

Bartonella Infections, Including Cat-Scratch Disease

Chapter 177 | Part 5: Infectious Diseases

KEY CLINICAL POINTS

- 1 Cat-scratch disease (CSD) is typically self-limited; systemic antibiotics are controversial unless severe or immunocompromised.
- 2 *B. henselae* is the primary agent of CSD; *B. quintana* causes trench fever and bacillary angiomatosis in homeless populations.
- 3 *B. bacilliformis* causes Carrión's disease (Oroya fever and verruga peruana) in South America.
- 4 Culture-negative endocarditis should raise suspicion for Bartonella; treatment requires gentamicin plus doxycycline plus ceftriaxone.
- 5 Bacillary angiomatosis in HIV patients requires macrolide or doxycycline therapy; lesions regress with antiretroviral therapy.
- 6 Suppurative lymph nodes in CSD should be drained by needle aspiration, not incision and drainage, to avoid chronic draining tracts.
- 7 Serologic cross-reactivity between *B. henselae*, *B. quintana*, *C. burnetii*, and *Chlamydia* species limits serologic specificity.
- 8 PCR of lymph node pus or primary lesion is highly sensitive and specific for definitive diagnosis in seronegative patients.
- 9 Trench fever is characterized by periodic fever episodes lasting 4–5 days with 5-day intervals between episodes.
- 10 *B. henselae* endocarditis usually involves preexisting valvulopathy; *B. quintana* often infects normal valves.

1. DEFINITION & OVERVIEW

- **Microbiology:** Fastidious, facultative intracellular, slow-growing, gram-negative bacteria.
- **Diversity:** >40 distinct species/subspecies; ≥ 20 confirmed or potential human pathogens.
- **Host Adaptation:** Most species adapted to specific domestic or wild mammals; chronic bacteremia is a typical finding in these hosts.
- **Mechanism of Pathogenicity:**
 - Adhesion to endothelial cells and erythrocytes via Bartonella adhesin A or variably expressed outer-membrane proteins.
 - Immune evasion through modification of virulence factors (e.g., lipopolysaccharides or flagella) and attenuation of the host immune response.
- **Host Status:** Humans are incidental hosts for most species, with the exception of *B. quintana* and *B. bacilliformis*, which are not considered zoonotic agents.

1.1 Cat-Scratch Disease (CSD)

- **Nature:** Usually a self-limited illness.
- **Clinical Presentations:**
 - Typical: Subacute regional lymphadenopathy.
 - Atypical/Extranodal: Involvement of various organs.
- **Etiology:** *B. henselae* is the principal agent; rare cases associated with *Afipia felis* and other *Bartonella* species.

1.2 Trench Fever

- **Synonyms:** Also known as 5-day fever or quintan fever.
- **Etiology:** Caused by *B. quintana*.
- **History/Context:** First described in World War I trenches; reemerged as chronic bacteremia in homeless populations (urban trench fever).
- **Clinical Pattern:** Periodic fever episodes lasting 4–5 days with 5-day intervals between episodes.

1.3 Bacillary Angiomatosis and Peliosis

- **Patient Population:** Seen in severely immunocompromised patients.
- **Etiology:** Caused by *B. henselae* or *B. quintana*.
- **Pathology:** Neovascular proliferative lesions involving various organs.
- **Clinical Manifestations:** Cutaneous lesions (tan, red, purple), subcutaneous nodules, ulcerated plaques, and lytic bone lesions.
- **Specific Findings:** Hepatosplenic lesions occur only with *B. henselae*.
- **Differential Diagnosis:** Kaposi's sarcoma, pyogenic granuloma, and verruga peruana.

1.4 Carrión's Disease

- **Etiology:** Caused by *B. bacilliformis*.
- **Stages:**
 - Oroya fever: Acute, fatal stage.
 - Verruga peruana: Chronic stage.
- **Geography:** Endemic to the Andes of South America.

2. EPIDEMIOLOGY

- **CSD Distribution:** Global; favors warm/humid climates; peaks in fall/winter in temperate regions.
- **Demographics:** Affects both adults and children (higher rates in children 5–9 years old in the US).
- **Reservoirs & Vectors:**
 - *B. henselae*: Healthy bacteremic cats are the primary reservoir; transmitted by cat fleas (*Ctenocephalides felis*).
 - *B. quintana*: Risk factors include homelessness, alcoholism, and louse infestation.
- **Bacillary Angiomatosis:** Occurs primarily in HIV-infected patients with CD4+ <100/μL.
- **Incidence (US):** 4–9 cases/100,000 population.

2.1 Geographic and Seasonal Variation

- **CSD:** Global; favors warm/humid climates; temperate regions peak in fall/winter.

2.2 Risk Factors

- **Modifiable:** Cat contact (especially kittens), flea infestation, homelessness, alcoholism, low income.
 - **Non-modifiable:** Age (children 5–9 years in US), sex (male > female for endocarditis), immune status (HIV, immunosuppression).
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3. ETIOLOGY & PATHOPHYSIOLOGY

- **Microbiology:** Fastidious, facultative intracellular, slow-growing, gram-negative.
- **Host Interaction:**
 - Adhesion to endothelial cells and erythrocytes via Bartonella adhesin A or outer-membrane proteins.
 - Immune evasion through modification of virulence factors (lipopolysaccharides/flagella) and attenuation of the immune response.
- **Persistence:** Chronic bacteremia persists in many hosts despite antimicrobial therapy.

3.1 Transmission

- **Cat-to-Cat:** Via cat fleas (*Ctenocephalides felis*).
- **Cat-to-Human:**
 - Contaminated flea feces via scratch/bite.
 - Mucosal exposure to infected saliva.
- **Pathogenesis:** Lymphatic drainage leads to granulomatous lymphadenitis in immunocompetent hosts.

3.2 Immune Evasion

- **Mechanism:** Modification of virulence factors (e.g., lipopolysaccharides) and attenuation of immune responses.
 - **Outcome:** Chronic bacteremia persists despite antimicrobial therapy in some hosts.
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4. CLINICAL FEATURES

- **Typical CSD (85–90% of cases):**
 - Primary lesion: 0.3–1 cm painless erythematous papule/pustule at inoculation site (seen in 1/3–2/3 patients).
 - Lymphadenopathy: Develops 1–3 weeks post-exposure; often axillary/epitrochlear.
 - Systemic symptoms: Fever (50%), malaise, anorexia.
 - Resolution: Weeks to months.
- **Atypical CSD:**
 - Includes Parinaud's oculoglandular syndrome, hepatosplenic disease, neuroretinitis, and FUO.
 - Elderly patients may present with encephalitis/FUO instead of lymphadenopathy.
- **Trench Fever:**
 - Incubation: 15–25 days (range 3–38).
 - Pattern: Periodic fevers lasting 4–5 days with 5-day intervals for 4–6 weeks.
 - Symptoms: Headache, back/limb pain, profuse sweating, myalgia, splenomegaly, maculopapular rash.

- **Bacillary Angiomatosis & Peliosis:**
- Cutaneous: Tan, red, or purple lesions; subcutaneous nodules; ulcerated plaques.
- Systemic: Fever, chills, weight loss.
- Bone: Lytic bone changes on radiography.
- **Carrión's Disease:**
- Oroya fever (acute, fatal) and Verruga peruana (chronic).

4.1 Typical Cat-Scratch Disease

- **Primary lesion:** 0.3–1 cm painless erythematous papule/pustule at inoculation site (1/3–2/3 patients).
- **Lymphadenopathy:** Develops 1–3 weeks post-exposure, often axillary/epitrochlear.
- **Systemic symptoms:** fever (50%), malaise, anorexia.
- **Resolution:** weeks to months.

4.2 Atypical Cat-Scratch Disease

- **Conditions:** Parinaud's oculoglandular syndrome, hepatosplenic disease, neuroretinitis, and FUO.
- **Elderly Presentation:** May present with encephalitis/FUO instead of lymphadenopathy.

4.3 Trench Fever

- **Incubation:** 15–25 days (range 3–38).
- **Pattern:** Periodic fevers lasting 4–5 days with 5-day intervals.
- **Symptoms:** headache, back/limb pain, profuse sweating, myalgia, splenomegaly, maculopapular rash.

4.4 Bacillary Angiomatosis and Peliosis

- **Cutaneous:** tan/red/purple lesions, subcutaneous nodules, ulcerated plaques.
- **Systemic:** fever, chills, weight loss.
- **Bone:** lytic bone changes on radiography.

4.5 Carrión's Disease

- **Oroya fever:** acute, fatal.
- **Verruga peruana:** chronic.

5. DIFFERENTIAL DIAGNOSIS

- **Lymphadenitis:** Pyogenic lymphadenitis, mycobacterial infection, brucellosis, syphilis, tularemia, plague, toxoplasmosis, sporotrichosis, histoplasmosis.
- **Endocarditis:** Culture-negative endocarditis (HACEK group), other infective endocarditis pathogens.
- **Cutaneous Lesions:** Kaposi's sarcoma, pyogenic granuloma, subcutaneous tumors, verruga peruana.

5.1 Lymphadenitis

- **Differential:** pyogenic lymphadenitis, mycobacterial infection, brucellosis, syphilis, tularemia, plague, toxoplasmosis, sporotrichosis, histoplasmosis.

5.2 Endocarditis

- **Differential:** culture-negative endocarditis (HACEK group) and other infective endocarditis pathogens.

5.3 Cutaneous Lesions

- **Differential:** Kaposi's sarcoma, pyogenic granuloma, subcutaneous tumors, verruga peruana.
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6. INVESTIGATIONS & DIAGNOSIS

1. **Routine Labs:** Typically normal or non-specific.
2. **Histopathology:** Identify lymphoid hyperplasia, stellate granulomata with necrosis, coalescing microabscesses, and multinucleated giant cells.
3. **Serology (IFA/EIA):** Check for high-titer IgG $\geq 1:800$; note potential cross-reactivity with *C. burnetii* and Chlamydia species.
4. **PCR:** Perform on lymph node pus or primary lesion $\rightarrow$ highly sensitive and specific; used as gold standard for seronegative patients.
5. **Culture:** Blood cultures positive in $\sim 25\%$ of cases (mostly *B. quintana*); requires prolonged incubation up to 6 weeks.
6. **Imaging:**
 - Radiography: Identify lytic bone lesions.
 - Technetium scan: Identify focal uptake in osseous disease.
 - CT/MRI: Identify hypodense hepatic areas in peliosis.
7. **Special Stains:** Warthin-Starry staining to reveal bacilli in angiomatosis or peliosis.

6.1 Laboratory Tests

- **Histopathology:** lymphoid hyperplasia, stellate granulomata with necrosis, coalescing microabscesses, multinucleated giant cells.
- **Serology:** IFA/EIA (high-titer IgG $\geq 1:800$), cross-reactivity with *C. burnetii*/Chlamydia.
- **PCR:** lymph node pus/primary lesion (high sensitivity/specificity).

6.2 Culture

- **Blood cultures:** positive in $\sim 25\%$ of cases (mostly *B. quintana*).
- **Incubation:** Prolonged incubation (up to 6 weeks) required.
- **Angiomatosis/Peliosis:** Cultures usually negative.

6.3 Imaging

- **Radiography:** lytic bone lesions.
 - **Technetium scan:** focal uptake in osseous disease.
 - **CT/MRI:** hypodense hepatic areas in peliosis.
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7. MANAGEMENT & TREATMENT

1. Cat-Scratch Disease:

- Typical cases: No routine antibiotics.

- Extensive lymphadenopathy: Azithromycin (500 mg PO day 1, then 250 mg/day imes 4 days).
- Severe cases: Doxycycline (100 mg PO bid) + Rifampin (300 mg PO bid) imes 4–6 weeks.

2. Trench Fever and Chronic Bacteremia:

- Gentamicin (3 mg/kg IV daily imes 14 days).
- Doxycycline (200 mg PO/day or 100 mg bid imes 6 weeks) for *B. quintana*.

3. Bacillary Angiomatosis and Peliosis:

- Erythromycin (500 mg PO qid imes 3 months) OR Doxycycline (100 mg PO bid imes 3 months).
- Peliosis specific: Erythromycin imes 4 months.

4. Carrión's Disease:

- Oroya fever: Chloramphenicol (500 mg PO/IV qid imes 14 days) + β -lactam OR Ciprofloxacin (500 mg PO bid imes 10 days) $\pm$ ceftriaxone (1–2 g IV once a day imes 10 days).
- Verruga peruana: Azithromycin (500 mg PO once a day imes 7 days) OR Ciprofloxacin (500 mg PO bid imes 7–10 days) OR Rifampin (10 mg/kg PO once a day, max 600 mg, imes 14 days) OR Streptomycin (15–20 mg/kg IM once a day imes 10 days).

Table Reference:

- Table 1 lists various species including *B. henselae* (CSD, angiomatosis), *B. quintana* (Trench fever, endocarditis), and *B. bacilliformis* (Carrión's disease).
- Table 2 provides specific dosages for CSD, Endocarditis (Gentamicin + Doxycycline + Ceftriaxone), and Bacillary Angiomatosis.

7.1 Cat-Scratch Disease

- **Typical:** No routine antibiotics; azithromycin (500 mg PO day 1, then 250 mg/day imes 4 days) for extensive lymphadenopathy.
- **Severe:** Doxycycline (100 mg PO bid) + Rifampin (300 mg PO bid) imes 4–6 weeks.

7.2 Trench Fever and Chronic Bacteremia

- **Gentamicin:** 3 mg/kg IV daily imes 14 days.
- **Doxycycline:** 200 mg PO/day or 100 mg bid imes 6 weeks.

7.3 Bacillary Angiomatosis and Peliosis

- **Erythromycin:** 500 mg PO qid imes 3 months.
- **Doxycycline:** 100 mg PO bid imes 3 months.
- **Peliosis:** Erythromycin imes 4 months.

7.4 Carrión's Disease

- **Oroya fever:** Chloramphenicol (500 mg PO/IV qid imes 14 days) + β -lactam or Ciprofloxacin (500 mg PO bid imes 10 days) $\pm$ ceftriaxone (1–2 g IV once a day imes 10 days).
- **Verruga peruana:** Azithromycin (500 mg PO once a day imes 7 days), Ciprofloxacin (500 mg PO bid imes 7–10 days), Rifampin (10 mg/kg PO once a day, max 600 mg, imes 14 days), or Streptomycin (15–20 mg/kg IM once a day imes 10 days).

8. PROGNOSIS & COMPLICATIONS

- **Typical CSD:** Resolves spontaneously without sequelae.

- **Atypical CSD:** May cause vision loss or FUO mimicking malignancy.
 - **Endocarditis:** High mortality if untreated.
 - **Bacillary Angiomatosis:** Progresses in immunocompromised patients.
 - **Carrión's Disease:** Oroya fever is fatal without treatment; Verruga peruana is chronic but non-fatal.
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9. SPECIAL CONSIDERATIONS

- **Immunocompromised Patients:**
 - Bacillary angiomatosis/peliosis require macrolide/doxycycline therapy.
 - Lesions regress with antiretroviral therapy in HIV patients.
- **Valvular Heart Disease:**
 - *B. henselae* endocarditis usually involves preexisting valvulopathy.
 - *B. quintana* often infects normal valves.

9.1 Immunocompromised Patients

- **Treatment:** Macrolide/doxycycline for BA/peliosis; ART for HIV patients.

9.2 Valvular Heart Disease

- *B. henselae*: Preexisting valvulopathy.
 - *B. quintana*: Normal valves.
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10. KEY PEARLS & CLINICAL TRAPS

- **Diagnostic Pearls:**
 - PCR of lymph node aspirate is gold standard for seronegative patients.
 - Warthin-Starry staining identifies bacilli in angiomatosis/peliosis.
- **Treatment Pearls:**
 - Avoid incision/drainage of suppurative nodes to prevent chronic tracts.
 - Use Gentamicin + Doxycycline + Ceftriaxone for suspected endocarditis.
- **Clinical Traps:**
 - Serologic cross-reactivity with *C. burnetii*/Chlamydia.
 - Culture-negative endocarditis should prompt Bartonella consideration.

10.1 Diagnostic Pearls

- **PCR:** Gold standard for seronegative patients.
- **Warthin-Starry:** Identifies bacilli in angiomatosis/peliosis.

10.2 Treatment Pearls

- **Incision/Drainage:** Avoid to prevent chronic tracts.
 - **Endocarditis:** Use Gentamicin + Doxycycline + Ceftriaxone.
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REFERENCE TABLES

TABLE 177-1

Bartonella Species Known or Suspected to Be Human Pathogens

BARTONELLA SPECIES ^a	DISEASE(S) ^b	RESERVOIR HOST(S) ^c	ARTHROPOD VECTOR
B. alsatica	Endocarditis, lymphadenitis, vascular graft infection	Rabbits	Fleas
	Verruga peruana, bacteremia	Unknown	
B. bacilliformis	Carrión's disease	Humans	Sandflies (<i>Lutzomyia verrucarum</i>)
	Possibly cat-scratch disease	Cats, dogs	
B. doshiae	Bacteremia, arthralgia, blurred vision	Voles, rats	Unknown
	Endocarditis	Rats, dogs	
B. grahamii	Lymphadenopathy, possibly retinitis and retinal vascular occlusion	Mice, voles, rats, deer	Fleas
	Cat-scratch disease, bacillary angiomatosis, bacillary peliosis, bacteremia, endocarditis	Cats, other felines	
B. koehlerae	Endocarditis	Cats	Unknown
	Lymphadenopathy	Rats	
"Candidatus Bartonella mayotimonensis"^d	Endocarditis	Bats	Unknown
	Various clinical manifestations	Sheep	
B. quintana	Trench fever, chronic bacteremia, bacillary angiomatosis, endocarditis	Humans	Human body lice (<i>Pediculus humanus corporis</i>)
	Bacteremia, fever, splenomegaly	Foxes, coyotes, dogs, skunks, rats, other rodents	
B. schoenbuchensis	Bacteremia, fever, myalgia, deer ked dermatitis?	Cattle, roe deer, moose	Unknown
	Bacteremia, fever, myalgia, rash	Rats	

BARTONELLA SPECIES ^a	DISEASE(S) ^b	RESERVOIR HOST(S) ^c	ARTHROPOD VECTOR
B. tribocorum	Bacteremia, myalgia, headache	Rats, mice	Unknown
	Endocarditis, febrile illness	Mice, dogs	
B. vinsonii subsp. berkhoffii	Endocarditis	Domestic dogs, coyotes, gray foxes	Ticks
	Endocarditis, myocarditis, meningitis	Squirrels, rabbits, prairie dogs, possibly other rodents	

TABLE 177-2

Antimicrobial Therapy for Disease Caused by Bartonella Species in Adults DISEASE Typical cat-scratch disease...

DISEASE	ANTIMICROBIAL THERAPY
Typical cat-scratch disease	Not routinely indicated; for patients with extensive lymphadenopathy, consider azithromycin (500 mg PO on day 1, then 250 mg PO once a day for 4 days)
Other atypical cat-scratch disease manifestations ^a	As per neuroretinitis. Treatment duration should be individualized.
Suspected Bartonella endocarditis	Gentamicin ^b (1 mg/kg IV q8h for ≥14 days) plus doxycycline (100 mg PO/IV bid for 6 weeks ^c) plus ceftriaxone (2 g IV once a day for 6 weeks)
Bacillary angiomatosis	Erythromycin ^d (500 mg PO qid for 3 months) or Doxycycline (100 mg PO bid for 3 months)
Carrión's disease	
Oroya fever	Chloramphenicol (500 mg PO/IV qid for 14 days) plus another antibiotic (β-lactam preferred) or Ciprofloxacin (500 mg PO bid for 10 days) ± ceftriaxone (1–2 g IV once a day for 10 days)
Verruga peruana	Azithromycin (500 mg PO once a day for 7 days) or Ciprofloxacin (500 mg PO bid for 7–10 days) or Rifampin (10 mg/kg PO once a day, to a maximum of 600 mg, for 14 days) or Streptomycin (15–20 mg/kg IM once a day for 10 days)