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STATE-OF-THE-ART REVIEW ARTICLE

Beyond Cat Scratch Disease: Widening Spectrum of *Bartonella henselae* Infection

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ABSTRACT

Bartonella henselae was discovered a quarter of a century ago as the causative agent of cat scratch disease, a clinical entity described in the literature for more than half a century. As diagnostic techniques improve, our knowledge of the spectrum of clinical disease resulting from infection with *Bartonella* is expanding. This review summarizes current knowledge regarding the microbiology, clinical manifestations, diagnostic techniques, and treatment of *B henselae* infection.

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Key Words
Bartonella, cat scratch disease, lymphadenopathy, fever of unknown origin, hepatosplenic disease

Abbreviations
CSD—cat scratch disease
VEGF—vascular endothelial growth factor
FUO—fever of unknown origin
CT—computed tomography
CSF—cerebrospinal fluid
Ig—immunoglobulin
PCR—polymerase chain reaction
IFA—indirect fluorescence assay
EIA—enzyme immunoassay

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CAT SCRATCH DISEASE (CSD) has been reported in the literature for more than half a century as a syndrome of regional lymphadenopathy and fever. However, it has been only a quarter of a century since *Bartonella henselae* was identified as the etiologic agent. As diagnostic techniques have improved, *Bartonella* has been found to be responsible for a broad range of clinical syndromes, particularly prolonged fever of unknown origin (FUO), hepatosplenic disease, encephalopathy, and ocular disease. Although other Bartonella species can cause human disease, this review will focus on those caused by *B henselae*.

HISTORICAL CONTEXT

The clinical syndrome of CSD was first reported in 1950 by Debré et al[1], although Parinaud[2] described similar symptoms in the context of oculoglandular syndrome in 1889. Despite numerous reports and studies of CSD, the causative agent eluded detection until 1983. At that time, Wear et al[3] discovered a small, pleomorphic Gram-negative bacillus by using a Warthin-Starry silver stain in infected lymph nodes of patients with CSD. It was not until 5 years later that this organism was successfully isolated and cultured.[4] In 1991, Brenner et al[5] named the CSD bacillus *Afipia felis*, after the Armed Forces Institute of Pathology, where the organism was discovered. In 1992, *Rochalimaea henselae* was isolated from HIV-infected patients with bacillary angiomatosis, peliosis hepatis, and fever syndromes. In that report, Regnery et al[6] noted that the majority of their patients with clinically suspected CSD had high serum titers to the *R henselae* antigen. Additional studies in the 1990s refuted the role of *A felis* in CSD, in favor of *Rochalimaea* species.[7,8] In 1993, the genera *Bartonella* and *Rochalimaea* were united, with *Bartonella* having nomenclatural precedence over *Rochalimaea*.[9] Thus, *B henselae* is currently recognized as the causative agent of CSD. Since that time, the most significant study of patients with *B henselae* infection has been undertaken by Hugh Carithers,[10] who saw and reported >1200 cases of CSD in pediatric private practice.

MICROBIOLOGIC FEATURES AND PATHOGENESIS

The genus *Bartonella* includes 19 distinct species, of which at least 6 are responsible for human disease (*B henselae, Bartonella bacilliformis, Bartonella quintana, Bartonella elizabethae, Bartonella vinsonii, Bartonella koehlerae*). These species are small, fastidious, intracellular Gram-negative bacilli that are aerobic and oxidase-negative. The organisms are most easily visualized by using a Warthin-Starry silver impregnation stain (see Fig 1) or a Brown-Hopps tissue Gram-stain. Two main genogroups of *B henselae* have been identified in humans and cats: Houston-1 and Marseille (also known as genotype II).[11] These 2 genogroups are further subdivided into 4 variants: Marseille, CAL-1, Houston-1, and ZF-1.[12] 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 nonnecrotic areas of inflammation, and in areas of expanding and suppurating necrosis.[13,14] Electron microscopy of lymph node tissues of patients with CSD confirms that the bacilli have an affinity for the vascular endothelium, with organisms seen in clumps in vessel walls, intracellularly and free in necrotic debris.[15]

Cats are the major reservoir for *B henselae*, with up to half of domestic cats having antibodies to *B henselae*, thus testing seropositive for the bacteria. Direct horizontal transfer of *B henselae* does not occur, but rather, spread of

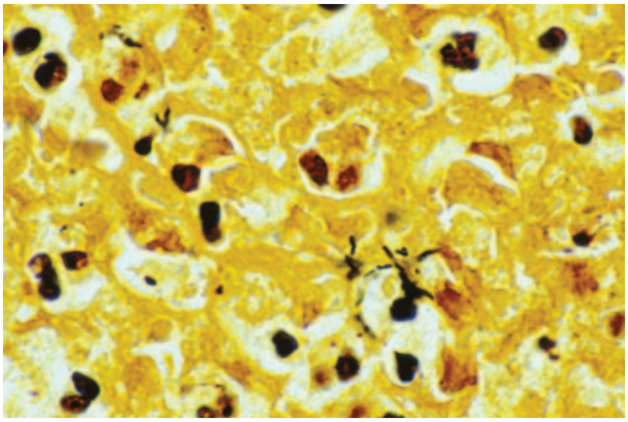

FIGURE 1
B henselae seen as short rods by using Warthin-Starry silver stain.[137]

infection between cats depends on the arthropod vector *Ctenocephalides felis*, or the cat flea.[16] After transmission, the number of bacteria reach high levels in the feline host as a result of being intraerythrocytic parasites, thereby evading the host immune response. Once transmitted to humans via cat saliva or the scratch of a cat, *B henselae* invades $CD34^+$ hematopoietic progenitor cells instead of human erythrocytes directly.[17] Bacterial infection does not affect erythroid differentiation of hematopoietic progenitor cells; thus, infection of these progenitor cells results in intracellular presence and replication of *B henselae* in erythroid differentiated cells.[17]

The response to infection with *B henselae* depends on the immune status of the infected host. In immunocompetent individuals, the response is granulomatous and suppurative, as compared with a vasoproliferative response in immunocompromised patients.[14] Early in the course of infection in an immunocompetent patient, lymphoid hyperplasia, arteriolar proliferation, and widened arteriolar walls are seen in biopsied lymph nodes. This progresses to granulomatous disease, with central areas of necrosis and multinucleated giant cells. *Bartonella* infection causes an interferon-γ-mediated T helper 1 cell response, resulting in macrophage recruitment and stimulation, ultimately producing granulomatous disease.[18] Late in the disease, stellate microabscesses form with suppuration of affected lymph nodes.[14] In individuals with an intact immune system, infection generally remains within the lymphatics, with a symptomatic immune response that lasts 2 to 4 months.[19]

Immunodeficient patients are at risk for bacillary angiomatosis, which manifests as cutaneous angiogenic lesions. These lesions consist of vascular proliferation composed of endothelial cells and a mixed inflammatory cell infiltrate. The mechanism by which *B henselae* induces angiogenesis is not fully understood. One hypothesis is that *Bartonella* modulates host or target cell cytokines and growth factors, which lead to angiogenesis. When *Bartonella* adheres to or is phagocytosed by macrophages, these cells secrete vascular endothelial growth factor (VEGF). It is thought that *Bartonella* adhesin A is crucial for the secretion of VEGF and other proangiogenic cytokines.[20] VEGF is thought to act as an endothelial cell inducer, leading to proliferation of endothelial cells and angiogenesis.[19] Another hypothesis involves *Bartonella* directly triggering proliferation and apoptosis of endothelial cells, resulting in increased angiogenesis.[21]

EPIDEMIOLOGICAL FEATURES OF *B henselae*

B henselae has a worldwide distribution, with cases of classic *Bartonella* infection reported in the United States,[10] Europe,[22] Japan,[23] New Zealand,[24] and Australia.[25] In the United States, there seems to be a seasonal distribution, with the majority of cases occurring between the months of July and January.[10,26] Peak hospitalizations for CSD in 2000 were in October, with most hospitalizations occurring between July and October.[27] Some authors have attributed this seasonal variation to the temporal breeding patterns of domestic cats, the acquisition of kittens as family pets, and the peak temporal presence of the cat flea, the major mode of *Bartonella* transmission among cats.[28] Seroprevalence of antibodies in humans to *B henselae* and *B henselae* bacteremia was found to be highest in regions with warm, humid climates.[29] One study concluded that in the United States, incidence in humans is higher in the south and lower in the west compared with the nation as a whole.[26] Among felines, kittens, outdoor cats, and cats infested with fleas are more likely to be seropositive to *B henselae*.[30–32] Overall seroprevalence in cats in the United States was found to be between 28% and 51%.[33,34] Of note is that culture-positive felines rarely seem sick, and cannot be clinically distinguished from those without *B henselae*. Although more common among felines, it was recently discovered that 10.1% of healthy dogs and 27.2% of sick dogs in the southeastern United States were found to have antibodies to *B henselae*.[35] It is unclear at this time if the presence of *Bartonella* in canines has clinical significance.

The true incidence of *Bartonella* infection is difficult to establish, because it is not a reportable disease in a majority of states in the United States. An analysis of 3 national databases found the incidence of patients discharged from the hospital with a diagnosis of CSD to be between 0.77 and 0.86 per 100 000 per year.[26] Incidence in this analysis was defined by number of patients discharged from the hospital per year with a listed diagnosis of CSD. This finding likely underestimates the true incidence, as most cases of *Bartonella* infection are not recognized or are treated on an outpatient basis. National CSD hospitalization rates in 2000 were found to be 0.60 per 100 000 children younger than 18 years of age and 0.86 per 100 000 children younger than 5 years of age.[27] These estimates are similar to earlier estimates, despite an increase in cat ownership in the United States by ~14%.[27] Clustering of cases within families has coincided with the acquisition of new pet cats, with as many as 3 siblings having clinical CSD simultaneously.[36] By using skin tests on family members of patients, Carithers[10] noted that there is significant asymptomatic infection, and close contact with cats increased the prevalence of positive skin-test reactions. In these family contacts, positive skin reaction occurred in 18% of the

TABLE 1 **Clinical Manifestations of *B henselae* Infection**

More Common	
	Typical CSD (fever and localized lymphadenopathy only)
	Prolonged fever/FUO
	Hepatosplenic disease
Less Common	
	Parinaud oculoglandular syndrome
	Neuroretinitis, posterior segment ocular disease
	Encephalopathy, status epilepticus
	Radiculopathy
	Facial nerve palsy
	Guillain-Barre syndrome
	Cerebral arteritis
	Transverse myelitis
	Epilepsia partialis continua
	Glomerulonephritis
	Pneumonia, pleural effusion
	Thrombocytopenic purpura
	Osteomyelitis
	Arthritis/arthralgia
	Endocarditis
	Pseudomalignancy
	Bacillary angiomatosis

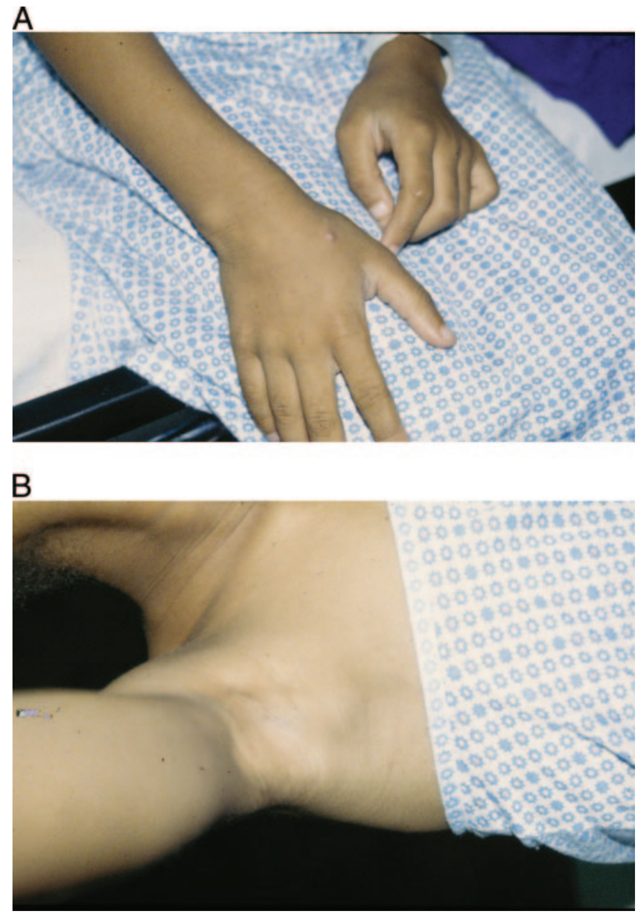

FIGURE 2
Typical CSD in a 10-year-old boy demonstrating a papule on the dorsum of the right hand near the base of the thumb (A) and right axillary lymphadenopathy (B). (Copyright Children's Hospital of Philadelphia. Reproduced with permission from Stephen Ludwig, MD and Walter W. Tunnessen Pediatric Image Library of Children's Hospital of Philadelphia, Philadelphia, PA.)

overall sample, 19% of those who were fond of cats, and 1.5% of those who disliked felines.

Bartonella infection was thought to be largely a disease of children, with studies reporting between 54% and 87% of cases of CSD in patients under 18 years of age.[10,26] Recent studies have suggested that CSD may be more common in adults than previously recognized, with some studies reporting >40% of their patients being older than 20 years of age.[30]

CLINICAL MANIFESTATIONS

The clinical manifestations of infection with *B henselae* are expanding with the improved ability to recognize the presence of the organism. Some forms of infection seem to be regional, but may be on a spectrum with more systemic forms. A list of various recognizable clinical forms of *B henselae* infection is provided in Table 1.

Typical Cat Scratch Disease

For the purposes of this review, "typical CSD" will refer to the syndrome of isolated lymphadenopathy with fever and no other signs or symptoms. Typical CSD is the most commonly recognized manifestation of infection with *B henselae*. Carithers'[10] original series noted typical CSD in ~95% of his 1200 patients. This is likely a slight overestimate of the prevalence of typical CSD, because many of the atypical presentations were not appreciated in 1985. There has not been an extensive prevalence study recently to elucidate recent prevalence data. The disease begins with an erythematous papule at the site of inoculation. The papule appears 3 to10 days after inoculation, and progresses through erythematous, vesicular, and papular crusted stages. The lesion persists for between 1 and 3 weeks.[37] Regional lymphadenopathy occurs 1 to 3 weeks after inoculation (Fig 2). Lymphadenopathy is seen in all patients with typical CSD, and 85% of patients have only a single node involved. Lymphadenopathy occurs most frequently in the axillary and epitrochlear nodes (46%), head and neck (26%), and the groin (17.5%).[10] The nodal distribution reflects the fact that feline contact occurs most often with the hands. On ultrasound, nodes are multiple, hypoechoic, and highly vascularized with increased echogenicity of the surrounding soft tissues.[38] On biopsy, nodes reveal granulomas with multiple microabscesses (Fig 3). Approximately 10% of nodes will suppurate, thereby requiring drainage.[39] Systemic illness is mild in the majority of patients, and can include fever, generalized aches, malaise, anorexia, nausea, and abdominal pain. Of note is that <10% of patients have a fever higher than 39°C, and one-third are without fever.[10]

Prolonged Fever/FUO

Although several definitions of FUO exist, a commonly accepted definition is fever that lasts for >2 weeks with no diagnostic signs or symptoms of an obvious clinical disease. Infectious etiologies dominate the long differential diagnosis for prolonged FUO, and new agents are

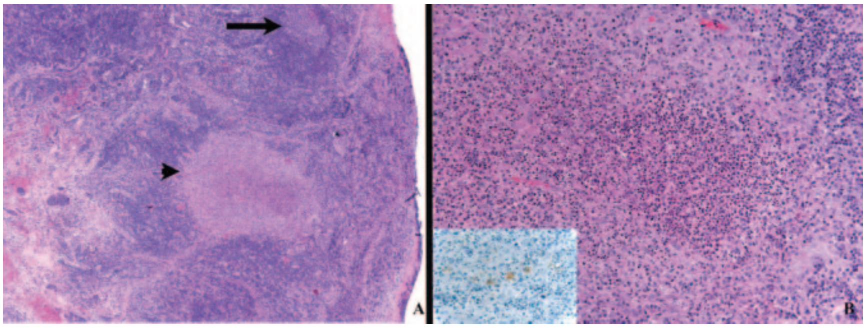

FIGURE 3
A, Low-power view of lymph node with suppurative granulomatous lymphadenitis. Note the normal germinal center (arrow), and compare it with the large, ovoid pale-appearing granuloma (arrowhead). (Hematoxylin and eosin staining, original magnification: ×50.) B, Higher-power view of granuloma with eosinophilic epithelioid histiocytes and small lymphocytes forming the rim. The necrotic central core contains numerous neutrophils. (Hematoxylin and eosin staining, original magnification: ×200. Inset, Immunohistochemical stain using mouse monoclonal antibody for *B henselae* organism with positive, granular brown staining of the bacterium in the central region of the granuloma. (Original magnification: ×630.) (Reproduced with permission from Linda M. Ernst, MD, MHS, Department of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia/University of Pennsylvania School of Medicine, Philadelphia, PA.)

continuously being added to this list. With the improvements in diagnostic methods for detecting *B henselae*, this agent is increasingly being recognized as a cause of prolonged FUO in children.[40] One recent study identified *B henselae* as the third leading infectious cause of FUO, after Epstein-Barr virus infection and osteomyelitis.[41] In this series, *Bartonella* accounted for 5% of the total 146 children with FUO and prolonged fever, 8% of the subset of 84 children with a confirmed diagnosis for their fever, and 11% of the subset of 64 children found to have an infectious disease. This study and other case reports in the literature reveal that a history of exposure to cats is not uniformly found among patients diagnosed with *Bartonella* infections, which suggests that such infections should be considered in the initial evaluation of FUO, irrespective of exposure to cats. Approximately 30% of cases of FUO caused by *B henselae* had hepatosplenic involvement. There have also been reported cases of *B henselae* presenting with intraabdominal lymphadenopathy, fever, and abdominal pain with no hepatosplenic disease.[42,43] Thus, *B henselae* infection should always be considered as a diagnostic possibility in patients with FUO and in patients with fever and abdominal pain.

Hepatosplenic Manifestations

Bartonella infection that involves the liver and/or spleen occurs more than previously acknowledged, and is being recognized more frequently as a result of improvements in serologic and imaging diagnostic modalities. Hepatosplenic *Bartonella* infection typically presents with systemic symptoms, such as prolonged fever, and microabscesses in the liver and/or spleen. Granulomatous disease in the spleen resulting from *Bartonella* can be severe enough to result in spontaneous splenic rupture.[44] In various studies, >60% of patients with hepatosplenic infection presented with abdominal pain, usually described as episodic dull pain over the periumbilical and/or upper quadrant regions with high severity.[45,46] Other presenting symptoms include weight loss, chills, headache and myalgias. More than half of all patients will present with hepatomegaly, splenomegaly, or hepatosplenomegaly on physical examination. Patients will typically have an elevated erythrocyte sedimentation rate and elevated titers of antibodies to *B henselae*. White blood cell and platelet counts are normal or slightly elevated in most cases. Liver enzymes are typically normal. In 1 study, all patients with hepatosplenic *Bartonella* infection had evidence of hepatosplenic disease by using abdominal imaging, with 68% percent of having microabscesses of both the liver and spleen.[45] In 1 interesting case, ultrasound revealed thickening of the terminal ileum in addition to hypoechogenic lesions in the liver and spleen, suggesting inflammatory bowel disease resulting from *B henselae* infection.[47]

Abdominal imaging is an important diagnostic step in patients with suspected hepatosplenic disease or in cases of prolonged FUO, because it can often identify changes characteristic of hepatic or splenic *Bartonella* infection. On ultrasound, hepatic lesions seem hypoechoic. On computed tomographic (CT) scan, hepatic lesions seem either hypoattenuated relative to the liver, isoattenuated to the surrounding tissues, or only marginally enhanced.[48] In patients who have had biopsies performed, the predominant lesion on histopathology was a necrotizing granuloma.[49] In general, symptoms and visceral lesions regress within 6 months; however, there have been rare reports of residual calcification.[49] It is interesting to note that only 55% of children with hepatosplenic disease had lymphadenopathy of any sort.[46] Based on the portal pattern of granulomas, hepatic disease may be due to organisms transmitted via the hands by ingestion, thus explaining the low incidence of nodal involvement in abdominal disease.

Bacillary peliosis hepatis is a specific form of hepatosplenic *Bartonella* disease seen in the immunocompromised hosts. Patients present with gastrointestinal symptoms, fever, chills, and hepatosplenomegaly. The liver demonstrates characteristic dilated capillaries or blood-filled cavernous spaces. The typical duration of fever ranges from 1 week to 2 months.[45]

Ocular Manifestations

Parinaud oculoglandular syndrome, consisting of fever, regional lymphadenopathy, and follicular conjunctivitis, was first described in 1889 and is the most common ocular presentation of *B henselae* infection, affecting ~5% of patients with CSD.[10] Only within the last decade was *B henselae* identified as the causative agent of this syndrome.[50] Route of infection is thought to be direct conjunctival inoculation. Typical symptoms include foreign body sensation, unilateral eye redness, serous discharge, and increased tear production. On examination, patients present with a necrotic granuloma with ulceration of the conjunctival epithelium and regional lymphadenopathy that affects the preauricular, submandibular, or cervical lymph nodes.[51] The granuloma typically disappears after several weeks without scarring.[10]

Neuroretinitis, a form of optic neuropathy with optic disk swelling and macular stellate exudate, is the most common posterior segment ocular complication of *Bartonella* infection.[51] *B henselae* is the most common identified etiology of neuroretinitis, with approximately two thirds of patients with neuroretinitis demonstrating serologic evidence of previous *B henselae* infection.[52] Symptoms include painless visual loss with abrupt onset that is typically unilateral.[53] On MRI, unilateral enhancement at the optic nerve-globe junction is highly specific for *B henselae* infection as cause for optic neuropathy.[54] Macular exudates may take months to resolve and, even after resolution, patients may experience abnormal color vision and evoked potentials, subnormal contrast sensitivity, residual disk pallor, afferent pupillary defects, retinal pigment changes, and mildly decreased visual acuity.[55] There are reports of ocular *Bartonella* disease with optic disk edema and retinal detachment without the classic macular stellate exudate seen with neuroretinitis.[56] Other posterior segment presentations of *B henselae* infection include panuveitis with diffuse choroidal thickening, retinal vasoproliferative lesions, macular hole, vitreal detachment, vitritis, branch retinal artery and venous occlusions, retinal white spots, and papillitis.[57–60] In HIV-positive patients, ocular *B henselae* infection presents as a subretinal mass associated with abnormal vascular network, which is best diagnosed by fluorescein angiography.[61]

Neurologic Manifestations

Neurologic complications of *B henselae* infection are rare, occurring in ~2% of infected patients. The most common presentation is encephalopathy, accounting for 90% of cases that affect the nervous system.[10] Neurologic symptoms generally occur 2 to 3 weeks after the onset of lymphadenopathy. Symptoms include headaches and mental status changes. Seizures develop in 46% to 80% of patients with Bartonella encephalopathy, with some presenting with status epilepticus.[62–64] Combative behavior has been reported in as many as 40% of patients with Bartonella encephalopathy.[63,65] In addition to mental status changes, patients with encephalopathy may present with a variety of neurologic findings, including weakness, alterations in tone, nuchal rigidity, extensor plantar responses, and hyporeflexia or hyperreflexia.[66]

Outside of specific identification of *B henselae* infection, laboratory evaluation of infected patients with encephalopathy generally yields variable results, and is not helpful in diagnosis. Cerebrospinal fluid (CSF) analysis typically yields normal results, although pleocytosis and elevated CSF protein have been reported.[62,64] Electroencephalography performed during the acute phase of illness reveals generalized slowing in 80% of patients, with complete normalization on follow-up.[63] Only 19% of patients have abnormal findings on CT scan or MRI of the brain, and these include lesions of the cerebral white matter, basal ganglia, thalamus, and gray matter.[67] Prognosis is generally excellent for patients with encephalopathy, with >90% of patients having complete, spontaneous recovery with no sequelae.[62,63] The published literature reveals only 1 report of fatal meningitis and encephalitis of an immunocompetent child as a result of *B henselae* infection.[68]

Less common neurologic complications include meningomyeloradiculopathy, manifesting with lower extremity paresthesias, weakness and sphincter dysfunction,[69] facial nerve palsy,[70,71] Guillain-Barre Syndrome,[72] epilepsia partialis continua,[73,74] acute hemiplegia,[75] transverse myelitis,[76] and cerebral arteritis.[77]

Dermatologic Manifestations

Skin lesions other than the papule seen at the site of inoculation are rare, occurring in ~5% of patients infected with *B henselae*. These consist of maculopapular and urticarial eruptions, granuloma annulare, erythema nodosum, erythema marginatum, and leukocytoclastic vascultis.[78]

Bacillary angiomatosis, once a common dermatologic condition of AIDS patients with *Bartonella* infection, is now diminishing in incidence as the use of prophylactic drugs increases in immunocompromised patients. Although this systemic disease can occur in various organ systems, skin lesions are most frequent, occurring in up to 90% of cases. Lesions are reddish-brown papules that are difficult to differentiate from Kaposi's sarcoma, epithelioid hemangioma, and pyogenic granuloma. An example of angioproliferation in immunocompromised individuals infected with *B henselae*, there is an accumulation of rounded blood vessels on biopsy, with plump epithelial cells and a mixed inflammatory infiltrate with neutrophil predominance.[37]

Hematologic Manifestations

Hematologic complications of *B henselae* are rare. Hemolytic anemia has been reported in both adults and children.[79,80] In children, there have been several cases in the literature of *Bartonella* resulting in thrombocytopenic purpura.[81] *Bartonella* has also been reported to be associated with development of lupus anticoagulant and prolongation of the activated partial thromboplastin time.[82] Anecdotally, a case is known of a red blood cell enzyme deficiency with chronic hemolysis that worsened intensely with the development of systemic *B henselae* infection, requiring transfusion therapy. This patient improved, and no longer required transfusion therapy, within 24 hours after treatment with gentamicin.

Orthopedic Manifestations

Bone lesions are a rare complication of infection with *B henselae*. Often, these lesions are osteolytic, and occur as an osteomyelitis. Clinical manifestations of bony disease include pain and tenderness over the affected bone and lymphadenopathy. The lytic lesions frequently occur in the context of systemic manifestations of *Bartonella* infection. Lymphadenopathy frequently occurs distant from the site of osteomyelitis, suggesting that bony infection occurs by hematogenous or lymphatic spread.[83] Abnormalities on radiograph include lytic lesions, with occasional sclerosis or periosteal reaction. Lesions are sometime subtle on plain radiograph, and may require an MRI or radionuclide bone scan for diagnosis.[84,85] In most patients, osteolytic disease is isolated to 1 bone. Vertebral infection has been most commonly described; however, infection has been reported in the skull, sternum,[85] vertebrae,[83] clavicles, humerus,[86] femur, tibia,[85] acetabulum,[87] metacarpals, and metatarsals.[88] Despite the propensity for *B henselae* to cause isolated bony disease, a recent case series reports 2 cases of multifocal bone marrow infection with *Bartonella*, with foci of increased MRI T2 signal intensity in the marrow of the sacrum, iliums, and femurs, with lesions in the hepatic parenchyma.[85] Biopsy reveals necrotizing granulomas of bone.[86] Bony lesions have been associated with adjacent abscesses.[89–91] Patients with osteomyelitis resulting from *B henselae* infection generally have an excellent prognosis.

A recent study published in 2005[92] revealed that ~3% of cases of *B henselae* infection in Israel had rheumatoid factor-negative arthritis/arthragia. Female gender, age of >20 years, and erythema nodosum were factors significantly associated with arthropathy in patients infected with *Bartonella*. The most frequently affected joints were the knee, wrist, ankle, and elbow joints. Often, the disease is severe enough to incapacitate and limit activities of daily living. In most patients, arthropathy began within 1 week of the appearance of lymphadenopathy and persisted for greater duration than the lymphadenopathy (13 weeks vs 9 weeks, median).

Cardiac Manifestations

The most commonly reported cardiac manifestation of *Bartonella* infection is endocarditis. Typically, this presentation is seen in adult males; however, it can occur in children, especially those with previous valvular disease. *Bartonella* species account for ~3% of cases of endocarditis.[93] Presentation is insidious and subacute, with fever, dyspnea, bibasilar rales, cardiac failure, and cardiac murmur as presenting signs and symptoms. The aortic valve is usually involved, and vegetations are found in 100% of patients.

Renal Manifestations

Renal complications of *Bartonella* infection are uncommon, with glomerulonephritis being the most frequently encountered. Glomerulonephritis secondary to *B henselae* 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.[94–98] Affected patients have normal serum complement 3 levels, normal renal function, and renal biopsies may reveal mesangial hypercellularity, IgA deposition, interstitial infiltrate and/or complement 3 deposition consistent with acute glomerulonephritis.[94–96] In general, spontaneous recovery can be expected in patients with renal manifestations of *B henselae* infection.

Pulmonary Manifestations

In general, rare cases of pulmonary involvement in *Bartonella* infection take the form of pneumonia or pleural thickening and/or effusion.[99] Pulmonary disease appears 1 to 5 weeks after the appearance of lymphadenopathy. Prognosis has been excellent, with complete recovery in a mean time of 2 months.

Pseudomalignancy

There have been increasing numbers of reports in the literature of *B henselae* infection mimicking various malignancies. Infection simulating lymphoma is one of the most frequently reported, especially with lymphadenopathy in the neck and abdomen.[100,101] The clinical picture is most confusing when splenic involvement occurs in the context of the so-called "B symptoms" of lymphoma, such as weight loss, night sweats, and prolonged fever.[102] Hepatosplenic lesions and intraabdominal lymphadenopathy have been noted to have an appearance on both ultrasound and contrast-enhanced CT scan consistent with lymphoma.[103] An interesting case was reported of a patient with a history of T cell lymphoblastic lymphoma that presented with inguinal lymphadenopathy and had a positron emission tomography scan consistent with lymphoma relapse, but had negative pathology on nodal biopsy and positive *B henselae* titers.[104]

Recently, *Bartonella* has been reported to mimic posttransplant lymphoproliferative disease in children who have undergone renal transplantation. Infection presented with fever, lymphadenopathy, and/or organomegaly 2 to 4 years posttransplantation. In some of these patients, *B henselae* infection was associated with acute rejection episodes that were reversed with intravenous corticosteroid therapy.[105]

There are several reports in the literature in both adults and children of *Bartonella* infection presenting as a solitary mass in the breast.[106–108] Initial clinical manifestations consist of a firm, mobile, tender breast mass, often in the lower outer quadrant of the breast, and inflammatory axillary lymphadenopathy. Disease in the breast has also presented as mastitis with soreness and erythema of the breast.[109] Characteristic features of *B henselae* infection of the breast are abscesses or granulomas in the breast parenchyma with bacteria in necrotic regions. *Bartonella* titers may be negative, but the bacteria may be detected on polymerase chain reaction (PCR) analysis of nodal aspirate.

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.[110] Another unusual presentation includes a patient with a solitary soft tissue mass overlying a lytic skull lesion, which was suggestive of Histocytosis X.[111] In adults, *B henselae* has presented similarly to pancreatic or biliary malignancy,[112] pharyngeal cancer,[113] and vascular neoplasms.[114]

DIAGNOSIS

Laboratory Findings

Other than tests targeting the identification of *Bartonella*, laboratory findings of *Bartonella* infection are often nonspecific. Infection may result in normal or mildly elevated white blood cell counts, and normal, elevated, or diminished platelet counts. As noted above, CSF examination typically yields normal results. Liver enzymes are usually normal. The erythrocyte sedimentation rate may be normal or elevated.

Diagnostic Testing

The evolution of diagnostic techniques over the past decade has made *B henselae* less elusive to clinicians and researchers. Diagnostic techniques have allowed clinicians to discover a multitude of clinical manifestations resulting from *Bartonella* infection compared with just 5 years ago. With this growing understanding of the wide range of clinical disease that can be caused by *Bartonella* infection, accurate diagnosis is necessary to rule out other diseases that it may mimic, including serious conditions that may require invasive, expensive, and expedient evaluations for serious pathology.

Isolation of *Bartonella* species in culture is difficult, requiring a 2- to 6-week incubation for primary isolation. In addition, isolating *B henselae* is usually unsuccessful, particularly if patients lack systemic disease.[28] Nodal culture of the organism also offers poor yield, because lymphadenopathy is thought to be due to an aggravated immune response rather than direct invasion.

An early laboratory aid in detection of *B henselae* infection was the intradermal skin test, which relies on a delayed-type hypersensitivity reaction within 48 to 96 hours of inoculation with *B henselae* antigen. The test had a specificity of 99%, with minimal cross-reactivity with other organisms.[10] The test was impractical, however, because different antigens had great variance in reactivity, there was concern over the safety of human-derived reagents, and there was a lack of generalized availability of the antigen. Other early diagnostic methods included histopathologic examination of affected lymph nodes. Pathology suggestive for *B henselae* infection includes granuloma formation, with microabscesses and follicular hyperplasia.[10,28] The bacillus is difficult to see with conventional staining methods, and it was not until 1983 that the Warthin-Starry silver stain was used to identify a bacterium as the cause of CSD.[3] It is now well accepted that the organism stains well with a Warthin-Starry silver impregnation stain. Despite this, histopathologic diagnosis remains impractical because of its invasive nature.

More recently, advanced diagnostic techniques such as serology and PCR have been applied to the detection of *Bartonella*. There have been 3 main approaches to using PCR to diagnose *Bartonella* infection: amplification of the 16S rRNA gene, amplification of the citrase synthase gene (*gltA*), and amplification of the *htrA* gene of *B henselae*. Specificity of PCR has been excellent (100% in 1 study); however, it has been lacking in sensitivity, ranging from 43% to 76%.[115,116] The true comparison of various methods of PCR analysis is difficult because of differences in the PCR target, the sample type, and the clinical criteria used. PCR provides the advantages of high specificity and rapid identification.[117] Pitfalls of the use of PCR include variable sensitivity and the need for highly specialized equipment and personnel.

A more practical means of laboratory diagnosis is serology for *B henselae* antibodies, because it avoids invasive sample collection, use of specialized equipment and techniques, and long incubation periods.[28] Although the Warthin-Starry stain was the first evidence that CSD was caused by a bacterium, serology was the means of recognizing *Bartonella* species as the etiologic agent of CSD.[6] The 2 major serologic diagnostic methods used are indirect fluorescence assay (IFA) and enzyme immunoassay (EIA). Sensitivities of these methods vary in different reports using different assays, depending on the antigen used, test procedures, and cutoff used, as noted in Table 2. The IFA is the most frequently used serologic method. The duration of serologic detection of antibodies is important in determining acute infection versus historical exposure to the bacterium. Positive IgM EIA indicates acute disease, with duration of detection of ≤3 months. The short duration of IgM antibodies makes them infrequently discovered on serology; thus, negative results do not exclude acute disease. IgG EIA titers also decrease with time, with only 25% of patients remaining seropositive after 1 year.[118] In the early stages of the disease, titers to IgG and IgM may be low, requiring a second serum sample at a later date for diagnosis.[119] In addition, because IgG antibodies persist for up to a year, it is difficult to diagnose active infection compared with previous infection. Disadvantages to serologic diagnosis include variable sensitivity and specificity, inability to distinguish between active versus prior infection, and lack of Bartonella species-specific antibody response, resulting in cross-reactivity.[28] Despite this, serology re-

TABLE 2 **Summary of Serologic Testing Available for *B henselae***

Serological Test	Sensitivity, %	Specificity, %
IgG IFA	14 to 100	34 to 100
IgM IFA	2 to 50	86 to 100
IgG EIA	10 to 25	97
IgM EIA	60 to 85	98 to 99

Testing data are from Bergmans et al,[138] Woestyn et al,[139] Sander et al,[140,141] Giladi et al,[142] Barka et al,[143] and Szelc-Kelly et al.[144]

TABLE 3 Diagnostic Criteria for *B henselae* Infection

Three of 4 of the following:

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 CT 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

Diagnostic criteria are adapted from Margileth.[120]

mains the most practical diagnostic tool in the laboratory detection of *B henselae* infection.

Diagnostic Criteria

Ultimately, no single criterion should be considered the diagnostic gold standard, and diagnosis of *B henselae* infection must rely on the combination of epidemiological, serological, clinical, histologic, and bacteriologic criteria. Initial diagnosis was based on 4 primarily anamnestic and clinical criteria: contact with a cat, regional lymphadenopathy, a site of inoculation, and a positive skin test. Carithers[10] developed the "Rule of Five" as a diagnostic tool in his original series. Points are given to each of the 4 criteria: 1 point for lymphadenopathy, 2 points for cat exposure, 2 points for the presence of an inoculation site, and 2 points for a positive skin test. Amassing 5 points strongly suggested CSD, 7 points made the diagnosis definite. Much of the diagnosis of *B henselae* infection is still considered a clinical diagnosis, with laboratory evaluation used to confirm initial suspicion. Updated criteria by Margileth in 2000[120] are listed in Table 3.

TREATMENT

The therapeutic approach to *Bartonella* infection varies on the basis of the clinical manifestations and immune status of the patient. There is a paucity of data in the literature as to the most effective therapy in all cases of *Bartonella* infection, with most data presented as part of case series rather than randomized, controlled trials. There is a significant divide in the literature between in vitro efficacy of antibiotics and the ability to successfully treat in clinical practice. In vitro, *Bartonella* species have been found to be susceptible to a number of antimicrobial agents, including macrolides (azithromycin, clarithromycin, erythromycin), aminoglycosides, β-lactams (penicillin G, amoxicillin), expanded-spectrum cephalosporins (cefotetan, cefotaxime, ceftazidime, ceftriaxone), and trimethroprim-sulfamethoxazole, rifampin, and ciprofloxacin.[121–124] This broad spectrum of activity has failed to be borne out in clinical practice; for example, penicillin has a very low mean inhibitory concentration in vitro, but has no in vivo efficacy. All antibiotics tested in vitro had only bacteriostatic activity, except for aminoglycosides, which have demonstrated bactericidal activity against *Bartonella* in vitro.[123,125] This lack of bactericidal activity and the lack of cell membrane penetration of many antibiotics are 2 hypotheses as to why these agents fail to reach the intracellular *Bartonella* bacillus.[126]

Typical CSD is a self-limited illness that resolves within 2 to 6 months, and usually does not respond to therapy. Most studies show no benefit to antibiotic therapy in CSD, but 2 studies have revealed some in vivo effect. A retrospective study by Margileth[127] of 268 patients with CSD revealed that mean duration of illness was 14.5 weeks in patients not treated, or those treated with antibiotics found to be ineffective against CSD. Mean duration of illness after treatment was 2.8 weeks in patients treated with antibiotics that the study found effective: rifampin, ciprofloxacin, gentamicin, and trimethoprim-sulfamethoxazole, in order of increasing effectiveness. Efficacy for these antibiotics ranged from 58% to 87%. There has been a single randomized, control trial of antibiotic therapy in typical CSD that used azithromycin.[128] This study revealed an 80% decrease in lymph node volume in 50% of the azithromycin-treated patients compared with 7% of the placebo-treated patients in the first 30 days. Aside from lymph node volume, there was no difference in clinical outcome between study groups, and there was no efficacy demonstrated for disseminated disease.[128] 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 mild-to-moderate infections in immunocompetent patients, management consists of reassurance, adequate follow-up and analgesics for pain. Nodes should be aspirated if they suppurate to relieve painful adenopathy; however, incision and drainage is not recommended because of the potential of chronic sinus tract formation.[127] During aspiration, the needle should be moved around in several different locations, because coalesced microabscesses often exist in multiple septated pockets. 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 anecdotally shown to be efficacious include rifampin (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 (10 mg trimethoprim/kg per day in 2–3 daily doses for 7–10 days).[120]

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 and other disease processes is derived from observational case studies rather than randomized trials. In many of these complicated *Bartonella* infections, antibiotic choice is based on the fact that immunocompromised individuals show a dramatic response to antibiotics compared with the minimal response of immunocompetent patients; thus, seriously ill immunocompetent individuals are treated with similar regimens despite the lack of data.[51] The lack of data are even more prevalent in the pediatric population; thus, pediatricians must use available adult data and the individual clinical situation to tailor therapy to children with complicated *B henselae* infections, preferably in consultation with a pediatric infectious diseases specialist.

For neuroretinitis, doxycycline is the preferred drug 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.[51] When coupled with rifampin, these antibiotics seem to promote disease resolution, improve visual acuity, decrease optic disk edema, and decrease the duration of disease.[55] Duration of treatment is at least 2 to 4 weeks in immunocompetent patients and 4 months for immunocompromised ones. Some authors suggest that *Bartonella* neuroretinitis is a self-limited disease with excellent prognosis for complete visual recovery; therefore, no antibiotic therapy is necessary and conservative management will suffice.[129]

There have been no randomized, controlled trials of antibiotics in *Bartonella* encephalopathy, and their efficacy is controversial; thus, conservative, symptomatic treatment is usually recommended.[66] If antibiotics were to be used, the combination of doxycycline and rifampin is suggested because of their strong penetration into the central nervous system.[126] For encephalitis with seizures, anticonvulsant therapy should be used to control seizure activity.

In hepatosplenic disease in the immunocompetent patient, gentamicin, trimethoprim-sulfamethoxazole, rifampin, and ciprofloxacin have anecdotally been shown to be effective.[39,45] In patients treated with gentamicin, trimethoprim-sulfamethoxazole, or rifampin, defervescence occurred between 1 and 5 days after the start of therapy.[45] Because of the variety of antibiotic regimens and study parameters, it is difficult to determine if any single antibiotic regimen is superior in the treatment of hepatosplenic disease. Arisoy et al[46] recommend rifampin at 20 mg/kg per day divided every 12 hours for 14 days alone or in combination.[45] Another regimen uses gentamicin (2.5 mg/kg per dose every 8 hours) until patient is afebrile, followed by trimethoprim-sulfamethoxazole (5 mg/kg per dose every 12 hours) and rifampin (10 mg/kg per dose every 12 hours) for 2 to 4 weeks.

Because of the high mortality rate of *Bartonella* endocarditis, this condition should be treated aggressively. Antibiotics, and frequently, surgery, are required to treat endocarditis, although no antibiotic regimen has been proven effective in the literature. Typical treatment is an aminoglycoside combined with doxycycline or ceftriaxone.[93] In a recent retrospective study in adults, patients who received an aminoglycoside, such as gentamicin, were more likely to fully recover, and those treated with an aminoglycoside for at least 14 days were more likely to survive compared with those with a shorter duration of therapy.[130] Several authors recommend treating with an aminoglycoside combined with a β-lactam agent, such as ceftriaxone, with or without doxycycline.[126]

Immunocompromised individuals may develop severe, disseminated disease; however, their response to antibiotics is usually significantly more dramatic than those with intact immune systems. Systemic *Bartonella* infection in these patients has been treated with a number of agents, including β-lactam agents.[131] Generally, bacillary angiomatosis tends to affect only those with impaired immunity and has been successfully treated with erythromycin, doxycycline, isoniazid, azithromycin, and rifampin.[131,132] Lesions often improve after 4 to 7 days, with complete resolution in ~1 month.[126] The drug of choice for children is erythromycin ethylsuccinate (40 mg/kg per day in 4 divided doses, with a maximum of 2 g/day) for 3 months. In cases of severe disease, combination therapy with intravenous erythromycin and rifampin is recommended. Relapses are more frequent if antibiotics are given for <3 months; thus, therapy should be given for at least 3 months' duration.[126]

The use of corticosteroids has been reported anecdotally for use in *Bartonella* encephalitis, hepatosplenic disease, ocular disease, and systemic disease; however, some patients failed to respond to these drugs.[127,133–136] More research is needed to determine if corticosteroids help to lessen the severity of disease or improve outcomes. At the current time, we do not recommend using corticosteroids in the treatment of *Bartonella* infection.

FUTURE DIRECTIONS

Over the last few decades, much has been learned about the spectrum of disease resulting from *Bartonella henselae* infection. As our knowledge of the microbiologic, pathologic, and clinical spectrum expands, an increasing number of questions develop. There has been no updated broad epidemiologic exploration of the various manifestations of disease. As more varied presentations of *Bartonella* are discovered, updated information on their patterns of occurrence, frequency, and distribution are needed. There is a significant gap in our knowledge of effective therapy for more complicated sequelae of infection. More randomized, rigorous trials are required to base our therapeutic decisions on meticulous evidence. Finally, clinicians should continue to include *Bartonella* in the differential diagnosis of prolonged fever, abdominal pain, and the many other varied presentations caused by this elusive bacterium.

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