Bartonella infections: clinical manifestations, diagnostic techniques and treatment

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Summary

Bartonella spp. are fastidious, hemotropic, Gram-negative bacteria responsible for emerging and re-emerging diseases around the world. The majority of human infections are caused by *Bartonella henselae, Bartonella quintana* and *Bartonella bacilliformis*. Clinical manifestations of *Bartonella* infection range from mild and self-limited to life-threatening disease, which must be treated with the appropriate antimicrobial regimen. The severity of *Bartonella* infection correlates with the immune status of patients. As diagnostic techniques improve, the spectrum of clinical disease is expanding and includes regional lymphadenopathy, bacteremia, fever of unknown origin, endocarditis, bacillary angiomatosis and peliosis hepatis. This review summarizes current knowledge regarding the microbiology, clinical manifestations, diagnostic techniques and treatment of *Bartonella* infections.

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Introduction

Members of the genus *Bartonella* are pleomorphic, aerobic, Gram-negative rod bacteria that taxonomically belong to the alpha 2 subgroup of the class *Proteobacteria* and are closely related to *Brucella, Agrobacterium* and *Rhizonium* species.[1]

They are urease, oxidase and catalase negative microorganisms and are characterized as fastidious and slow-growing. They require specific conditions for optimal growth such as erythrocyte-enriched blood agar growth media and CO_2-rich environment, and extended incubation periods (6–8 weeks) for visible colonies to appear.[2] The successive culture passaging decreases the incubation time for colony generation to approximately 3 days and alters the morphology of the bacteria. Initially, rough, "cauliflower-like" aggregates develop and are deeply embedded in the medium but, after subculturing, smooth and less adherent cells appear.[3]

Bartonella spp are hemotropic, intracellular bacteria that cause prolonged intraerthrocytic bacteremia in their hosts[4,5] and are typically transmitted by haematophagous insects such as phlebotomine sand flies, human body lice and cat fleas or via animal scratch and bites.[6,7]

In vitro, they have been found to be susceptible to various antimicrobial agents, including macrolides (azithromycin, clarithromycin, erythromycin), aminoglycosides, β-lactams (penicillin G, amoxicillin), expanded-spectrum cephalosporins (cefotetan, cefotaxime, ceftazidime, ceftriaxone), rifampin and ciprofloxacin.[8-11] However, clinical use of these antimicrobial agents in vivo has proven less efficacious, with frequent cases of relapse and treatment failure[12] that may be due to the lack of bactericidal activity and of cell membrane penetration of many antibiotics.[13]

The genus *Bartonella* comprises 24 different species which subdivide evolutionarily into four lineages. *Bartonella bacilliformis* is the sole representative of the ancestral lineage 1. Members of lineages 2 (e.g. *Bartonella schoenbuchensis*), 3 (e.g. *Bartonella clarridgeiae* and *Bartonella rochalimae*) and 4 (e.g. *Bartonella henselae* and *Bartonella quintana*) are considered modern species.[14]

B. bacilliformis, B. quintana and *B. henselae* are responsible for the majority of infections in humans.[6,13] The ability to cause vascular proliferative or suppurative manifestations and acute or chronic infections is a remarkable feature of *Bartonella* spp. The severity of clinical manifestations correlates with the patient's immune status.

Bartonella bacilliformis

B. bacilliformis was the first infectious agent of the genus *Bartonella* and was formally described as a species by the Peruvian physician Alberto Barton in 1909.[15] Humans are the exclusive reservoirs of *B. bacilliformis* and they serve as sources of infection for sand flies *Lutzomya verrucarum*,[16] which are the vectors of the disease. Present since the pre-Incan times,[17,18] *B. bacilliformis* is the causative agent of Carrion's disease, which was named in 1885 after Daniel Carrión, a Peruvian medical student, who died from Oroya fever after he inoculated himself with blood from a verruga peruana nodule and contributed to the understanding of the biphasic nature of this disease.[19,20]

The acute hematic phase or Oroya fever is characterized by an intraerythrocytic bacteremia that often results in a fatal febrile anemia due to the massive hemolysis of infected erythrocytes.[21] Studies involving patients with acute phase of *Bartonella* infection revealed the most common clinical features (fever, malaise, abdominal pain, arthralgia and nausea) and signs (lymphadenopathy, hepatomegaly, cardiac murmur, pallor and jaundice) of the disease. Oroya fever has one of the highest lethality (40-90%) of all human bacterial infections. The mortality during this phase ranges from close to zero in the case of hospitalized patients receiving prompt antibiotic treatment to up to 80% in untreated cases.[5] The infection-induced temporal immunosuppression due to decrement and alteration in the number and function of T lymphocytes increases the susceptibility to opportunistic superimposed infections. Non-typhoid *Salmonella* infection, toxoplasmosis, histoplasmosis, reactivation of tuberculosis, *Staphylococcus aureus* arthritis, *Shigella dysenteriae* sepsis, *Pneumonocystis jirovecii* pneumonia, *Enterobacter* spp. and *Pseudomonas aeruginosa* infections have been described in children as infectious complications.[22-24] Non-infectious complications such as altered mental status, ataxia, seizures, agitation, coma, congestive heart failure, pericardial effusions, myocarditis, acute renal failure and adult respiratory distress syndrome have been recorded in severe cases.[22,23]

Patients surviving this acute intraerythrocytic phase may develop the eruptive phase or Peruvian wart (verruga peruana)[25] which results in vascular tumors that originate from the proliferation of colonized endothelial cells. The pathological angiogenesis during this phase usually occurs in the skin, adopting three patterns: a military eruption (multiple, widely distributed lesions, 2-3 mm in diameter), a nodular eruption (few eruptions, 8-10 mm in diameter) and a "mular" eruption (unique, large, deep-seated lesion).[22]

Atypical cases have been reported in other organs such as spleen. The most commonly reporter symptoms and signs of the eruptive phase are bleeding of the wart, fever, malaise, arthralgia and pallor, lymphadenopathy, respectively.

Aside from causing Carrion's disease, *B. bacilliformis* infection may result in a chronic, asymptomatic bacteremia, which may last for up to 15 months, and *B. bacilliformis* may be transmitted to sand flies that feed on patients during this time. Bacterial or host factors that determine whether infection results in clinical disease or the asymptomatic carrier state are unknown. No fatal cases have been described in the subsequent chronic phase of the disease for many decades.[26]

Carrion's disease has a very limited geographic distribution, with most cases having been reported in arid areas at 500 to 3,000 m above sea level in the Peruvian Andes between southwestern Colombia and central Peru,[27] where ecological conditions for the development of *L. verrucarum* are found.[28] However, in the last 150 years, the epidemiology of the disease has changed due to climate change and increased migration into and out of the areas of endemicity.[29-32] It is now affecting new habitats and is reported to occur sporadically in Guatemala, Bolivia, and Chile, at low elevations in Colombia and at an arid coastal province in Ecuador.[33] It is thought that El Ninõ events, which cause a warming in sea temperature every 5–7 years, favorably affect vectors due to a change in climatic conditions.[26,30]

B. bacilliformis is responsible for the most dramatic recorded outbreak of human disease that occurred from 1869 to 1873, when 8,000 of 10,000 mostly nonlocal workers, involved in the construction of the Oroya railway through a region of endemicity (the foothills of Andes Mountains of Peru) died from Oroya fever.[34] For a long time it was reported that foreigners developed the acute febrile form of the disease while natives in endemic areas rarely suffered from Oroya fever but frequently developed verruga peruana without prior haemolytic anemia.[35,36]

A prospective study in the national hospital Cayetano Heredia in Peru has shown that 58.8% of the 145 patients with Oroya fever were in fact born in areas of endemicity. Seroepidemiological studies in areas of endemicity have shown that more than half of the human population (45-77%) may harbor antibodies against *B. bacilliformis*, while 10-15% of them bear asymptomatic bacteremia, serving as reservoirs for infection. Young children are the most affected people in endemic areas, likely due to the presumed protective immunity that develops after repeated infections.[24] Although the mortality among inpatients is currently low, it remains variable in new affected areas and can be high among persons lacking endemic exposure.

Bartonella quintana

B. quintana is globally distributed and is transmitted by the human body louse (*Pediculus humanus corporis*).[37] It is well known that infected body lice excreta on human skin cause pruritis, and skin breakdown that follows scratching allows *B. quintana*, present at high concentrations in the feces of infected lice, to enter the body.[37] People are the only known animal hosts and are probably the natural reservoirs for *B. quintana*. It is the causative agent of trench fever, a louse-borne disease that was widespread in armies of the modern era. *B. quintana* was detected in the mortal remains of soldiers of Napoleon's Grand Army in Vilnious, Lithouania.[38] The majority of the 500,000 soldiers who started the Russian campaign died of dysentery, pneumonia or fever. It is estimated that of the 25,000 soldiers who reached Vilnius, only 3,000 survived. Many were infected with louse-transmitted diseases. *B. quintana* caused large epidemics in Europe during World War I and II,[37,39-40] since it affected approximately 800.000 allied soldiers in France during World War I[41] and a smaller number in World War II. The introduction of louse control measures by armed forces decreased considerably the incidence of trench fever, which was thought to no longer be a threat.[42,43] Toward the end of the twentieth century, however, *B. quintana* reemerged as the cause of chronic bacteremia and endocarditis, termed "urban trench fever" among alcoholics, drug addicts and homeless people, who are at higher risk of human body louse exposure.[44-48]

An outbreak of bacteremia due to *B. quintana* was reported in Seattle, Washington, in 1994 and subsequent studies have shown that the seroprevalences of antibodies against *B. quintana* are high in homeless people in both the United States and Europe. A 1997 study at the emergency departments of the university hospitals of Marseille, France demonstrated that the blood of 14% of homeless people was found to be positive by culture, and half of these people had chronic bacteremia without fever. Serology showed that 30% had specific antibodies to *B. quintana*, and the DNA of the organism was detected in lice from three homeless patients.[45-46,49-50]

Trench fever is characterized by an intraerythrocytic bacteremia with recurrent, five-day cycling fever (periodical feverish relapses), severe headache and pretibial pain. The acute signs usually resolve spontaneously, but they may recur after about 5 days. In

some patients there may be six or more recurrences of the disease. Relapses may occur many years after the initial illness or the patients may be bacteremic but have no clinical signs. The prolonged bacteremias that present in *B. quintana* infections may be associated with the development of bacillary angiomatosis (BA) and endocarditis.[51] BA is a vasoproliferative disorder characterized by cutaneous manifestations of vascular tumors of the skin and subcutaneous tissues, including single or multiple discolored cutaneous nodules, hyperpigmented lichenoid plaques and subcutaneous nodules with the potential to ulcerate. It often occurs in immunocompromised individuals, especially human immunodeficiency virus (HIV)-infected patients.[52] The lesions are often indistinguishable from those observed in the Carrion's disease and resemble pyogenic granulomas, hemangiomas, or Kaposi's sarcoma.[53]

The vasoproliferative infection is usually progressive and fatal unless treated by antibiotic therapy. Bacillary peliosis, often occurring in conjunction with BA, is also characterized by angiogenesis and involves dissemination of infection to the reticuloendothelial organs, the most common of which is the liver (peliosis hepatis) and spleen.

Bartonella henselae

Domestic and feral cats (*Felis catus*), the primary vertebrate reservoir hosts of *B. henselae*, become infected when skin abrasion, scratch wounds or flea bite sites are contaminated with feces from *B. henselae* infected fleas.[54-57] During periods of cats' intraerythrocytic bacteremia, cat fleas (*Ctenocephalides felis*),[56] the primary arthropod vector for *B. henselae*, acquire infection through blood meal and shed infectious organisms in their feces.[58-61] Among cats, casual or sexual contact, sharing of food or water dishes are not significant sources of exposure. Studies have shown that cats younger than one year old (kittens),[62] cats from shelters or adopted as strays are more prone to carry the infection due to a higher probability of being bacteremic.[63,64] Once a cat has been infected, bacteremia can last for weeks to months and the number of bacteria in the blood can fluctuate greatly during this time.[65] Humans may become infected through intradermal inoculation of bacteria in either cat saliva or flea feces lodged in under claws at an open wound, such as a scratch or a bite.

Naturally-infected cats are usually asymptomatic, although they may suffer from lymphadenitis, gingivitis, and stomatitis, and are predisposed to urological diseases. Cats experimentally inoculated with *B. henselae* experience nonspecific febrile illness, transient anemia and lymphadenopathy.

Although cats are the major reservoir for *B. henselae*, some patients deny the possibility of a cat scratch or bite wound or indicate no contact with cats. The transmission is probably achieved by other animal hosts or arthropod vectors. Dogs are suggested to represent a reservoir for *B. henselae*[66] as the pathogen was found to be the causative agent in a case of human osteomyelitis following a dog scratch. Furthermore, a *B. henseale* seroreactive dog owner suffering from lymphadenopathy was reported and *B. henselae* DNA was amplified from gingival swabs of the dog.[67-68] Transmission by other arthropods, in particular ticks, has also been suggested. *B. henselae* DNA was detected in *Ixodes pacificus* and *I. persulcatus* ticks in North America and Eastern Europe, respectively,[69-71] and in *I. ricinus* and *Dermacentor* ticks feeding on people or domestic animals in Central Europe.[72-75]

B. henselae has a worldwide distribution with cases of Bartonella infection reported in the United States,[76-78] Europe (France,[79,80] Germany,[81] Switzerland,[82] Spain,[83] Italy,[84] Greece,[85-92] The Netherlands,[93-95] and the United Kingdom[96]), Japan[97-99], New Zealand,[100] Israel[101] and Australia.[102] It was estimated at the end of the 20th century that 22,000 cases of CSD may appear every year in the United States, and roughly 10% of these were considered to require hospitalization.[44] Serologic studies indicate that the rate of bacteremia and the prevalence of antibodies against *B. henselae* are higher in infected cats living in warm, humid climates.[54] These climatic conditions increase the prevalence and intensity of cat flea infestations.

Cat scratch disease (CSD) was first described in 1950 by the French physician Debré in patients suffering from suppurative lymphadenitis following cat scratches.[103] Although CSD may occur in people of any age, most patients are under 18 years of age, perhaps because children are more likely to have close and rough contact with cats. The incidence of CSD is seasonal, with most cases occurring in fall and winter (onset of most CSD cases between September and January)[53] as it has been described in the United States,[44,104] Japan[98] and France.[105] Seasonal variation is usually attributed to the temporal breeding patterns of domestic cats, the acquisition of kittens as family pets, the peak temporal presence of the cat flea and the fact that during summer cats spend most time outside the house, whereas during autumn they stay indoors.[106] The prevalence of the disease also varies with the geographic location. Incidences of CSD have been found to directly correlate with increasing climate temperature, which leads to the increase of the number of fleas.

Initially, 3-10 days after inoculation, CSD presents as one or more, small, reddish-brown, erythematous papules, pustules or macules at the site of scratch or bite. These lesions gradually disappear and may be mistaken for insect bites. Within 1-3 weeks after exposure, regional lymphadenopathy, the predominant clinical feature of CSD, occurs proximal to the inoculation site, most frequently affecting the axillary and epitrochlear nodes (46%), head and neck (26%) and the groin (17,5%) that drain the primary inoculation site.[76] The lymph nodes are often tender, painful and movable with solid consistency. In 20-30% of patients, inflamed lymph nodes produce suppuration with purulent fistulas to the skin and approximately 10% of nudes require drainage.

CSD is one of the most common causes of benign regional lymphadenopathy in children and adults[53] and may require aggressive assessment to rule out more serious causes of lymphadenopathy such as lymphoma. Other less prevalent symptoms of CSD include a low grade fever, malaise, anorexia, headache, splenomegaly, pharyngitis, conjunctivitis and arthralgia.[53] In addition, dermatologic manifestations, such as macular or papulovesicular rash, urticaria eruptions, erythema annulare, erythema nodosum[76] and leukocytoclastic vasculitis[107] have been observed.[108]

Atypical CSD manifests in 5-25% of immunocompetent patients and involves various organs such as the eyes, liver, spleen, central nervous system, skin and bones. Unusual manifestations of CSD include Parinaud's oculoglandular syndrome, encephalitis,[109] hepatosplenic granulomas,[110,111] osteomyelitis[95,112] and pulmonary disease.[113,114]

Parinaud's ocular syndrome (POS), the most common form of atypical infection, follows contamination of the eye, often from the patient's own hand. It occurs in approximately 5% of all CSD cases[76] and is characterized by conjunctival granuloma together with preauricular, submandibular or cervical lymphadenopathy.[115] Typical symptoms include foreign body sensation, unilateral eye redness, serous discharge and increased tear production.[89]

Neuroretinitis, another optical manifestation of atypical CSD, manifests as painless acute onset of unilateral visual field loss in association with optic nerve edema and stellate exudative macular lesions. [115,116] Symptoms of POS and neuroretinitis typically resolve with full recovery of vision within several months with or without antibiotic treatment. However, some patients may present with mildly decreased visual acuity and abnormal color vision or contrast sensitivity.[117]

Encephalopathy accounts for 1-7% of CSD cases and presents as acute onset of severe headache, confusion, seizure or coma, 1-6 weeks after the classic symptoms.[118-122] Typically, in immunocompetent patients, the course of CSD is self-limited and the majority of cases resolve in 6 to 12 weeks in the absence of antibiotic treatment.

In infected patients, the organisms are found most commonly in vessel walls, in macrophages lining the sinuses of lymph nodes, in nodal germinal centers, in non-necrotic areas of inflammation and in areas of expanding and suppurating necrosis.[114,123] With hematoxylin and eosin stains, the primary inoculation lesion of CSD reveals small areas of frank necrosis surrounded by concentric layers of histiocytes, lymphocytes and nucleated giant cells. Electron microscopy of infected lymph node tissues confirms that the bacteria have a high affinity for the vascular epithelium, with organisms seen in clumps in vessel walls, intracellularly and free in necrotic debris.[124]

The clinical presentation and severity of CSD can be quite different among immunocompromised patients (HIV or HCV patients, individuals of decreased immunity system response, organ transplant recipients). These patients present with disseminated, often tissue-invasive forms of CSD which have the potential to be life-threatening. Systemic bartonellosis manifests as BA, bacillary parenchymous peliosis and persistent bacteremia with recurrent fever.

Clinical manifestations

The clinical manifestations of *Bartonella* infection are expanding with the improved ability to recognize the presence of the bacteria.

1) Bacteria-induced neoangiogenesis: bacillary angiomatosis (BA), peliosis hepatis

BA, the most common sequelae of *B. quintana* and *B. henselae* infections, is a vascular proliferative disorder that was originally described as involving the skin and regional lymph nodes of HIV-infected persons.[52] BA has also been described in immunosuppressed transplant recipients and in patients receiving cancer chemotherapy.[125-128] The most apparent symptom is one to hundreds of cutaneous papules and nodules on the external skin surface.[56,113,125,129] The lesions may also be found in the gastrointestinal tract and the genitourinary system and in a variety of other internal organs including liver, heart, spleen, bones and central nervous system.[130,131] *Bartonella* spp. are observed in close association with proliferating endothelial cells and bacterial eradication by antibiotic treatment results in tumor regression.[132] The differential diagnosis for BA includes Kaposi's sarcoma, epithelioid hemangioma and pyogenic granuloma. The increased use of proph-

ylactic drugs in immunocompromised patients with *Bartonella* infection decreases the incidence of BA.

It is speculated that *Bartonella* species cause vascular proliferation by three mechanisms which may act synergistically: i) triggering the proliferation of endothelial cells, ii) inhibition of endothelial cell apoptosis and iii) angiogenic reprogramming of infected host cells. The activation of hypoxia-inducible factor 1 (HIF-1), a transcription factor involved in the induction of angiogenesis and subsequent secretion of angiogenic cytokines (vascular endothelial growth factor, VEGF), seems to regulate this bacteria-induced angiogenic gene program. VEGF, which is secreted by macrophages, may act as an inducer of endothelial cells proliferation and angiogenesis.[133]

The exact incidence of BA is not known, but the disease has been reported in almost all United States of America, especially in those with high frequency of HIV infection (e.g. New York, Florida, Texas and North California). It is reported less commonly in Europe than in North America, which may imply that either diagnoses are missed or that Europe has a minimal reservoir of bacilli. Cases have also been reported in Africa, Peru, Argentina, Brazil,[134,135] Turkey,[136] Saudi Arabia,[137] Thailand[138] and Australia.[139]

Peliosis hepatis is characterized by vascular proliferation of sinusoidal hepatic capillaries, which can result in multiple cystic blood-filled cavities distributed randomly throughout the liver parenchyma. It can also affect the spleen,[140] abdominal lymph nodes and bone marrow, and typically presents with prolonged fever with abdominal pain, usually described as episodic dull pain over the periumbilical and/or upper quadrant regions with high severity.[141,142] Other presenting symptoms include weight loss, nausea, vomiting, diarrhea, chills, headache and myalgia. The prevalent lesion on histologic examination of biopsy specimen is a necrotizing granuloma. The low incidence of nodal involvement in hepatic disease may be due to bacteria transmitted via the hands by ingestion. This disorder can mimic other hepatic masses, such as hemangioma, hepatocellular carcinoma, abscess, metastasis, adenoma and focal nodular hyperplasia.

2) Endocarditis

Chronic, blood-negative endocarditis occurs most often in people with pre-existing abnormalities of the heart valves. Fever is usually present (90%), a vegetation is observed via echocardiography (90%) and >90% of patients require valvular surgery.[143] It causes significant destruction of the valves characterized by mononuclear cell inflammation, extensive fibrosis, large classification and small vegetations.[144] Most cases of *Bartonella* endocarditis involve native valves,[145] but infection of prosthetic valves is possible. Previous valve lesions predispose an individual to endocarditis with non-human *Bartonella* species, with *B. quintana* endocarditis being more frequently diagnosed in patients without previous heart diseases. Known risk factors are alcoholism, homelessness and body lice infestation. Blood samples from most patients with *B. henselae*-associated endocarditis yield no growth of the organism in bacteriologic culture but yield positive results for *B henselae* via DNA amplification.[143] The DNA of *B. henselae* and *B. quintana* were detected in the cardiac tissue of 4 young Swedish orienteers that died suddenly and unexpectedly as a result of cardiac conditions.[146]

3) Dermatologic manifestations

Except from the brown-reddish papules seen at the site of inoculation, other skin lesions including maculopapular and urticarial eruptions, granuloma annulare, erythema nodosum, erythema marginatum and leukocytoclastic vascultis occur in ~ 5% of patients infected with *B. henselae*.[108]

4) Neurologic manifestations

Neurologic complications of *B. henselae* infection are rare, occurring in 2-4% of infected patients. The most common presentation is encephalopathy, accounting for 90% of cases that affect the nervous system. Neurologic symptoms, generally occurring 2 to 3 weeks after the onset of lymphadenopathy, include headaches, mental status changes and seizures. Patients with encephalopathy may present with weakness, alterations in tone and hyporeflexia or hyperreflexia. *Bartonella* infections of the central nervous system have also been proposed as a cause of meningitis and neuropsychiatric deterioration in HIV-infected patients.[6,147]

5) Rare manifestations

Hematologic complications of *B. henselae* are rare. Hemolytic anemia has been reported in both adults and children.[148,149] In children, there have been several cases in the literature of *Bartonella* resulting in thrombocytopenic purpura.[15] *Bartonella* has also been reported to be associated with development of lupus anticoagulant and prolongation of the activated partial thromboplastin time.[151]

Bone lesions are a rare complication of *B. henselae* infection. These lesions are osteolytic, and occur as an osteomyelitis. Clinical manifestations include pain and tenderness over the affected bone and lymphadenopathy, which frequently occurs distant from the site of osteomyelitis, suggesting that bony infection occurs by hematogenous or lymphatic spread.[95] Infec-

tions have been reported in the skull, sternum, vertebrae, ckavicles, humerus, femur, tibia, acetabulum, metacarpals and metatarsals.[95,152-155] Biopsy reveals necrotizing granulomas in the infected bones with adjacent abscesses.[156] Rheumatoid factor-negative arthritis/arthragia was observed in ~3 % of cases of *B. henselae* infection.[157,158] Factors significantly associated with arthropathy were female gender, age >20 years and erythema nodosum while the more frequently affected joints were the knee, wrist, ankle and elbow.[159]

Renal complications of *B. henselae* infection are uncommon, with glomerulonephritis being the most frequently encountered. It presents with gross or microscopic hematuria, low-grade proteinuria, and cola-colored urine, often accompanied by fever and lymphadenopathy. The renal disease can present as immunoglobulin A (IgA) nephritis, acute postinfectious glomerulonephritis or necrotizing glomerulonephritis.[160-164]

Pneumonia or pleural thickening and/or effusion associated with Bartonella infection occur rarely, 1 to 5 weeks after the appearance of lymphadenopathy.[165]

In children, *B. henselae* infection is one of the common causes of **prolonged fever of unknown origin (FUO)** that lasts for >2 weeks with no diagnostic signs or symptoms of an obvious clinical disease.[97,166] *B. henselae* is identified as the third leading infectious cause of FUO, following Epstein-Barr virus infection and osteomyelitis.[167] The absence of lymphadenopathy in patients with CSD was closely related to the presence of persistent fever, FUO or systemic complications. Thirty of 186 patients with a serological diagnosis of CSD had no regional lymphadenopathy, but they presented with persistent fever and more frequent systemic complications than patients with lymphadenopathy.[168]

6) Pseudomalignancy

B. henselae infections may mimic various malignancies.[53] Infection simulating lymphoma is one of the most frequently reported, especially with lymphadenopathy in the neck and abdomen.[169,170] Recently, *Bartonella* has been reported to mimic post-transplant lymphoproliferative disease in children who have undergone renal transplantation.[171] There are several reports in the literature in both adults and children of Bartonella infection presenting as a solitary mass in the breast.[172-174] Although not a malignant process, a recent case series also suggests an association of *B. henselae* with Kikuchi's disease, or histiocytic necrotizing lymphadenitis, in children.[175] In adults, *B henselae* has presented similarly to pancreatic or biliary malignancy,[176] pharyngeal cancer,[177] and vascular neoplasms.[178]

Laboratory diagnosis of *Bartonella* infections

As there are no sufficiently specific criteria or clinical features that prove the CSD etiology in patients with lymph node enlargement, especially among a wide variety of potential differential diagnoses, laboratory testing is required for the confirmation and the definitive diagnosis of *Bartonella* infection. A variety of methods has been employed including histological examination, isolation and culturing of *Bartonella* spp., molecular and serological approaches.

Bartonella infection may result in normal or mildly elevated white blood cell counts and normal, elevated or diminished platelet counts. The erythrocyte sedimentation rate may be normal or elevated. CSF and liver enzymes examination typically yields normal results.[53]

According to Bergmans et al., a diagnosis of CSD usually requires three of the following four criteria: (i) a history of contact with a cat and the presence of a scratch or primary lesion of the skin, eye or mucous membrane, (ii) a positive cat scratch skin test reaction, (iii) negative laboratory testing for other causes of lymphadenopathy and (iv) characteristic histopathological findings in a lymph node biopsy specimen or at a site of systemic involvement.[93]

Intradermal skin test relies on a delayed-type hypersensitivity reaction within 48 hours of inoculation with *B. henselae* antigen. The test had a specificity of 99% with minimal cross-reactivity with other organisms.[76] The test is no longer recommended, however, because different antigens had great variance in reactivity, there was concern over the safety of human-derived reagents and there was luck of antigen availability.[53]

Bacterial culturing of blood or tissue samples is impractical and unreliable due to the fastidious nature of the organisms, the prolonged incubation period and the highly specific conditions they require for optimal growth. It is well known that Bartonella spp. have peculiar and demanding nutritional requirements such as the apparent inability to utilize glucose as the carbon source. Typically, the bacteria are grown in vitro on sheep blood or chocolate agar plates under 5% CO_2 atmosphere, and this may easily take several days or even weeks with primary isolates for visible colonies to appear. To overcome these problems, there have been attempts to establish liquid growth media and growth conditions which improve isolation and also have great value for basic research. Attempts to isolate *Bartonella* spp. are driven by clinical picture, but the wide spectrum of manifestations and the non-specific symptoms of *Bartonella* infections are not distinctive enough to inform the laboratories that

special cultures are needed. Since most isolates require more than 7 days (2-6 weeks) of incubation before they can be detected,[179] culture is not routinely recommended for diagnostic purposes. Additionally, it has been found that successful isolation of *Bartonella* spp. from the blood or tissues of infected immunocompetent patients is rare in the absence of systemic disease.[106] For example, *B. henselae* can be isolated from immunocompromised patients with endocarditis, BA, peliosis hepatis and relapsing fever, which result from bacterial invasion and proliferation. On the contrary, the pathogen is rarely isolated from specimens of immunocompetent patients with CSD, since the lymphadenopathy and other pathologic manifestations of CSD are considered secondary to a cell-mediated immune response against *B. henselae* antigenic components. Thus, culture for *Bartonella* bacteria is not recommended for routine cases of patients with CSD lymphadenopathy.

Specimen handling, media selection and growth conditions all may affect results and must be optimized in order to provide the highest likelihood of identifying the organism. Colonies of *Bartonella* spp. are of two morphologic types, which are usually present in the same culture. The degree of colony heterogeneity varies by species and by strain. *B. henselae* is typically characterized by a greater proportion of rough colonies than *B. quintana*. Repeated subcultures of *B. henselae* tend to have increasing proportions of smooth colonies. A novel chemically modified liquid medium supports the growth of 7 *Bartonella* species.[181] Minced tissues may be cultured on chocolate agar plates in a humid atmosphere with carbon dioxide to facilitate growth. Culture methods have improved over the past decade demonstrating increased sensitivity, but still require prolonged periods before isolation of the organism. Since culturing of *Bartonella* spp. is difficult and time-consuming, alternative means of identifying the infectious agent are important.

Microscopic evaluation of infected tissue using a Warthin-Starry silver impregnation strain[182] or a Brown-Hopps tissue Gram stain, immunohistochemistry and transmission electron microscopy has been utilized to detect Bartonella spp., which appear as pleomorphic bacilli in clumps or as single forms. Staining with murine monoclonal antibodies to detect the intracellular bacteria directly has also been used either solely or in conjunction with Warthin-Starry staining. However, the silver stains are cumbersome and expensive to perform, and difficult to interpret due to the background of silver precipitate in necrotic material and within macrophages.

The histopathologic findings in lymphadenopathy associated with CSD are nonspecific and often depend on the stage of the disease. Thus, histological examination at an early stage of the disease shows only lymphoid hyperplasia and arteriolar proliferation and cannot differentiate between several infections that cause the development of granulomas.[76,106] A typical CSD histology demonstrates a granuloma with central necrosis, multinucleated giant cells, histiocytes, lymphocytes, plasma cells and stellate micro abscesses. Histopathology is suggestive but not diagnostic and remains impractical because of its invasive nature.

PCR technique is a highly specific and rapid method for definitive species identification in the diagnosis of *Bartonella* spp. infections. The genes and genetic loci most commonly targeted in diagnostic PCR assays and phylogenetic analyses include the 16S rRNA-encoding gene,[183] the citrate synthase gene (gltA),[184] the high-temperature requirement A gene (htrA), the 16S/23S intergenic spacer region (ITS),[181,185] the cell division protein-encoding gene (ftsZ) and the 60 kDa heat-shock protein-encoding gene (groEL). Amplification of *Bartonella* spp DNA from skin, lymph nodes, granulomatous lesions, osteolytic lesions or less frequently from other organ biopsies or in leukoclastic vasculitis has been often reported in patients suffering CSD or BA. Advancements in PCR methodology using real-time PCR or quantitative PCR in the place of conventional PCR have led to decreased risk of carryover contamination and increased quantitative capability, speed, simplicity and reproducibility.[186] Pitfalls of the use of PCR include variable sensitivity, ranging from 43 to 76%, and the need for highly specialized equipment and personnel. In addition, the detection of the causative agent of CSD or other manifestations of *Bartonella* infections by histology or PCR requires invasive procedures to obtain clinical material (biopsy, fine needle aspiration). PCR analysis of blood specimens offers a minimally invasive approach to diagnosis, but clinical data are scarce and further studies are needed.

Serological testing for *B. henselae* antibodies is a more practical means of laboratory diagnosis because it avoids invasive sample collection, use of specialized equipment and techniques and long incubation periods.[106] The indirect immunofluorescent assay (IFA), using whole-cell antigen from *Bartonella* co-cultivated with Vero cells, has proven the most commonly employed highly sensitive and specific serologic assay for the detection of *Bartonella* spp.[6,187,188] Commercially prepared antigen slides are now available for *B. henselae* and *B. quintana* serology in the diagnosis of CSD. The enzyme-linked immunosorbent assay (ELISA) is used routinely as well. Sensitivities of these methods vary from one laboratory to another, since they use different antigens, test procedures and cut-

offs, and range from near 100% to less than 30%. Accurate diagnosis of CSD is necessary because the presentation and course of the disease may resemble more severe diseases such as malignant tumors or mycobacterial infections.

Serologic tests, although more sensitive than culture, lack specificity because many asymptomatic persons have positive serology because of previous, often asymptomatic exposure. The percentage of the general population that has a positive serologic test varies widely, but appears to be higher in cat owners.[97]

An immunoglobulin (Ig) M titer of >1:24 or greater is indicative of acute *Bartonella* infection, but anti-*B. henselae* IgM response disappears within approximately 100 days after the onset of the symptoms. Although the short duration of IgM antibodies makes them infrequently discovered on serology, the negative results do not exclude acute disease. High IgG titers of >1:64 are strongly suggestive of recent infection, and a four-fold or greater rise in IgG titer between acute and convalescent serum samples is confirmatory of infection. Titers between 1:64 and 1:256 represent possible infection and the results are equivocal. Since IgG antibodies may be detected for more than two years after inoculation, it is difficult to diagnose the active infection compared to the previous one.[53,104] Since IgM Abs are detectable earlier and for a shorter period (~100 days after exposure) than IgG (~22-28 weeks after inoculation), the moment of sampling is of great importance. The first symptoms of infection occur relatively late, often after more than 8 weeks from infection onset; therefore IgM antibodies may not be detectable in many patients at the time of testing. A titer of 1:800 or more for IgG antibodies to either *B. henselae* or *B. quintan*a has a positive predictive value of 0.810 for the detection of chronic bartonellosis in the general population and a value of 0.955 for the detection of bartonellosis among patients with endocarditis.[187] Additionally, patients with delayed decreases in antibody titers may be at risk for endocarditis relapse. When clinical suspicion is high, titers should be repeated in 10-14 days for comparison.[92]

Though these serological methods are widespread and efficient, they present variable sensitivity and specificity, inability to distinguish between active versus prior infection and lack of *Bartonella* species-specific antibody response, resulting in cross-reactivity.[106]

The low specificity of *B. henselae* IgG detection is related to high seroprevalence, reported up to 66%, in the normal population.[189] Anti-*B. henselae* IgG antibodies are found in sera from patients with CSD, but they are also found in 2 to 6% of the healthy control sera and in 29% of sera from healthy family members of CSD patients. Cut off values for the serologic assays are set by determining antibody titers in healthy blood donors. In limited cases, individuals infected with *Bartonella* spp. never mount a detectable antibody response, while others remain seropositive for years after exposure and recovery from the illness. Despite this, serology remains the most practical diagnostic tool in the laboratory detection of *B. henselae* infection.

Immunological cross-reactivity is a result of conserved epitope recognition across species. A serological cross-reaction between a *Bartonella* species and a heterologous pathogen was published in 1976, when *Coxiella burnetii* sera was found to cross-react with *Rochalimaea* (later *Bartonella*) *quintana* antigen in the diagnosis of trench fever using a passive hemagglutination test.[190] Numerous reports have documented cross-reactivity in serologic assays between *Bartonella* and other heterologous agents, including Gram-positive and negative bacteria as well as viruses, such as *Afipia felis, Anaplasma phagocytophila, Brucella* spp., *Borrelia* spp., *Mycoplasma pneumonia, Chlamydia pneumonia, C. psittaci, C. trachomatis, Coxiella burnetii,* Cytomegalovirus, Ebstein-Barr virus, *Ehrlichia canis, Orientia tsutsugamushi, Bordetella pertussis, Treponema pallidum, Rickettsia conorii, R. prowazekii, R. rickettsii* and *R. typhii*.[191-202] Cross-reactions among the different species of the genus *Bartonella* have been documented in numerous studies. Elevated titers to both *B. henselae* and *B. quintana* are frequently found in the serologic analyses of suspected or confirmed CSD patient sera. Studies employing serologic assays other than the IFA, such as EIA and immunoelectrophoresis, have also reported significant cross-reactivity for these antigens.

Treatment

The therapeutic approach to *Bartonella* infection varies on the basis of the clinical manifestations and immune status of the patient.

Typical CSD is a self-limited illness that resolves within 2 to 6 months, and usually does not respond to antibiotic treatment. For mild-to-moderate infections in immunocompetent patients, management consists of reassurance, adequate follow-up and analgesics for pain.[203] Most studies show no benefit to antibiotic therapy in CSD, except from 2 studies that have revealed a decrease in the mean duration of illness on patients treated with rifampin, ciprofloxacin, gentamicin, trimethoprim-sulfamethoxazole and azithromycin.[10,77] Because of the natural history of uncomplicated CSD, and the risk of adverse effects of antibiotics and the evolution of resistant flora, antibiotics are not suggested for regional CSD.

For patients with significant lymphadenopathy, treatment with azithromycin at doses of 10 mg/kg on day 1 and 5 mg/kg per day on days 2 to 5 can be considered. Other antibiotic options include rifampicin (20 mg/kg per day divided in 2 doses for 2–3 weeks), ciprofloxacin (20–30 mg/kg per day in 2 daily doses for 2–3 weeks), or trimethoprim-sulfamethoxazole (trimethoprim 10 mg /kg per day in 2–3 daily doses for 7–10 days or trimethoprim 8 mg/kg per day, sulfamethoxazole 40 mg/kg per day, in two divided doses).[204]

As the clinical spectrum of disease caused by *B. henselae* expands, choosing the proper treatment of these conditions becomes more difficult. The current knowledge of the treatment of neuroretinitis, encephalopathy, hepatosplenic disease, endocarditis and bacillary angiomatosis is derived from case studies rather than randomized trials.[53]

For neuroretinitis, doxycycline is preferred because of its excellent intraocular and central nervous system penetration. For children <8 years of age in whom tooth discoloration is a concern, erythromycin may be substituted for doxycycline.[115] When coupled with rifampin, they promote disease resolution, improve visual acuity and decrease optic disk edema.[117] On the contrary, it is suggested that no antibiotic therapy is necessary since neuroretinitis is a self-limited disease with excellent prognosis for complete visual recovery.[205]

In *Bartonella* encephalopathy, doxycycline is combined with rifampin because of their strong penetration into the central nervous system.[13] In hepatosplenic disease, gentamicin, trimethoprim-sulfamethoxazole, rifampin and ciprofloxacin have been shown to be effective.[142,206] Due to the rapid development of rifampicin resistance, some experts recommend adding a second agent, such as gentamicin or azithromycin.[204]

Patients with *Bartonella* endocarditis have a higher death rate and undergo valvular surgery more frequently than patients with endocarditis caused by other pathogens.[187] Their recovery rate was higher when gentamicin was used in combination with ceftriaxone or doxycycline.[13,207-208] Patients with suspected or confirmed Bartonella endocarditis should be treated with 3 mg/kg/day gentamicin for 2 weeks in combination with 200 mg of doxycycline daily for 6 weeks.[51]

Immunocompromised individuals may develop severe disease but their response to antibiotics is usually significantly more dramatic than in immunocompetent ones. Systemic *Bartonella* infection has been successfully treated with β-lactam antimicrobials while bacillary angiomatosis with erythromycin, doxycycline, isoniazid, clarithromycin, azithromycin and rifampin.[209,210]

Table 1 Reservoirs, vectors and geographic distribution of *Bartonella* spp.

***Bartonella* spp.**	**Year of discovery**	**Year of first cultivation**	**Reservoir**	**Vector**	**Geographic distribution**
B. bacilliformis	1909	1919	Humans	Phlebotomines (Lutzomya verrucarum)	Peru, Ecuador, Colombia, Bolivia, Chile, Guatemala
B. quintana	1914	1961	Humans	Human body lice (Pediculus humanis corporis)	worldwide
B. henselae	1950	1990	Cats	Fleas (Ctenocephalides felis)	worldwide

Table 2 Human diseases caused by *B. bacilliformis, B. quintana* and *B. henselae.*

***Bartonella* spp.**	**Human diseases**	
	Immunocompetent hosts	**Immunocompromised hosts**
B. bacilliformis	Carrion's disease acute form: Oroya fever chronic form: verruga peruana	
B. quintana	trench fever chronic bacteremia endocarditis	chronic adenopathies bacillary angiomatosis
B. henselae	cat scratch disease bacteremia neuroretinitis encephalopathy	bacillary angiomatosis hepatis peliosis endocarditis (previous valvulopathy)

Table 3 List of media used, incubation conditions and growth description of *B. henselae*.[180]

Medium	Incubation conditions	Growth description
Biphasic medium (BM)	37°C, 5% CO_2, high humidity	Broth medium: abundant growth, dense granular turbidity, no pigmentation Solid medium: circular, smooth surfaced, whitish translucent colonies (1-3mm)
Tryptic soy broth (TSB)		abundant growth, dense granular turbidity, no pigmentation
Tryptic soy agar (TSA) with 5% sheep blood		circular, smooth surfaced, iridescent, viscid, non haemolytic, autoadherent, not embedded in the medium colonies (1-3mm)
Brain heart infusion agar (BHIA) with 5% sheep blood		circular, smooth surfaced, iridescent, viscid, non haemolytic, autoadherent, not embedded in the medium colonies (1-3mm)
Blood agar (BA) with 5% sheep blood	37ºC, 3% CO_2	no growth
MacConkey agar	37ºC	no growth

Table 4 Treatment of *Bartonella* spp. infections.[7,13]

Clinical manifestations	Treatment	Duration of treatment
Typical CSD – Lymphadenitis [211]	No treatment	
Atypical CSD - Neuroretinitis [117,212]	Doxycycline (200 mg/day) and rifampicin (600 mg/day)	4-6 weeks
Atypical CSD - Hepatosplenic [142]	Rifampicin (20 mg/kg/day) alone or with gentamicin (3 mg/kg/day)	4-6 weeks
Oroya fever [13,22,24,26]	Chloramphenicol 50 mg/kg/day for 3 days and then 25 mg/kg/day for 11 days	2 weeks
Verruga peruana [13,22,26,211]	Rifampicin (10 mg/kg/day) or Streptomycin (15-20 mg/kg/day)	2 weeks 10 days
Trench fever or chronic bacteremia [50,214]	Gentamicin (3 mg/kg/day, 2 weeks) and doxycycline (200 mg/day, 4 weeks)	6 weeks
Endocarditis [51,208]	Gentamicin (3 mg/kg/day, 2 weeks) and doxycycline (200 mg/day, 6 weeks)	8 weeks
Bacillary angiomatosis [13,52,114,215]	Erythromycin (2 g/day) or doxycycline (200 mg/day)	3 months
Peliosis hepatis [13,52,114,215]	Erythromycin (2 g/day) or doxycycline (200 mg/day)	4 months

Περίληψη

Λοιμώξεις από *Bartonella*: κλινικές εκδηλώσεις, διαγνωστικές τεχνικές και θεραπεία

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Τα είδη *Bartonella* spp. αποτελούν Gram-αρνητικά βακτήρια που είναι υπεύθυνα για αρκετές αναδυόμενες και επανεμφανιζόμενες ασθένειες σε όλο τον κόσμο. Η πλειοψηφία των λοιμώξεων στον άνθρωπο προκαλείται από την *Bartonella henselae*, την *Bartonella quintana* και την *Bartonella bacilliformis*. Οι κλινικές εκδηλώσεις της λοίμωξης από *Bartonella* κυμαίνονται από ήπια και αυτοπεριοριζόμενη μέχρι απειλητική για τη ζωή ασθένεια, η οποία πρέπει να αντιμετωπίζεται με την κατάλληλη αντιμικροβιακή αγωγή. Η σοβαρότητα των λοιμώξεων σχετίζεται άμεσα με την ανοσολογική κατάσταση των ασθενών. Λόγω βελτίωσης των διαγνωστικών τεχνικών, το φάσμα των κλινικών εκδηλώσεων της νόσου έχει επεκταθεί και περιλαμβάνει την περιφερειακή λεμφαδενοπάθεια, τη βακτηριαιμία, τον πυρετό αγνώστου αιτιολογίας, την ενδοκαρδίτιδα, τη βακτηριακή αγγειωμάτωση και την ηπατική πελίωση. Σε αυτή την ανασκόπηση συνοψίζονται οι τρέχουσες γνώσεις σχετικά με τη μικροβιολογία, τις κλινικές εκδηλώσεις, τις διαγνωστικές τεχνικές και τη θεραπεία των λοιμώξεων από *Bartonella*.

Λέξεις κλειδιά
Bartonella, λεμφαδενοπάθεια, βακτηριακή αγγειωμάτωση πελίωση ήπατος, ανοσοφθορισμός, θεραπεία

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