Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

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Bartonellosis (Last updated May 7, 2013; last reviewed May 7, 2013)

Epidemiology

Bartonella species cause infections that include cat scratch disease, retinitis, trench fever, relapsing bacteremia, endocarditis, bacillary angiomatosis (BA), and bacillary peliosis hepatis.[1] The latter two manifestations occur only in individuals who are immunocompromised. BA is caused by either *Bartonella quintana* or *Bartonella henselae*.[1,2] Twenty-four species and three subspecies of *Bartonella* have been isolated and are officially recognized (http://www.bacterio.cict.fr/b/bartonella.html), and eight have been isolated from humans. However, only *B. henselae* and *B. quintana* infections have been identified in HIV-infected patients.[2] BA most often occurs late in HIV infection, in patients with median CD4 T lymphocyte (CD4 cell) counts <50 cells/mm^3.[2] In HIV-infected patients, bartonellosis is often a chronic illness, lasting for months to years, with BA lesions and intermittent bacteremia.

Development of BA lesions caused by *B. henselae* is statistically linked to cat exposure in patients with HIV infection.[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* in humans. To avoid exposure to *B. quintana*, HIV-infected patients should avoid body lice and, if infected, treat the infestation. 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] Control of cat flea infestation and avoidance of cat scratches are therefore critical strategies for preventing *B. henselae* infections in patients who are HIV infected.

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* can cause bacillary peliosis hepatis. 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 late-stage AIDS and should be considered in the differential diagnosis of patients with fever and CD4 counts <100 cells/mm^3.[4] *Bartonella* is a relatively common cause of culture-negative endocarditis in immunocompetent and immunocompromised humans and is most commonly caused by *B. quintana* and, less frequently, *B. henselae*.[5]

Diagnosis

Diagnosis 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 serologic test was developed at Centers for Disease Control and Prevention[7] and is also available at some state health labs. In addition, several private laboratories offer serological testing, but none of these private laboratory tests has been evaluated for sensitivity or specificity with sera from HIV-infected patients with culture-documented *Bartonella* infection. 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 for months or even >1 year. Note that 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 correlate with resolution and recrudescence of *Bartonella* infection.

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Bartonella species can be isolated (with difficulty) from blood, using ethylenediaminetetraacetic acid (EDTA) tubes. The organisms have been isolated from tissue in only a few laboratories because of the fastidious nature of *Bartonella*.[2] Polymerase chain reaction methods have been developed for identification and speciation of *Bartonella* but are not widely available.

Preventing Exposure

HIV-infected patients, specifically those who are severely immunocompromised (CD4 counts <100 cells/mm^3), are at high risk of severe disease when infected by *B. quintana* and *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)**. Patients who want cats should acquire animals that are older than age 1 year 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 HIV-infected individuals should avoid rough play with cats and situations in which scratches are likely **(AII)**. Patients 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. Patients who are homeless or in marginal housing should be informed that body louse infestation can be associated with serious illness and provided with appropriate measures to eradicate body lice, if present **(AII)**.

Preventing Disease

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

Treating Disease

All HIV-infected patients with *Bartonella* infection should receive antibiotic treatment **(AII)**. Guidelines for treatment of *Bartonella* infections have been published.[8] No randomized, controlled clinical trials have evaluated antimicrobial treatment of bartonellosis in HIV-infected patients. Erythromycin and doxycycline have been used successfully to treat BA, peliosis hepatis, bacteremia, and osteomyelitis and are considered first-line treatment for bartonellosis on the basis of reported experience in case series **(AII)**.[1,2] Therapy should be administered for ≥3 months **(AII)**. Doxycycline, with or without a rifamycin, is the treatment of choice for bartonellosis infection involving the central nervous system (CNS) **(AIII)**. For severe *Bartonella* infections, combination therapy using erythromycin or doxycycline with a rifamycin is recommended **(BIII)**; intravenous therapy may be needed initially **(AIII)**. Treatment of confirmed *Bartonella* endocarditis should include doxycycline with the addition of gentamicin for 2 weeks (if tolerated); a rifamycin can be substituted for gentamicin in the setting of renal insufficiency **(BII)**.[8]

Clarithromycin or azithromycin treatment has been associated with clinical response and either of these can be an alternative therapy *Bartonella* infections (except for endocarditis or CNS infections) **(BIII)**. Azithromycin is recommended for patients who are less likely to comply with the more frequent dosing schedule for doxycycline or erythromycin. A third-generation cephalosporin, ceftizoxime,[9] was used successfully to treat *Bartonella* in a pregnant HIV-infected woman, but because there are no other data, a macrolide is the drug of first choice. Penicillins and first-generation cephalosporins have no *in vivo* activity and should not be used for treatment of bartonellosis **(BII)**. Quinolones and trimethoprim-sulfamethoxazole (TMP-SMX) have variable *in vitro* activity and an inconsistent clinical response in case reports and are not recommended **(BIII)**.

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Special Consideration with Regard to Starting ART

Antiretroviral-naive patients with *Bartonella* CNS or ophthalmic lesions should probably be treated with doxycycline and a rifamycin for 2 to 4 weeks before instituting antiretroviral therapy **(CIII)**.

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

Patients should have anti-*Bartonella* IgG antibody titers checked at the time of diagnosis and, if positive, should be followed with sequential titers every 6 to 8 weeks until a four-fold decrease is documented. This test is available at the Centers for Disease Control and Prevention and several large commercial labs. Patients treated with oral doxycycline should be cautioned about pill-associated ulcerative esophagitis that occurs most often when a dose is taken with only a small amount of liquid or at night just before retiring.[10] Photosensitivity also can occur during doxycycline treatment. Adverse effects associated with macrolides include nausea, vomiting, abdominal pain, and elevations of liver transaminase levels. Serious side effects can occur during treatment with rifamycins, including hypersensitivity reactions (including thrombocytopenia, interstitial nephritis, and hemolytic anemia), and hepatitis. Administration of rifamycins strongly induces the cytochrome P450 enzyme system, which is an important consideration when other medications, including many ARV drugs, are taken simultaneously.

Immune reconstitution inflammatory syndrome (IRIS) has not been described in association with Bartonellosis and treatment with ART in HIV-infected persons.

Managing Treatment Failure

Among patients who fail to respond to initial treatment, 1 or more of the second-line alternative regimens should be considered **(AIII)**, again with treatment duration of ≥3 months. For patients with positive or increasing antibody titers, treatment should continue until a fourfold decrease is documented.

Preventing Recurrence

If a relapse occurs after a minimum 3-month course of primary treatment, long-term suppression of infection with doxycycline or a macrolide is recommended, as long as the CD4 count remains <200 cells/mm^3 **(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 for ≥6 months **(CIII)**. Some specialists would discontinue therapy only if the *Bartonella* titers have also decreased by four-fold **(CIII)**.

Special Considerations During Pregnancy

Infection with *Bartonella bacilliformis* in immunocompetent patients during pregnancy has been associated with increased complications and risk of death.[11] No data are available on the effect of *B. henselae* or *B. quintana* infections in pregnant women with concomitant HIV infection.

The approach to diagnosis of *Bartonella* infections in pregnant women is the same as in non-pregnant women. Erythromycin treatment should be used **(AIII)** rather than tetracyclines 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[9] or ceftriaxone may have efficacy against *Bartonella* in pregnant women who are HIV infected, 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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Recommendations for Treating *Bartonella* Infections

Preferred Therapy

For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis:

- Doxycycline 100 mg PO or IV q12h **(AII)**, *or*
- Erythromycin 500 mg PO or IV q6h **(AII)**

For Infections Involving the CNS:

- Doxycycline 100 mg PO or IV q12h +/- rifampin 300 mg PO or IV q12h **(AIII)**

For Confirmed Bartonella Endocarditis:

- (Doxycycline 100 mg IV q12h + gentamicin 1 mg/kg IV q8h) x 2 weeks, then continue with doxycycline 100 mg IV or PO q12h **(BII)**, *or*
- For patients with renal insufficiency: (doxycycline 100 mg IV q12h + rifampin 300 mg IV or PO q12h) x 2 weeks, then continue with doxycycline 100 mg IV or PO q12h **(BII)**

For Other Severe Infections

- Doxycycline 100 mg PO or IV q12h + rifampin 300 mg PO or IV q12h **(BIII)**, *or*
- Erythromycin 500 mg PO or IV q6h + rifampin 300 mg PO or IV q12h **(BIII)**

Alternative Therapy for Bartonella Infections (Not for Endocarditis or CNS Infections):

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

Duration of Therapy:

- At least 3 months

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 to 4 months of treatment; and
- CD4 count >200 cells/mm^3 for at least 6 months
- Some specialists would only discontinue therapy if *Bartonella* titers have also decreased by four-fold

Other Considerations

- Rifampin is a potent hepatic enzyme inducer and may lead to significant interaction with many drugs; including ARV agents (see Table 5 for dosing recommendations)

Key to Abbreviations: ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte cell; CNS = central nervous system, IV = intravenously, PO = orally; q(n)h = every "n" hours

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