Bartonellosis

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Epidemiology

Bartonella species cause infections that include cat scratch disease, retinitis, trench fever, relapsing bacteremia, culture-negative endocarditis, bacillary angiomatosis (BA), and bacillary peliosis hepatis.[1] The latter two manifestations occur almost exclusively in individuals who are immunocompromised. Thirty-seven species and three subspecies of *Bartonella* have been described and are officially recognized (see Bartonella on the List of Prokaryotic Names with Standing in Nomenclature); fourteen of these *Bartonella* species have been implicated in human infections.

BA most often occurs late in HIV infection[2] in patients with median CD4 T lymphocyte (CD4) cell counts <50 cells/mm^3. In people with HIV, bartonellosis is often a chronic illness, lasting for months to more than a year, with BA lesions and intermittent bacteremia. Development of BA lesions caused by *B. henselae* is statistically linked to cat exposure in people with HIV.[2] In contrast, BA caused by *B. quintana* is associated with body louse infestation and homelessness.[2] The body louse serves as the vector of *B. quintana* to humans. To avoid exposure to *B. quintana*, people with HIV should avoid body lice exposure and have prompt eradication of lice if infestation occurs. The cat flea is the vector of *B. henselae* in cats. Cats are the most common vector (via a scratch) responsible for transmitting *B. henselae* to humans, most likely when their claws become contaminated with feces from *B. henselae*-infected fleas. In some areas of the United States, the prevalence of *B. henselae* bacteremia in pet cats approaches 50%;[3] infection is more common among kittens and feral cat populations. Controlling cat flea infestation and avoiding cat scratches are therefore critical strategies for preventing *B. henselae* infections in people with HIV.

Clinical Manifestations

BA lesions have been associated with nearly every organ system, but cutaneous lesions are the most readily identified. These lesions can be clinically indistinguishable from Kaposi sarcoma, pyogenic granuloma, and other skin conditions. BA also can cause subcutaneous nodules. Osteomyelitis is usually caused by *B. quintana*, and only *B. henselae* causes bacillary peliosis hepatis.[2] Although isolated organs can appear to be the principal focus of disease, BA represents a hematogenously disseminated infection, and systemic symptoms of fever, night sweats, and weight loss often accompany BA. *Bartonella* infection is a major cause of unexplained fever in patients with advanced HIV and should be considered in the differential diagnosis of patients with CD4 counts <100 cells/mm^3 and fever.[4] *Bartonella* is a frequent cause of culture-negative endocarditis in immunocompetent and immunocompromised humans and is most commonly caused by *B. quintana*, less frequently by *B. henselae*, and rarely by other *Bartonella* species.[5] Immune complex disease (such as glomerulonephritis) may complicate endocarditis or other systemic *Bartonella* infections; assessment for immune complex formation may be warranted in such cases so that nephrotoxic agents can be avoided.

Diagnosis

Diagnosis of BA can be confirmed by histopathologic examination of biopsied tissue.[6] BA lesions are characterized by vascular proliferation, and a modified silver stain (such as Warthin-Starry stain) usually demonstrates numerous bacilli. Tissue Gram staining and acid-fast staining are negative.

A well-characterized indirect fluorescent antibody (IFA) serologic test was developed at the Centers for Disease Control and Prevention (CDC)[7] and is available at the CDC Infectious Diseases Laboratories. In addition, several private laboratories offer IFA serological testing, but the performance characteristics of these tests have not been validated for people with HIV. In immunocompetent patients, anti-*Bartonella* antibodies might not be detectable for 6 weeks after acute infection; in contrast, by the time *Bartonella* infection is suspected in patients with late-stage HIV infection, they usually have been infected with *Bartonella* for months or even >1 year. However, as many as 25% of *Bartonella* culture-positive patients never develop antibodies in the setting of advanced HIV infection.[4] In those patients who do develop anti-*Bartonella* antibodies, monitoring of antibody levels can be useful in following treatment response of *Bartonella* infection to antibiotics, reflecting resolution[8] or recrudescence. Because of interlaboratory variability, longitudinal testing should be conducted at the same laboratory to enable direct comparison of titers over time.

Because of their fastidious nature, *Bartonella* organisms can be isolated only with difficulty from blood (drawn into ethylenediaminetetraacetic acid [EDTA] tubes, centrifuged, and then plated directly onto fresh chocolate agar). *Bartonella* has been cultured directly from tissue in only a few laboratories.[2] Removing samples from blood culture bottles after 8 days of incubation, followed by staining with acridine orange, has facilitated identification and subsequent culture of *Bartonella* species.[9] Additionally, the CDC can perform polymerase chain reaction (PCR) amplification with universal and/or specific primers to detect *Bartonella* in EDTA blood samples (see *Bartonella quintana* Molecular Detection); these molecular detection tests also are increasingly available through private laboratories. Finally, molecular detection of *Bartonella* in BA skin lesions or other vascular lesions, lymph nodes, or resected cardiac valves from unfixed tissue biopsy samples (at the University of Washington) or from formalin-fixed tissue (at the CDC Infectious Disease Pathology Branch) can be performed.[8,10] *Bartonella* species may also be detected from blood or plasma using metagenomic next generation sequencing.[11-13] Clinicians should be aware that results from the CDC may take longer—several weeks to months—for serologic and molecular testing, respectively, compared with some private laboratories. A notable update was published in the 2023 Duke-ISCVID Criteria for Infective Endocarditis, indicating that an IFA immunoglobulin G (IgG) titer of ≥1:800 for *B. quintana* or *B. henselae* or identification of a *Bartonella sp.* by PCR or other nucleic acid–based techniques (including metagenomic sequencing) from blood are now considered major criteria for the diagnosis of *Bartonella* endocarditis.[14]

In summary, diagnosis of bartonellosis may require multiple testing modalities, including serologic testing (which is the most accessible test, and when positive, is helpful both for diagnosis and subsequent monitoring of treatment response), histopathology, and, especially, molecular testing for biopsied or resected tissue (e.g., BA lesion tissue or heart valve tissue).

Preventing Exposure

People with HIV, specifically those who are severely immunocompromised (CD4 counts <100 cells/mm^3), are at high risk of severe disease when infected by *B. quintana* or *B. henselae*. The

major risk factors for acquisition of *B. henselae* are contact with cats infested with fleas and receiving cat scratches. Immunocompromised individuals should consider the potential risks of cat ownership **(AIII).** People with HIV who want cats should acquire animals that are older than 1 year of age and in good health **(BII).** Cats should be acquired from a known environment, have a documented health history, and be free of fleas. Stray cats and cats with flea infestation should be avoided. Declawing is not advised, but individuals with HIV should avoid rough play with cats and situations in which scratches are likely **(AII).** People with HIV should avoid contact with flea feces (i.e., flea dirt), and any cat-associated wound should be washed promptly with soap and water **(BIII).** Care of cats should include a comprehensive, ongoing flea-control program under the supervision of a veterinarian **(BIII).** No evidence indicates any benefits to cats or their owners from routine culture or serologic testing of the pet for *Bartonella* infection or from antibiotic treatment of healthy, serologically positive cats **(BII).** The major risk factor for *B. quintana* infection is body lice infestation. People with HIV who are experiencing homelessness or are in marginal housing should be informed that body louse infestation can be associated with serious illness and should be provided with appropriate measures to eradicate body lice, if present **(AII).** Regardless of CD4 count, people with both HIV and solid organ transplantation may be at risk of developing more severe *Bartonella* infections, similar to transplant recipients without HIV.[15]

Preventing Disease

Primary chemoprophylaxis for *Bartonella*-associated disease is not recommended **(BIII).** However, note that in a retrospective case-control study, use of a macrolide (such as for *Mycobacterium avium* complex prophylaxis) was protective against developing *Bartonella* infection.[2]

Treating Disease

Recommendations for Treating *Bartonella* Infections
Preferred Therapy
For Cat Scratch Disease, Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis
o Doxycycline 100 mg PO or IV every 12 hours (AII), *or*
o Erythromycin 500 mg PO or IV every 6 hours (AII)
For Infections Involving the CNS
o Doxycycline 100 mg PO or IV every 12 hours +/– rifampin 300 mg PO or IV every 12 hours (AIII)
For Confirmed Bartonella Endocarditis
o (Doxycycline 100 mg IV every 12 hours + rifampin 300 mg IV or PO every 12 hours) for 6 weeks, then continue with doxycycline 100 mg IV or PO every 12 hours for ≥3 months (BII), *or*
For Other Severe Infections (Multifocal Disease or with Clinical Decompensation)
o Doxycycline 100 mg PO or IV every 12 hours + rifampin 300 mg PO or IV every 12 hours (BIII), *or*
o Erythromycin 500 mg PO or IV every 6 hours + rifampin 300 mg PO or IV every 12 hours (BIII)
Note: IV therapy may be needed initially (AIII).
Alternative Therapy
For Confirmed Bartonella Endocarditis

- (Doxycycline 100 mg IV every 12 hours + gentamicin 1 mg/kg IV every 8 hours) for 2 weeks, then continue with doxycycline 100 mg IV or PO every 12 hours for ≥3 months (BII)

For Bartonella Infections Other than Endocarditis or CNS Infections

- Azithromycin 500 mg PO daily (BIII), *or*
- Clarithromycin 500 mg PO twice daily (BIII)

Duration of Therapy

- At least 3 months for all manifestations of *Bartonella* infection in patients with HIV

Long-Term Suppressive Therapy

Indication for Long-Term Suppressive Therapy

If a relapse occurs after a ≥3-month course of primary treatment:

- A macrolide or doxycycline as long as the CD4 count remains <200 cells/mm^3 (AIII)

Indications for Discontinuing Long-Term Suppressive Therapy (CIII)

- Received at least 3–4 months of treatment, *and*
- CD4 count >200 cells/mm^3 for at least 6 months
- Some specialists would discontinue therapy only if *Bartonella* titers have also decreased by 4-fold (CIII).

Other Considerations

- Rifamycin class antibiotics are potent hepatic enzyme inducers and may lead to significant interaction with many drugs, including ARV agents (see the Dosing Recommendations for Anti-TB Drugs table in the Mycobacterium tuberculosis Infection and Disease section for dosing recommendations).
- In pregnancy, erythromycin or an alternative macrolide should be used as first-line therapy (AIII) rather than tetracyclines (such as doxycycline) due to toxicity profile; third-generation cephalosporins may have efficacy but are second line. First- and second-generation cephalosporins are not recommended because of their lack of efficacy against *Bartonella* (AII).

Key: +/− = with or without; ARV = antiretroviral; CD4 = CD4 T lymphocyte; CNS = central nervous system; IV = intravenously; PO = orally

All patients with HIV and *Bartonella* infection should receive antibiotic treatment **(AII).** No randomized, controlled clinical trials have evaluated antimicrobial treatment of bartonellosis in patients with HIV. Erythromycin and doxycycline have been used successfully to treat BA, peliosis hepatis, bacteremia, and osteomyelitis; either drug is considered first-line treatment for bartonellosis on the basis of reported experience in case series **(AII).**[1,2] Anecdotal and limited published case reports[16] suggest that other macrolide antibiotics (such as azithromycin or clarithromycin) are effective in treating *Bartonella* infections in patients with HIV and may be better tolerated than erythromycin; either of these can be an alternative therapy for *Bartonella* infections (except for endocarditis or central nervous system [CNS] infections) **(BIII).** Therapy should be administered for at least 3 months **(AII).** Doxycycline, preferably in combination with a rifamycin class antibiotic, is the treatment of choice for bartonellosis infection involving the CNS **(AIII).** For severe *Bartonella* infections (i.e., patients with multifocal disease or evidence of clinical decompensation), combination therapy using erythromycin or doxycycline with a rifamycin class antibiotic is recommended **(BIII);** intravenous therapy may be needed initially **(AIII).** Treatment of *Bartonella* endocarditis should include doxycycline with the addition of a rifamycin class antibiotic for a minimum of 6 weeks **(BII).** Doxycycline for 6 weeks plus gentamicin for the first 2 weeks may also be considered but is less

preferred due to the intrinsic nephrotoxicity of gentamicin and the frequency of vasculitis-induced renal dysfunction complicating *Bartonella* endocarditis **(BII).**[17]

Penicillins and first-generation cephalosporins have no *in vivo* activity and should not be used for treatment of bartonellosis **(AII).**[18] *Bartonella* species have been isolated from patients with HIV during documented treatment or prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX);[2] quinolones and TMP-SMX also have variable *in vitro* activity and an inconsistent clinical response in case reports and are not recommended **(AIII).**

Monitoring of Response to Therapy and Adverse Effects (Including IRIS)

The potential exists for immune reconstitution inflammatory syndrome (IRIS) in association with bartonellosis treatment and initiation of antiretroviral therapy (ART) in people with HIV. In ART-naive patients, ART generally can be initiated at the same time as *Bartonella*-directed treatment; however, patients with *Bartonella* CNS or ophthalmic lesions probably should be treated with doxycycline and a rifamycin class antibiotic for 2 to 4 weeks before instituting ART **(CIII).**

Because of the propensity for relapse of *Bartonella* infection, patients should have anti-*Bartonella* IFA IgG antibody titers checked at the time of diagnosis (Note: It is important to specify to the receiving lab that the sample must be diluted to endpoint.) and, if positive, should be followed with sequential endpoint titers every 6 to 8 weeks during treatment, preferably until at least a fourfold decrease is documented **(CIII).**[8] Patients treated with oral doxycycline should be cautioned about pill-associated esophagitis and photosensitivity. Adverse effects associated with macrolides include nausea, vomiting, abdominal pain, and elevations of liver transaminase levels; potential QT interval prolongation also should be considered. Serious side effects can occur during treatment with rifamycin class antibiotics, including hypersensitivity reactions (thrombocytopenia, interstitial nephritis, and hemolytic anemia) and hepatitis. Administration of rifamycin class antibiotics strongly induces the cytochrome P450 enzyme system, which is an important consideration when other medications, including many antiretroviral drugs, are taken simultaneously.

Managing Treatment Failure

Relapse of *Bartonella* infections occurs frequently, especially in patients with BA. Among patients who fail to respond to initial treatment, switching to a different preferred regimen (for example, from doxycycline to erythromycin) may be considered, again with treatment duration of ≥3 months **(AIII).** For severe infections, the addition of a rifamycin class antibiotic is indicated **(AIII).** For patients with positive or increasing antibody titers, but with clinical improvement, treatment should continue until at least a fourfold decrease in the antibody titers is documented **(CIII).**[8]

Preventing Recurrence

After a primary course of treatment (minimum of 3 months), treatment may be discontinued, with close monitoring for evidence of relapse (e.g., symptoms, increase in antibody titers).

If a relapse occurs, an additional course of treatment is recommended, followed by long-term suppression of infection with doxycycline or a macrolide **(AIII).**

Long-term suppression can be discontinued after the patient has received at least 3 to 4 months of therapy and when the CD4 count remains >200 cells/mm^3 on effective ART for ≥6 months **(CIII).**[8]

Some specialists would discontinue therapy only if the *Bartonella* titers also have decreased at least fourfold **(CIII).**

Special Considerations During Pregnancy

Infection with *B. bacilliformis* in immunocompetent patients during pregnancy has been associated with increased complications and risk of death, but no data are available on the effect of *B. quintana* or *B. henselae* infection during pregnancy.

The approach to diagnosis of *Bartonella* infections in pregnant people is the same as in nonpregnant people. Erythromycin treatment (or an alternative macrolide) should be used as first-line therapy **(AIII)** rather than tetracyclines (such as doxycycline) during pregnancy because of the increased risk of hepatotoxicity and the accumulation of tetracycline in fetal teeth and bones, resulting in dark, permanent staining of fetal teeth. Third-generation cephalosporins, such as ceftizoxime[19] or ceftriaxone, may have efficacy against *Bartonella* in pregnant people with HIV, but it should be considered second-line therapy after a macrolide. First- and second-generation cephalosporins are not recommended because of their lack of efficacy against *Bartonella* **(AII).**

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