoxazole (10 mg trimethoprim/kg per day) in 2 – 3 daily doses for 7 – 10 days). [4] (Table 3) However, there are no prospective controlled clinical trials to prove the effectiveness of antimicrobial therapy, and its efficacy is contradictory, especially in disseminated forms. Therefore, the use of antibiotics in a patient with disseminated CSD should be decided on a case-by-case basis.

**Table 3.** Antibiotic therapy for CSD.

antibiotic	route	dosage	frequency	duration
ciprofloxacin	PO	20 – 30 mg/kg	Q 12 h	10 – 21 days or more
gentamicin sulfate	IM or IV	5 mg/kg	Q 8 h	5 – 10 days
rifampin	PO	10 – 20 mg/kg (max. 600 mg/kg daily)	Q 8 – 12 h	10 – 21 days
trimethoprim - sulfamethaxazole	PO	10 – 20 mg/kg (trimethoprim) 50 – 100 mg/kg (sulfamethaxazole)	Q 8 – 12 h	10 – 14 days
doxycycline		3 – 4 mg/kg	BD	10 – 14 days

Nodes should be aspirated or drained if they become purulent to relieve painful inflammatory adenopathy [23]. During aspiration, the needle should be positioned in several different places, as fused microabscesses often exist in multiple pockets [4].

Recently, corticosteroid supplements have been suggested in patients with long-standing disease, especially when an excessive immune response is found [17], although no controlled studies are available yet.

### Prognosis

The overall prognosis for complete recovery in immunocompetent patients with CSD is good. Significant morbidity occurs in 5 – 10 % of cases, usually due to involvement of the central or peripheral nervous system or due to multisystemic disease. The cat scratch disease provides lifelong immunity against *Bartonella henselae* to all patients. [14]

### CONCLUSION

The spectrum of *Bartonella henselae* diseases has been focusing an increased professional interest, especially since the start of the 21st century. Their diagnosis and treatment still remain a challenge due to the wide range of clinical symptoms and often non-specific course. There have been no regular updates of the epidemiological studies in the various disease manifestations, patterns of occurrence, frequency and distribution. A significant information gap about the effective therapeutic protocols in complex *Bartonella* infections and their consequences exists. Single or multicenter randomized control trials and studies are further needed to base the clinical approaches and decisions on a clear evidence basis. Clinicians are advised to continue to refer to *Bartonella* in the differential diagnosis of chronic fever, abdominal pain and other complex and diverse manifestations of this unusual and frequently elusive bacteria.

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**Address for correspondence:**

Bistra Blagova, DDS, DMD  
Maxillofacial Surgery Division, University Multiprofile Hospital for Active Treatment and Emergency Medicine N. I. Pirogov, Sofia,  
21, Gen. Totleben Blvd., 1606, Sofia, Bulgaria  
E-mail: [dr\\_blagova@abv.bg](mailto:dr_blagova@abv.bg)