BARTONELLA INFECTIONS

(Carrión's disease, cat scratch disease, trench fever)

DISEASE	ICD-10 CODE
OROYA FEVER	ICD-10 A44.0
VERRUGA PERUANA	ICD-10 A44.1
CARRIÓN'S DISEASE (South American bartonellosis, Oroya fever, Verruga peruana)	ICD-10 A44.0
ZOONOTIC BARTONELLOSIS (other forms of bartonellosis, emerging bartonellosis, rodent-borne bartonellosis, flea-borne bartonellosis)	ICD-10 A44.8
CAT SCRATCH DISEASE (cat scratch fever, benign lymphoreticulosis)	ICD-10 A28.1
TRENCH FEVER (quintana fever)	ICD-10 A79.0

1. Clinical features—*Bartonella* spp. can cause several diseases.

1) Carrión's disease: a bacterial infection with 2 clinical forms: a life-threatening febrile anemia (Oroya fever) and a benign dermal eruption (verruga peruana). Asymptomatic infection and a carrier state may both occur. Oroya fever is characterized by fever, headache, myalgia, arthralgia, pallor, severe hemolytic anemia (macrocytic or normocytic, usually hypochromic), and generalized nontender lymphadenopathy. Verruga peruana has a preeruptive stage characterized by shifting pains in muscles, bones, and joints; the pain, often severe, lasts minutes to several days at any one site. The dermal eruption may be miliary with widely disseminated small hemangioma-like nodules, or nodular with fewer (but larger) deep-seated lesions, most prominent on the extensor surfaces of the limbs. Individual nodules, particularly near joints, may develop into tumor-like masses with an ulcerated surface. Atypical cases of Oroya fever with milder manifestations (prolonged splenomegaly and mild anemia) may occur.
2) Cat scratch disease (CSD): a subacute, usually self-limited bacterial disease characterized by malaise, granulomatous lymphadenitis, and variable patterns of fever. Most often preceded by a cat scratch that develops into a red papular lesion(s) with subsequent development of lymphadenitis in the draining lymph nodes, usually within 2 weeks. Lymphadenitis may progress to suppuration. The papule at the inoculation site can be found in 50%–90% of cases. When the direct inoculation site is in the conjunctiva, Parinaud's oculoglandular syndrome can develop, with granulomatous conjunctivitis

and pretragal lymphadenopathy. Approximately 10% of CSD cases can be complicated by systemic disease including prolonged high fever, malaise, fatigue, myalgia, arthralgia, weight loss, neuroretinitis, or hepatosplenomegaly. Rarely neurological complications such as encephalopathy and optic neuritis can also occur. Cat scratch disease can be clinically confused with other diseases that cause regional lymphadenopathies (e.g., tularemia, brucellosis, tuberculosis, plague, pasteurellosis, and lymphoma).

In immunocompromised individuals (e.g., patients with acquired immunodeficiency syndrome [AIDS], organ transplant, or cancer), the *Bartonella* bacteria can disseminate and cause lesions distinctly different from the CSD manifestations observed in immunocompetent people: vascular cutaneous lesions (bacillary angiomatosis [BA]), hepatic vascular proliferation (bacillary peliosis hepatis), widespread lymphadenopathy, and bacteremia. In AIDS patients, BA can be clinically indistinguishable in appearance from Kaposi's sarcoma. In immunocompromised patients, *Bartonella* infection is sometimes fatal.

3) Trench fever: a typically nonfatal, febrile bacteremic disease varying in manifestations and severity, characterized by headache, malaise, shin pain, and dizziness. Onset is either sudden or gradual, and fever may be relapsing (usually with a 5-day periodicity), prolonged (typhoid-like), or limited to a single episode lasting several days. Splenomegaly, transient macular rash, and conjunctivitis may also be present. Symptoms may continue to recur many years after the primary infection; persistent bacteremia has been described. Bacteremia can be complicated by osteomyelitis, lymphadenopathy, and BA in immunocompromised patients, especially those with human immunodeficiency virus infection. Endocarditis has been associated with trench fever infections, especially among homeless or alcoholic persons.
4) Zoonotic bartonellosis acquired from wild animals: although much less common, several other *Bartonella* spp. infecting various mammalian species have been associated with human infections. Clinical presentations include vegetative endocarditis, neuroretinitis, lymphadenitis, myocarditis, fever of unknown origin, and asymptomatic bacteremia.

2. Causative agents—Members of the genus *Bartonella* are fastidious, hemotropic, Gram-negative bacteria of the alpha-2 subgroup of the class Proteobacteria and taxonomically closely related to *Brucella* spp. Among more than 30 reported species of *Bartonella*, 3 species account for the great majority of recognized human infections: *B. bacilliformis* (Carrión's disease),

B. henselae (CSD), and *B. quintana* (trench fever). However, at least a dozen other *Bartonella* spp. have been associated with various human illnesses, including *B. alsatica, B. clarridgeiae, B. doshiae, B. elizabethae, B. grahamii, B. koehlerae, B. mayotimonensis, B. rochalimae, B. schoenbuchensis, B. tamiae, B. tribocorum, B. vinsonii*, and *B. washoensis. B. vinsonii* subsp. *arupensis* was isolated from an American patient with acute onset of confusion, difficulty in walking, and facial numbness. Subsequently, the same subspecies was identified as an etiologic agent of blood culture-negative endocarditis and febrile illnesses in Europe and Asia. Another subspecies of *B. vinsonii* (*B. vinsonii* subsp. *berkhoffii*) has been identified as a cause of endocarditis and neurological disease. *B. washoensis* was responsible for human cases of myocarditis and meningitis in the western USA. *B. elizabethae* was originally isolated from a patient with endocarditis in Massachusetts; evidence of *B. elizabethae* infection also has been demonstrated in patients with neuroretinitis, hepatic granulomas, ulcers, endocarditis, and myocarditis. *B. alsatica* was reported as a cause of several cases of culture-negative endocarditis and lymphadenitis in France. *B. rochalimae* was diagnosed in a US traveler who presented at the hospital with fever, insomnia, myalgia, headache, and a mild cough after returning from a trip to Peru. *B. tamiae* was recognized as a new pathogen in Thailand after isolation and characterization of the strains from blood of 3 patients with fatigue, myalgia, headache, and rash. *B. schoenbuchensis, B. doshiae*, and *B. tribocorum* were identified in individuals with chronic illness, history of tick exposure, or lymphadenopathy and fever. The novel species *B. mayotimonensis* was isolated from a patient with endocarditis in the US Midwest.

3. Laboratory diagnosis—Methods for laboratory diagnosis include serology, culture, and polymerase chain reaction (PCR). Several techniques are available for serological diagnostics, including antibody-capture enzyme-linked immunosorbent assay and direct immunofluorescence using fluorescein-conjugated polyclonal antibodies. The indirect immunofluorescence assay (IFA) for detection of *Bartonell*a antibodies is the most common and convenient serologic method, with a common cutoff value of 1:64 (sometimes 1:128 or 1:256) for most *Bartonella* spp. For most commercial laboratory IFA tests, there is substantial cross-reactivity between different *Bartonella* spp. (e.g., *B. quintana* and *B. henselae)*. Titration of positive sera against several *Bartonella* antigens can greatly improve serological diagnostics and reduce a possibility of cross-reactive results, but this is rarely available in commercial laboratories. IFA immunoglobulin class G testing for *Bartonella* antibodies has been much more sensitive than IFA immunoglobulin class M testing. Isolation of the organisms is very challenging but can be accomplished by bacteriological culture of patient blood or tissue biopsies using specific agar medium enriched with mammalian blood or chocolate agar and prolonged incubation in a moist, CO_2–enhanced environment. Molecular techniques, particularly

conventional and real-time PCR assays, increasingly have been used for detection and identification of *Bartonella* deoxyribonucleic acid (DNA) in most types of clinical materials, including tissues and body fluids. Nonspecific histological stains such as the tissue Warthin-Starry silver stain may provide presumptive evidence of infection. More specific immunohistological methods have been used for detection of *Bartonella* bacteria in cardiac valves and other tissues. Well-validated assays offered by Clinical Laboratory Improvement Amendments (CLIA)-certified reference laboratories are recommended for all clinical diagnostics.

4. Laboratory capability—Most commercial laboratories offer serologic testing for *B. henselae* and *B. quintana*. PCR testing is offered by several commercial laboratories and is becoming more widespread but is still not readily available in most hospital clinical laboratories. Cultures are generally available only at specialized reference laboratories.

5. Safety requirements—Biosafety level 2 practices, containment equipment, and facilities are recommended for all activities involving known or potentially infectious tissues, body fluids, and cultures. As with any human specimens, universal precautions should be strictly applied. Although laboratory-associated *Bartonella* infections have not been reported, the agent may be present in blood, urine, and tissues of infected animals and ectoparasites. The importance of aerosol exposure is not known but considered minimal. Vaccines are not available for use in humans or animals. None of the *Bartonella* spp. is designated as a select agent, although viable *B. quintana* shipment is regulated by the US Department of Commerce. Laboratorians working with *B. quintana* in other countries should check with their respective commerce or health officials.

6. Nonhuman hosts—*Bartonella* spp. persist in nature through a wide range of mammalian reservoir hosts including cats, dogs, wild carnivores, ungulates, rodents, bats, marine mammals, and nonhuman primates. They cause long-term bacteremias and can be transmitted among hosts by diverse arthropod species. Cats represent the main reservoir for *B. henselae*, *B. clarridgeiae*, and *B. koehlerae.* Dogs and wild canids are major reservoirs for *B. vinsonii* subsp. *berkhoffii.* Urban and wild rats of the genus *Rattus* constitute the main reservoir of *B. elizabethae* and other phylogenetically related species (e.g., *B. tribocorum*). In North America, rodent-borne *Bartonella* are commonly associated with a specific genus of rodent host, for example, *B. vinsonii* subsp. *arupensis* with deer mice (*Peromyscus* spp.) and *B. washoensis* with ground squirrels (*Spermophilus* spp.). In Europe, host-specific relationships between *Bartonella* spp. and rodents are less evident. *B. alsatica* has been described and isolated from the blood of wild rabbits and also detected from rabbit fleas. *B. rochalimae* has been isolated or detected from canids, raccoons, and rodents. Animal reservoirs for *B. tamiae* have not been identified, but the patients infected with this organism stated

that they had previous contact with rats and *B. tamiae* DNA has been detected in chigger mites collected from rats. *B. mayotimonensis,* a recently identified etiological agent of human endocarditis, was detected in bats from Europe and North America. Recently, *B. quintana*, which was thought to be only a human pathogen, has been isolated from macaques in various Asian countries raising a possible zoonotic origin. Numerous isolates of *Bartonella* spp. have been obtained from wildlife including marsupials from Australia.

7. Sample/specimen requirements—Paired serum samples (the acute taken at first presentation and the convalescent taken 3–6 weeks later) should be collected for evaluation of antibodies reactive with *Bartonella* spp. The preferable specimen types for culture isolation of *Bartonella* are blood, tissues, and lymph node aspirate. The samples should be kept frozen at –20°C or below before shipping to a laboratory on dry ice. Overnight shipment of refrigerated specimens is also suitable. Blood can be collected into either ethylenediaminetetraacetic acid-anticoagulant tubes or Isolator blood lysis tubes, although blood clots can also be used for culturing and molecular detection. Check with the clinical laboratory regarding specimen submission requirement. Because of the broad susceptibility of *Bartonella* spp. to antibiotics, it is very desirable to collect blood specimens before antibiotic therapy. It was reported that growth of *B. henselae* was inhibited by concentrations of sodium polyanethol sulfonate in collection tubes. Tissue samples other than blood suitable for culture or PCR detection methods include cardiac valves from the patients suspected of having *Bartonella* endocarditis, skin biopsies, lymph nodes, liver, spleen, and osteomedullar biopsies. Tissues and fluid from affected lymph nodes can be collected by fine-needle aspiration and submitted for testing.

8. Testing requirements—Well-validated assays offered by CLIA–certified reference laboratories are recommended for clinical diagnostics. All isolation work should be performed in a biosafety cabinet after preparation of workplace and tools. *Bartonella* is optimally cultured at 35°C with an atmosphere containing 5% CO_2. However, growth of *B. bacilliformis* is optimal at a lower temperature of incubation (25°C–28°C) and in the absence of CO_2 enrichment. Tissue samples can be triturated in M199 medium with 20% fetal bovine serum prior to inoculation, then spread onto freshly poured agar plates. Recovery of primary isolates may require several days to several weeks. Initial identification of the bacteria is mainly based on colony and bacterium morphology with subsequent confirmation by DNA amplification and sequencing. Long-term storage of the cultures is achieved by freezing at –80°C or below in a final concentration of 10% glycerol in Brain Heart Infusion. DNA extracts suitable for use as templates in PCR assays are prepared from blood samples or crushed tissues by using extraction reagents available from various manufacturers. Identification of *Bartonella* spp. needs to be carefully addressed by using 3 to 5 housekeeping loci as genetic markers. In the case of isolates, only well isolated

colonies with at least 2 subcultures from single colonies are recommended for the characterization. Sensitivity and specificity of IFAs may be improved by using a variety of antigens prepared by cocultivation of *Bartonella* strains with antibiotic-free Vero cells.

9. Reporting requirements—*Bartonella* infection is not a nationally notifiable condition in the USA. Laboratories outside the USA should determine whether *Bartonella* infections are reportable within their respective jurisdictions.

10. Referral network—Testing for bartonellosis does not utilize a special tiered referral laboratory testing system. Clinical laboratories must determine if they have the requisite capability and request a confirmation of their results from CLIA-certified reference laboratories when they are available.

11. Special considerations—None.

[M. Kosoy, B. Chomel]

BEJEL

(Njovera, nonvenereal endemic syphilis)

DISEASE	ICD-10 CODE
BEJEL	ICD-10 A65

1. Clinical features—A chronic skin and tissue disease characterized by an eruption on skin and mucous membranes, usually without an evident primary sore, as seen in yaws.

During the primary stage, lesions are painless, and tiny papules or ulcers that appear on the mouth and lips often go undetected. Secondary lesions are characterized by shallow, painless mucous patches of the mouth, soon followed by moist papules in skinfolds and by drier lesions on the trunk and extremities. Other secondary skin lesions are macular or papular, often hypertrophic, and frequently circinate; lesions resemble those of venereal syphilis. Plantar and palmar hyperkeratoses occur frequently, often with painful fissuring; alopecia and patchy depigmentation/hyperpigmentation of the skin are common. Inflammatory or destructive lesions of skin, long bones, and nasopharynx are late manifestations. Unlike venereal syphilis, bejel rarely shows neurological or cardiovascular involvement. The case-fatality rate is low.

2. Causative agents—*Treponema pallidum* subsp. *endemicum*, a spirochete.