≥10^6; yet these cats are usually asymptomatic. Free-ranging and captive wild felids in California also have a substantial prevalence of antibodies reactive with *B. henselae*,[55] and *B. henselae* has been isolated from the blood of free-ranging mountain lions *(Puma concolor)* and bobcats *(Lynx rufus)* in California.[56]

B. henselae bacteremia in pet cats is significantly associated with development of bacillary angiomatosis (BA)[43,51] or typical cat-scratch disease (CSD) in their human contacts[57]; transmission of *B. henselae* to humans also is linked to domestic cats by serologic and epidemiologic studies.[58,59] A recent review of cases of CSD in the United States from 2005–13 suggests an incidence of 4.5 outpatient diagnoses and 0.19 inpatient admissions per 100,000 population, with a higher incidence among children (age 5–9 years) and women, and in southern regions (Fig. 234.1).[60] For epidemiologic studies, diagnosis of human *B. henselae* infection has been confirmed by detection of anti-*Bartonella* antibodies, culture recovery of *B. henselae* from lymph nodes with the pathologic findings of CSD lymphadenitis,[53,61] and by detection of *B. henselae* DNA by polymerase chain reaction (PCR) in tissue from cases of CSD lymphadenitis,[62,63] CSD skin test antigen,[64] and BA lesions.[43,51] For *B. henselae*, one potential case of human-to-human transmission has been reported: donor-derived *B. henselae* infection in the recipient of an orthotopic liver transplant.[65] The major arthropod vector of *B. henselae* is the cat flea, *Ctenocephalides felis,* as demonstrated by epidemiologic associations,[43,53,58,59] identification of *B. henselae* by culture and DNA amplification from cat fleas,[51,52] and transmission of *B. henselae* to cats by infected fleas under controlled experimental conditions.[66] Cat fleas appear to serve as efficient vectors for cat-to-cat transmission[66]; their contribution to human infection likely occurs after inoculation of *B. henselae*–infected flea feces into the human during a cat scratch. Additional *Bartonella* spp. also have been identified in cat fleas.[67] Other types of fleas, as well as ixodid and *Dermacentor* ticks, have been found to harbor various *Bartonella* spp., but transmission to humans via ticks has not yet been demonstrated.[68–73]

Epidemiology of Other *Bartonella* Species Associated With Human Infection

In addition to *B. henselae*, *Bartonella clarridgeiae*[20–22] and *Bartonella koehlerae*[74] also cause asymptomatic, persistent bloodstream infection in cats. Although *B. koehlerae* is infrequently isolated from domestic cats, *B. clarridgeiae* is quite prevalent, especially in European domestic cats.[21,75] Of 50 *Bartonella* isolates recovered from 94 stray cats in France, Heller and colleagues[21] found that 34% were *B. henselae* genotype I, 36% were *B. henselae* genotype II, and 30% were *B. clarridgeiae.* Of interest, despite the high prevalence of *B. clarridgeiae* in cats, this species has neither been isolated from, nor DNA amplified from, lymph nodes of an immunocompromised or immunocompetent human with CSD. *B. koehlerae* is occasionally transmitted to humans and represents an uncommon cause of endocarditis.[32] Because *Bartonella elizabethae* has been isolated only once from a human,[18] little is known of its epidemiology, except that it has been cultured from the blood of rodents,[76] and its DNA has been amplified from the blood of rodents,[76] fleas from rodents,[76] and dogs.[77] Recently, a new species, *Bartonella ancashensis*, was isolated from the blood of two patients with verruga peruana in Ancash, Peru. The patients, age 3 and 12 years, had clinical features typical of verruga peruana (multiple chronic skin nodules). Sequencing of this blood isolate revealed a *Bartonella* spp. that was phylogenetically related to, but distinct from, *B. bacilliformis.*[78] Another recently described human pathogen, *Candidatus* Bartonella tamiae, was isolated from three patients during a study of people presenting with febrile illness in Thailand; it has been proposed as a new *Bartonella* spp. but is not yet formally recognized.[35] To date the definitive mammalian reservoir for *Candidatus* Bartonella tamiae has not been identified, although rodents and bats have been implicated.[36,79] *Bartonella rochalimae* was isolated from the blood of a patient with a febrile illness after travel to Peru; subsequently, this organism was isolated from gray foxes *(Urocyon cinereoargenteus)* in northern California[34] and detected by PCR in fleas *(Pulex irritans)* from dogs in Peru,[69] implicating a canid reservoir.

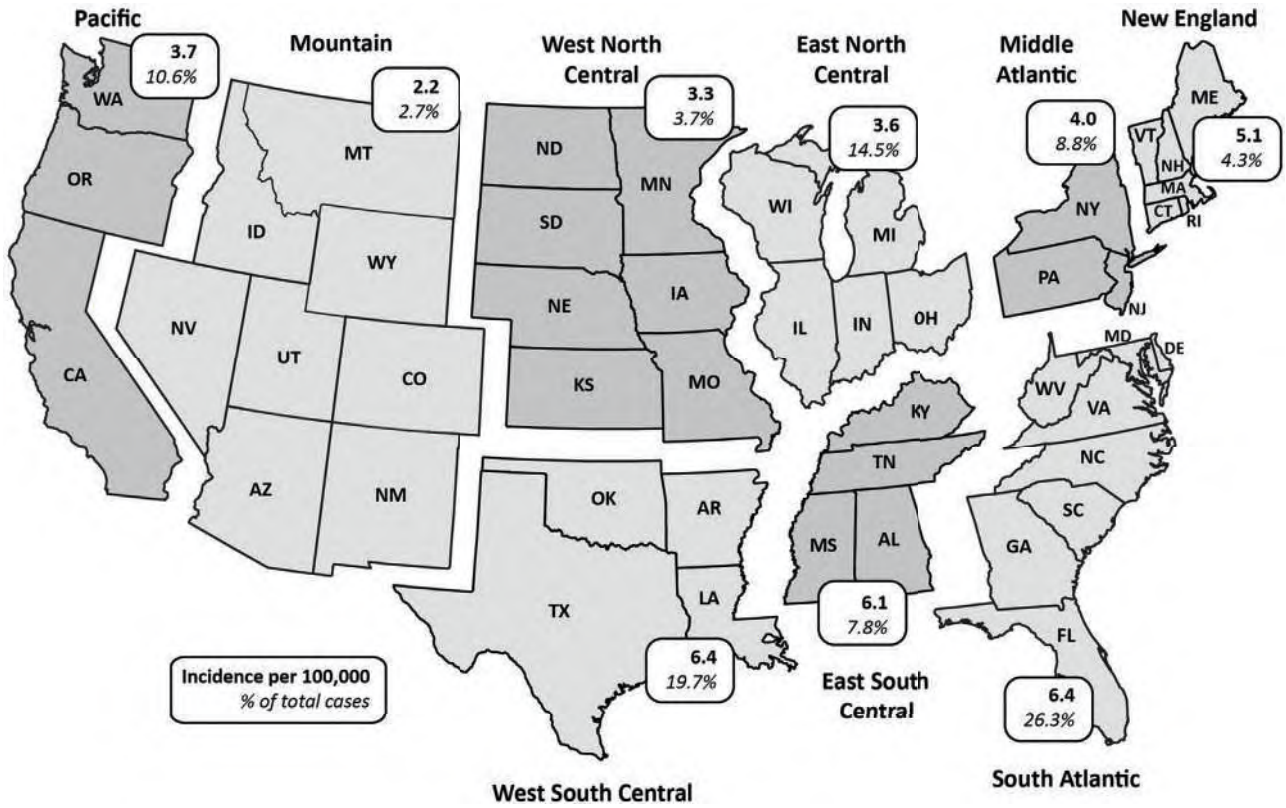

FIG. 234.1 Geographic distribution of cat-scratch disease by US census division, United States, 2005–2013. Rates are reported as average incidence per 100,000 population per year. During the study period there were <10 cases in Alaska and <10 cases in Hawaii. *(Reproduced with permission from Nelson CA, Saha S, Mead PS. Cat-scratch disease in the United States, 2005–2013.* Emerg Infect Dis. *2016;22:1741–1746.)*

Bartonella vinsonii is generally not considered a human pathogen, although *B. vinsonii* subsp. *arupensis* and *B. vinsonii* subsp. *berkhoffii* have been associated with isolated cases of endocarditis in humans by serology and DNA amplification; these *Bartonella* subspp. have not yet been directly isolated from a human with endocarditis.[28–30] *B. vinsonii* subsp. *arupensis* was isolated from the blood of an otherwise healthy rancher from the western United States who had fever without endocarditis,[27] and this strain was implicated as the cause of endocarditis in another patient.[28] *B. vinsonii* subsp. *berkhoffii* also can cause bacteremia and endocarditis in dogs.[23,24] *Bartonella alsatica* has been associated with endocarditis in humans,[31,80] and wild rabbits (a known reservoir of *B. alsatica*) were a possible source of infection in these two patients.

CLINICAL MANIFESTATIONS OF THE COMMON HUMAN PATHOGENIC *BARTONELLA* SPECIES: *B. BACILLIFORMIS, B. HENSELAE,* AND *B. QUINTANA* (Table 234.2)

Bartonella Bacilliformis Clinical Manifestations: Oroya Fever and Verruga Peruana

The long-suspected link between Oroya fever and verruga peruana was confirmed tragically in 1885 by Daniel Carrión, a medical student who injected himself with blood from a verruga peruana lesion and subsequently died of Oroya fever.[81] The eponym "Carrión disease" has since

TABLE 234.2 Characteristic Features of the Most Common Human Infections With *Bartonella* Species

BARTONELLA SPECIES	RISK FACTORS	VECTOR	RESERVOIR	DISTRIBUTION	CLINICAL FEATURES (VARIES BY HOST IMMUNE STATUS)	PATHOLOGIC FEATURES
Bartonella bacilliformis	Living in endemic area; poor housing/ exposure to vector	Sand fly	Humans	Endemic in Andes mountains (Peru)	**Biphasic illness:** Acute phase (Oroya fever): fever, malaise, hemolytic anemia; high mortality if untreated **Late phase (verruga peruana):** eruptions of nodular skin lesions	**Acute phase:** Intraerythrocytic organisms on blood smear **Late phase:** Vascular proliferative pattern
Bartonella henselae	Exposure to cats (especially kittens); CSD more common in pediatric population; immunocompromised patients (HIV, transplant recipients) at risk for disseminated disease	Cat flea (transmitted to humans via cat scratch)	Cats (especially kittens)	Worldwide; more common in warm, humid climates	**Immunocompetent:** CSD: self-limited, regional lymphadenopathy Atypical CSD, including Parinaud oculoglandular syndrome (granulomatous conjunctivitis with ipsilateral regional lymphadenopathy) Ophthalmic manifestations including neuroretinitis FUO in children Culture-negative endocarditis (in patients with pre-existing valvular abnormality) Chronic endocarditis: vasculitis/ glomerulonephritis **Immunocompromised:** Bacteremia FUO Systemic/erythematous/ violaceous skin lesions (BA) Hepatic/splenic lesions (BP)	**Immunocompetent:** Necrotizing granulomatous inflammation **Immunocompromised:** Usually vascular proliferative (BA/BP) process in patients with severe immune compromise (e.g., advanced AIDS, early period post–solid-organ transplant), although histologic appearance may be more suppurative in those with moderate immunosuppression (e.g., several years post–solid-organ transplant)
Bartonella quintana	Homelessness, body lice, conditions of poor sanitation	Human body louse	Humans	Worldwide	**Immunocompetent:** Trench fever: self-limited febrile illness Culture-negative endocarditis (with or without preexisting valvular abnormality) **Immunocompromised:** Bacteremia FUO Skin, subcutaneous, osseous vascular lesions (BA)	No specific histopathology in setting of trench fever/endocarditis/ bacteremia **Immunocompromised:** vascular proliferative process (BA)

AIDS, Acquired immunodeficiency syndrome; *BA,* bacillary angiomatosis; *BP,* bacillary peliosis; *CSD,* cat-scratch disease; *FUO,* fever of unknown origin; *HIV,* human immunodeficiency virus.

denoted the full spectrum of *B. bacilliformis* infection. Oroya fever, an acute hematologic disease resulting from primary *B. bacilliformis* bacteremia and erythrocyte invasion, develops 3 to 12 weeks after cutaneous inoculation with infected sand fly feces.[82] In its mildest insidiously developing form, a febrile illness can last less than a week and go unrecognized, giving rise to subsequent cutaneous manifestations that are the first-recognized clinical findings.[83–85] When illness onset is abrupt, high fever, chills, diaphoresis, anorexia, prostration, headache, and mental status changes are associated with rapidly developing, profound anemia resulting from bacterial invasion and destruction of erythrocytes.[4,85,86] Intense myalgias and arthralgias, abdominal pain and emesis, jaundice, lymphadenopathy, thrombocytopenia, and complications such as seizures, delirium, meningoencephalitis, obtundation, dyspnea, hepatic/gastrointestinal dysfunction, and angina pectoris can occur during this stage,[85,87,88] believed to be a consequence of the anemia and microvascular thrombosis, with subsequent end-organ ischemia.

Without antimicrobial therapy, the fatality rate is high for the severe, abrupt form of bacteremic illness, Oroya fever.[87] With appropriate treatment in the modern era, mortality is reported to be less than 10%.[85] For survivors, convalescence is associated with a decline of fever and disappearance of bacteria on blood smears, but also a temporarily increased susceptibility to subsequent (opportunistic) infections, such as salmonellosis[85,88,89] or toxoplasmosis.[85,90,91] Asymptomatic persistent bacteremia with *B. bacilliformis* infection can occur in up to 15% of survivors of acute infection.[92] It has been suggested that initial infection may be asymptomatic, or only mildly symptomatic, more often than was previously thought.[84,93] Both the Oroya fever survivors and asymptomatically bacteremic individuals are suspected to serve as the reservoir for *B. bacilliformis*.

Verruga peruana lesions, the eruptive phase of *B. bacilliformis* infection, usually become evident within weeks to months after resolution of untreated acute infection. This late-stage manifestation is characterized by crops of skin lesions marked by an evolution of stages[85]: miliary, then nodular (Fig. 234.2), and subsequently what are called mulaire lesions (Fig. 234.3). Of the eruptive manifestations, mulaire lesions are the most superficial and obviously vascular: often bulbous, engorged with blood, and prone to ulceration and bleeding. Mucosal and internal lesions also can occur. The nodules may develop at one site while receding at another. Healing at a particular skin site is often punctuated by recurrences and usually takes place over several weeks to 3 or 4 months. Subsequently, fibrosis of mulaire lesions can occur. Histology of active lesions demonstrates vascular proliferation with occasional bacteria evident in interstitial spaces. Bacterial invasion of/replication within endothelial cells (long believed to be the cause of cytoplasmic inclusions first described by Rocha Lima) is actually rare.[94]

FIG. 234.2 Multiple nodular subcutaneous lesions of verruga peruana in an inhabitant of the Peruvian Andes. Nodular verruga peruana eruptions are localized around the flexures of the elbows and knees, as well as on the thighs and legs. *(Courtesy Dr. J.M. Crutcher, Oklahoma State Department of Health, Oklahoma City, OK.)*

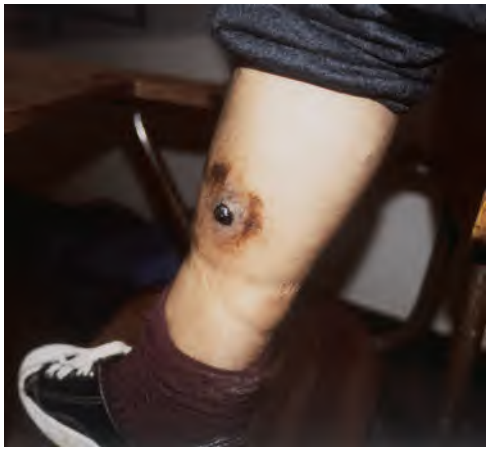

FIG. 234.3 A single, large, mulaire lesion of verruga peruana on the leg of an inhabitant of the Peruvian Andes. Mulaire lesions frequently develop superficial ulceration, and copious bleeding can occur as a result of their highly vascular nature. Ecchymosis of the skin surrounding the lesion is also evident. *(Courtesy Dr. J.M. Crutcher, Oklahoma State Department of Health, Oklahoma City, OK.)*

Bartonella henselae and *Bartonella quintana*: Clinical Manifestations Depend on the Infecting *Bartonella* Species and Immune Status of Host

The clinical manifestations of infection with these two *Bartonella* spp. depend on a combination of species-specific microbiologic and host-specific immunologic factors (Fig. 234.4). Species-specific epidemiologic risk factors, such as exposure to cats and cat fleas for *B. henselae*, and homelessness and exposure to lice for *B. quintana*, are applicable to both immunocompetent and immunocompromised hosts. In immunocompetent hosts, infection with *B. henselae* typically manifests as CSD: regional, granulomatous lymphadenitis (Fig. 234.5A). Both *B. henselae* and *B. quintana* can present as fever of unknown origin (FUO). Endocarditis, usually due to *B. quintana,* most commonly occurs in immunocompetent hosts, often in the absence of a history of valvular abnormalities.[95–98,99] *B. henselae* endocarditis is a less frequent cause of endocarditis and most often occurs in patients with underlying valvular pathology or congenital heart disease (CHD).[100,101] Immunocompromised solid-organ transplant (SOT) recipients and persons living with human immunodeficiency virus (HIV; CD_4^+ cell count <100/mm^3) who are infected with either *B. henselae* or *B. quintana* can develop BA (see Fig. 234.5B–D) but also can present with other clinical manifestations, for instance, bacillary peliosis (BP) hepatis (*B. henselae*), bacteremia (*B. quintana* or *B. henselae*), endocarditis (*B. quintana* or *B. henselae*), and/or FUO (*B. quintana* or *B. henselae*).[43,102,103] Additional host/immunologic risk factors for more severe *Bartonella* infection, such as the use of biologic disease-modifying antirheumatic drugs, have been reported, although a clear association between the use of these agents and a particular clinical manifestation of *Bartonella* infection is not clearly defined.[104]

Bartonella henselae and *Bartonella quintana:* Bacteremic Illness

Acute mortality resulting from bacteremia with non-*bacilliformis Bartonella* spp., even when persistent, is uncommon in immunocompetent hosts in the absence of endocarditis. In recent years, *B. quintana* bacteremic infection in immunocompetent individuals ("trench fever") has been identified sporadically and in small clusters, predominantly in homeless people in North America and Europe.[14,105,106] Trench fever is characterized by a self-limited fever, often with a 5-day periodicity (quintan pattern).[7,8] The incubation period may span 3 to 38 days before the usually sudden onset of chills and fevers. In the most limited form of trench fever, a single bout of fever lasts 4 or 5 days. In the more typical periodic form, there are three to five, and sometimes up to eight, febrile paroxysms, each approximately

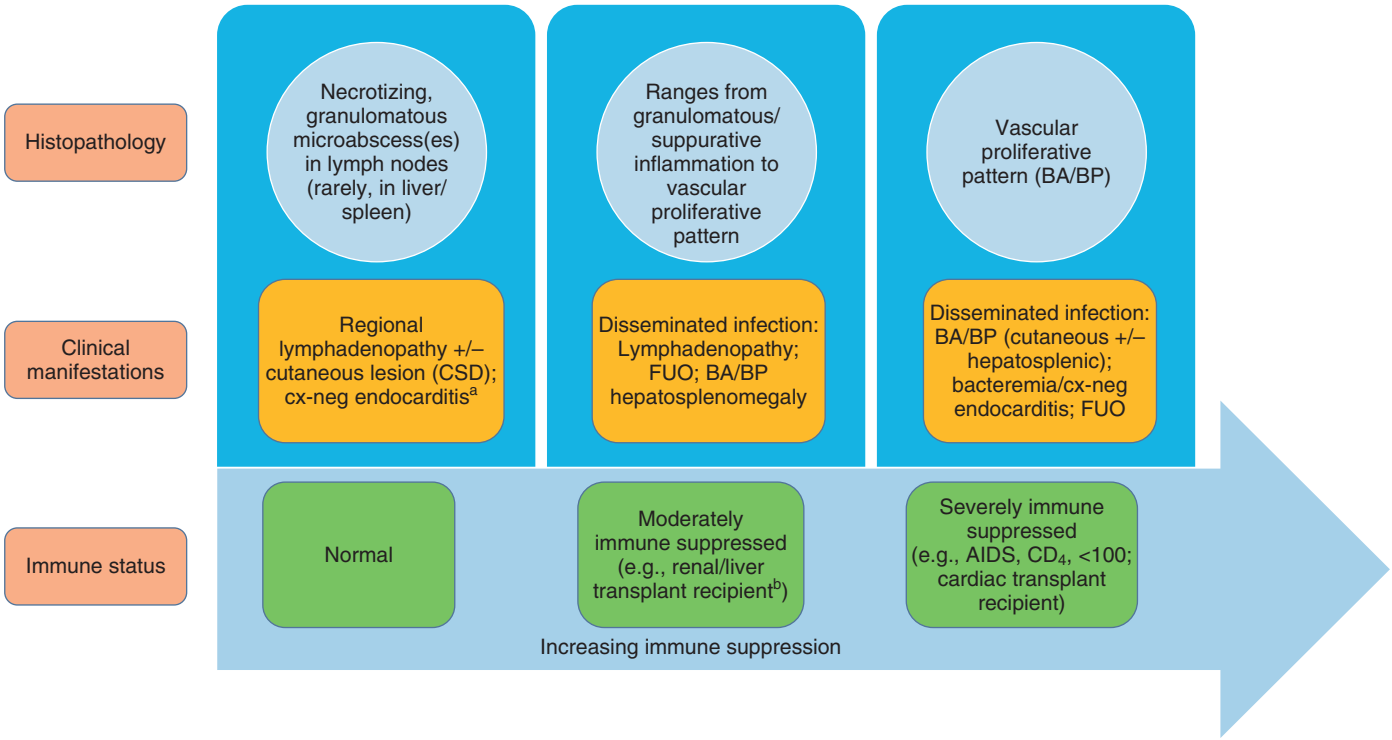

FIG. 234.4 Host immune status is associated with different clinical and pathologic manifestations of *Bartonella henselae* or *Bartonella quintana* infection. [a]Endocarditis can occur in healthy hosts with underlying valvular pathology (e.g., *B. henselae*) or on native, normal valves (e.g., *B. quintana*). [b]Among transplant patients, disseminated infection and vascular proliferative pattern on pathology occur earlier in the posttransplant period, likely due to higher levels of immunosuppression. *AIDS,* Acquired immunodeficiency syndrome; *BA/BP,* bacillary angiomatosis/bacillary peliosis; *CSD,* cat-scratch disease; *cx-neg,* culture-negative; *FUO,* fever of unknown origin.

5 days apart. Patients are often asymptomatic between febrile paroxysms. The continuous form is manifested by 2 or 3 weeks, and up to 6 weeks, of uninterrupted fever. Afebrile infection with *Bartonella* is very common; one study found 8 of 10 homeless individuals with active *B. quintana* bacteremia were afebrile.[107] Other nonspecific symptoms and signs, such as headache, retro-orbital pain, conjunctival injection, myalgias, arthralgias, bone pain, hepatosplenomegaly, rash, leukocytosis, and albuminuria can accompany *B. quintana* bacteremia. *B. quintana* bacteremia has the potential to evolve into long-term persistence if not treated appropriately.[106,108] *B. henselae* bacteremia in immunocompetent hosts is rare, and localizing symptoms or physical findings are unusual.[108] However, *B. henselae* bacteremia can present with abrupt onset of isolated fever or, rarely, accompany CSD lymphadenitis.[109] Aseptic meningitis concurrent with *B. henselae* bacteremia also has been documented.[108,109] *B. henselae* bacteremia is much less likely to persist or become relapsing than *B. quintana* in immunocompetent people.

HIV-infected patients with advanced immunosuppression (CD_4^+ cell count <100/mm^3) are more likely to develop severe and prolonged bacteremia with *B. quintana* or *B. henselae.*[102,103] In these patients *Bartonella* bacteremia has been associated with cutaneous BA (*B. henselae* or *B. quintana*), hepatic and splenic BP *(B. henselae),* granulomatous hepatitis *(B. henselae),* infiltration of the bone marrow *(B. henselae),*[110] FUO (*B. quintana* and *B. henselae*), and occasionally endocarditis (*B. quintana* much more frequently than *B. henselae*).[11,102,103] In one area of high HIV prevalence, evidence of *B. henselae* or *B. quintana* infection was found in 18% of people evaluated for acute or persistent unexplained fever, 97% of whom were HIV infected and had a median CD_4^+ cell count of 35 per mm^3 and no antiretroviral exposure.[103] In a study of 49 patients with documented BA/BP (92% had HIV infection), 50% of patients sampled had bacteremia with either *B. quintana* or *B. henselae.*[43] The clinical presentation of *Bartonella* bacteremia often is characterized by insidious development of malaise, body aches, fatigue, weight loss, progressively higher and longer recurring fevers, and sometimes headache.[43,103] Hepatosplenomegaly and/or splenomegaly may occur, but localizing symptoms or physical findings can be lacking. Secondary hemophagocytic lymphohistiocytosis has been associated with *B. henselae* in both HIV-infected and transplant hosts, heralded by hepatosplenomegaly and cytopenias.[111,112]

Bartonella henselae and *Bartonella quintana:* Endocarditis

Bartonella spp. are recognized as one of the most important causes of blood culture-negative endocarditis.[11,13,95–101,113] Two large European studies of patients with blood culture-negative endocarditis found *Bartonella* spp. to be the second most frequently identifiable cause, after *Coxiella burnetii.*[99,113] In the United States, where *Coxiella* endocarditis is less common than in Europe, *Bartonella* spp. are quite likely the most common cause of culture-negative endocarditis. Patients with *B. quintana* endocarditis are usually homeless, often substance abusers, and have exposure to body lice, whereas people with *B. henselae* endocarditis more commonly have cat exposure and preexisting valvular heart disease.[99] *B. henselae* endocarditis is infrequent in humans; despite the frequency of CSD in the pediatric population, *B. henselae* endocarditis has been recognized only rarely.[97] The reports of pediatric endocarditis usually involve patients with CHD.[101] The more common cause of human endocarditis, *B. quintana,* is extremely rare in pediatric practice because of the less frequent exposure of children to risk factors associated with *B. quintana:* homelessness and body lice.

Patients with *Bartonella* endocarditis typically present with a prolonged (weeks to months) history of nonspecific symptoms, such as fever, fatigue, and weight loss. In a retrospective study of 101 patients with *Bartonella* endocarditis,[98] ≈83% were febrile and 43% had evidence of embolic phenomena at the time of presentation. Fifty-eight patients (57%) had previously known valvular heart disease, 58 (57%) had involvement of the aortic valve, and 18 (18%) had involvement of multiple valves. Irrespective of antimicrobial therapy, 76 patients had severe valvular damage and required valvular surgery. Twelve patients ultimately died; two were cured only after treatment for a relapse, and the remaining 87% were cured with the initial therapy.[98]

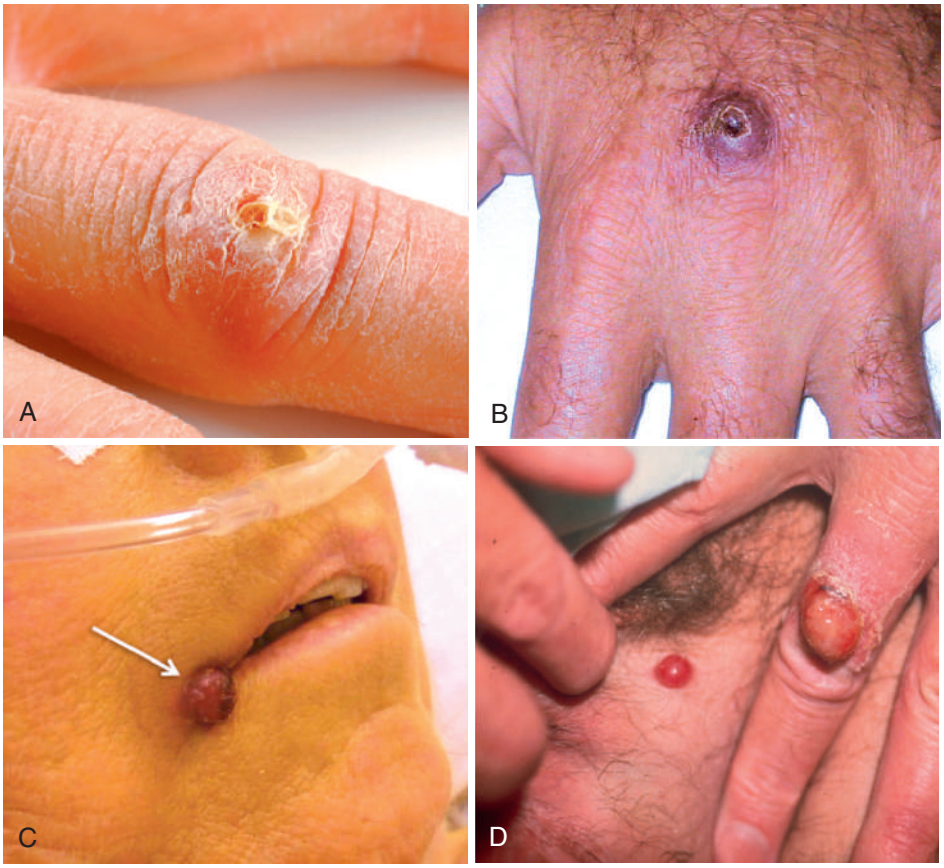

FIG. 234.5 The degree of host immunocompromise determines the clinical cutaneous manifestations of *Bartonella henselae* infection. (A) Primary inoculation lesion of *B. henselae* causing cat-scratch disease (CSD) in an immunocompetent host; this erythematous lesion is typically transient, and usually the lesion and lymphadenopathy resolve without antimicrobial therapy. (B) CSD in a moderately immunocompromised host (5 years after cadaveric kidney transplant), presenting as a chronic, single, violaceous nodule on the dorsum of the hand with a flat, necrotic eschar on top and poorly formed granulomas on histopathology (see Fig. 234.7A1–A3). (C) Bacillary angiomatosis (BA) in a more immunocompromised host (6 years after combined pancreas-kidney transplant) appearing as a 4-mm vascular nodule on the lip *(arrow);* shave biopsy demonstrated vascular proliferation consistent with BA. Patient also had bacilllary peliosis hepatis (see Fig. 234.8F) with severe liver failure. (D) BA in a patient with advanced AIDS (CD_4^+ cell count <100/mm^3), who presented with a 2-month-old friable, vascular BA finger lesion and a 2-week-old vascular scrotal lesion. *(Image A courtesy Dr. Anna Sander, Merian Schule, Freiburg, Germany. Image B reprinted with permission from Koehler JE, Duncan LM. Case records of the Massachusetts General Hospital. A 56-year-old man with fever and axillary lymphadenopathy.* N Engl J Med. *2005;353:1387–1394. Image C reproduced with permission from Freed MM, Ramirez-Valle F, Chandran S. Fever, hepatosplenomegaly and a skin nodule in a kidney-pancreas transplant recipient.* Am J Transplant. *2012;12:2556–2558. Image D reproduced with permission from Koehler JE, LeBoit PE, Egbert BM, Berger TG. Cutaneous vascular lesions and disseminated cat-scratch disease in patients with the acquired immunodeficiency syndrome [AIDS] and AIDS-related complex.* Ann Intern Med. *1988;109:449–455.)*

It is important to be aware of the rapidly increasing number of reports of vasculitis associated with *Bartonella* endocarditis. Patients with *B. henselae* and *B. quintana* endocarditis can present with clinical features of a systemic, small vessel vasculitis associated with a positive cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA), anti–proteinase 3 antibodies (anti-PR3), and/or kidney injury with glomerulonephritis.[101,114–117] In these patients, detection of *Bartonella* infection is critical to avoid exposure to immunosuppressive therapy for vasculitis and to institute timely antimicrobial therapy for *Bartonella* endocarditis. In c-ANCA–positive patients the c-ANCA titers may be useful for clinical monitoring of endocarditis treatment,[115] and antimicrobial treatment of the underlying endocarditis usually results in resolution of the vasculitis, without steroids.[101,114,115]

As noted earlier, in addition to antimicrobial therapy (see "Treatment") *Bartonella* endocarditis requires surgical intervention in the majority of cases. Delays in surgical intervention have been associated with morbid complications, such as stroke[30] and acute myocardial infarction.[118]

The diagnosis of culture-negative endocarditis due to *Bartonella* has been established with serology, amplification of *Bartonella* DNA from blood or valve tissue, immunohistochemistry, or a combination of these modalities. A series of 106 cases from a single center in France revealed the sensitivity of two of their diagnostic tests: immunoblotting with patient serum (100%) and PCR of DNA extracted from valvular tissue (92%). Serology testing for *Bartonella* immunoglobulin G (IgG) antibodies by immunofluorescence was positive (defined as ≥1:100) in 91% of *Bartonella* endocarditis patients; an IgG titer ≥1:800 had a positive predictive value of 94% for endocarditis.[100] In a review of *Bartonella* endocarditis among 13 patients with CHD, serology was positive in 100% of cases, and PCR on DNA extracted from valvular tissue detected *Bartonella* in all 11 patients who underwent surgery.[101] Evaluation of homeless individuals or SOT recipients with fever and glomerulonephritis, cutaneous small vessel vasculitis, and/or positive c-ANCA or anti-PR3 should prompt a clinical workup for *Bartonella* endocarditis.

Other *Bartonella* Species: Endocarditis and Bacteremia

B. elizabethae has been isolated from a single patient with bacteremia and endocarditis.[18] *B. vinsonii* subsp. *arupensis* and *B. vinsonii* subsp. *berkhoffii* have been associated with a few isolated cases of endocarditis in humans.[28–30] *B. vinsonii* subsp. *arupensis* also was isolated from a US rancher who had bacteremia and fever.[27] In addition, *B. koehlerae* and *B. alsatica* have been associated with endocarditis in humans.[31,32,80] *B. rochalimae* caused a febrile bacteremic illness with splenomegaly in an immunocompetent traveler returning from Peru, who had sustained numerous arthropod bites.[33] A novel species, *Candidatus* Bartonella tamiae, was isolated from the blood of three patients being evaluated

for fever in Thailand.[35] It is evident that many *Bartonella* spp. associated with wild and peridomestic animals can infect humans, albeit rarely, especially patients with abnormal heart valves or CHD.

Bartonella henselae and *Bartonella quintana* Infections in Immunocompromised Patients: Bacillary Angiomatosis/Bacillary Peliosis

BA (also referred to as bacillary epithelioid angiomatosis) is a manifestation of *B. quintana* or *B. henselae* infection involving vascular proliferation in skin and regional lymph nodes, which was initially described in patients with advanced HIV-infection (CD_4^+ cell count <100/mm^3).[102,103,119–121] Subsequently, BA has been identified in a variety of internal organs, including liver, spleen, bone, brain, lung, bowel, and uterine cervix.[121–127] BA has been increasingly identified in other hosts with compromised immunity (such as SOT and chemotherapy recipients)[128–135] and, very rarely, immunocompetent hosts.[136,137] *B. henselae* and *B. quintana* have been found to be a cause of BA both by direct culture[10,17,51,138] and by PCR amplification of *Bartonella*-specific DNA sequences from tissue.[10,43,128,139] Either species can cause cutaneous BA lesions, but subcutaneous and osseous lesions are more often associated with *B. quintana* and hepatic and splenic BP only with *B. henselae.*[43] In addition, patients with *B. henselae* genotype I infection may be more likely to have hepatic and splenic peliosis, whereas patients with *B. henselae* genotype II are more likely to develop BA lesions involving the skin or lymph node, or both.[140]

Cutaneous BA lesions often arise in crops (Fig. 234.6D and E), but both the temporal pattern of development and the gross morphologic characteristics can vary. Of interest, the clinical and histopathological appearance of verruga peruana lesions caused by *B. bacilliformis* in immunocompetent hosts closely resembles the cutaneous BA lesions caused by *B. henselae* and *B. quintana* in immunocompromised hosts. BA lesions also can resemble pyogenic granuloma, but the major clinical differential diagnosis in HIV-infected patients is Kaposi sarcoma.[141] In gross appearance, BA skin lesions can be subcutaneous (see Fig. 234.6F); form dermal nodules (see Fig. 234.6C); or form single or multiple papules that are flesh colored, red, or purple (see Fig. 234.6E).[142] Skin lesions also can display ulceration (see Fig. 234.6D), serous or bloody drainage, and crusting (see Fig. 234.6B). Lesions can range in diameter from millimeters to centimeters (see Fig. 234.6C), number from a few to hundreds (see Fig. 234.6E), be fixed or freely mobile, be associated with enlargement of regional lymph nodes, involve mucosal surfaces or deeper soft tissues (see Fig. 234.6A), occur in a variety of distributions, and bleed copiously when incised. Osteomyelitis also can be associated with BA lesions (see Fig. 234.6F). Visceral BA lesions can be quite dramatic as well, in both their number and heterogeneity of gross appearance.

Although BA can closely resemble other neovascular tumors clinically, BA can be distinguished from other vascular proliferative tumors histologically.[142,143] BA consists of lobular proliferation of small blood vessels containing plump, cuboidal endothelial cells, interspersed with mixed inflammatory cell infiltrates having a neutrophil predominance (Fig. 234.7B1). Endothelial cell atypia, mitoses, and necrosis may be present. Fibrillar- or granular-appearing amphophilic material is often present in interstitial areas when stained by hematoxylin and eosin (H&E) stain. Warthin-Starry staining or electron microscopy shows this material to be clusters of bacilli (see Fig. 234.7B2 and B3).

When cutaneous BA lesions are absent, diagnosis is often delayed because of the nonspecific features associated with hepatic or splenic BP (fever, lymphadenopathy, hepatomegaly, splenomegaly, anemia, pancytopenia, and serum alkaline phosphatase elevation).[102] BP, originally described as a process involving the liver, sometimes occurs in the spleen and occasionally lymph nodes in HIV-infected people[144,145] and has since been identified in other immunocompromised people.[129,133] Molecular epidemiologic investigation has revealed that *B. henselae* (and not *B. quintana*) appears to be the only *Bartonella* spp. eliciting this host response of BP.[43] Involved organs contain numerous blood-filled cystic spaces (peliosis) that can range from microscopic to several millimeters in size. Hepatic and splenic BP appear as multiple hypodense or low-attenuation lesions on ultrasonographic or computed tomographic (CT) abdominal scanning (Fig. 234.8C).[146] H&E-stained tissue reveals that the peliotic spaces (see Fig. 234.8F) are partially lined with endothelial cells and often separated from surrounding parenchymal cells by fibromyxoid stroma containing a mixture of inflammatory cells, dilated capillaries, and clumps of granular material. Such clumps are composed of aggregates of bacilli that stain with Warthin-Starry stain.[144] Presenting clinical features of BP hepatis are often nonspecific, although there is a dramatic report of an HIV-infected patient presenting with fever and abdominal pain, who developed massive hemoperitoneum from hepatic BP.[147]

B. henselae–related inflammatory reactions in immunocompromised hosts, in the absence of associated angiomatosis or peliosis, have been reported in liver (see Fig. 234.8B), spleen, lymph nodes, heart, lung, and bone marrow.[112,129,148–152] They are characterized by nodular collections of lymphocytes and nonepithelioid histiocytes that can become centrally necrotic, containing aggregates of neutrophils and karyorrhectic debris suggestive of microscopic abscess formation (see Fig. 234.8E).[148,149] These may represent a clinical-pathologic link with CSD and are more likely to occur in HIV-infected patients who have less severe immunosuppression or SOT recipients with a later disease presentation (mean, 5.2 years) posttransplantation.[129]

Bartonella henselae: Cat-Scratch Disease

Cat-Scratch Disease Background

The various clinical manifestations of CSD have been recognized for more than a century, but "la maladie des griffes de chat" was not defined as a syndrome until 1950.[153] CSD remained an infection in search of an agent for more than 40 years after that. Thus most cases have been identified by clinical-pathologic criteria, supplemented by reactions to unstandardized skin test antigens before identification of *B. henselae*. Historically, the diagnosis of a case of typical CSD required fulfillment of three of the four following criteria (all four were necessary in an atypical case): (1) history of an animal (usually cat or dog) contact, with the presence of a scratch or primary skin or eye lesion; (2) aspiration of "sterile (culture-negative)" pus from the lymph node, or culture and other laboratory testing that excluded other etiologic possibilities; (3) a positive CSD skin test; and (4) a lymph node biopsy revealing pathology consistent with CSD. Skin test antigen, originally described by Hanger and Rose, was prepared by heating saline-diluted "sterile (culture-negative)" pus aspirated from CSD lymphadenitis at 56°C for 72 hours. It was never standardized or produced commercially. It is of historic interest because of its confirmatory role in diagnosis of CSD before the identification of *B. henselae* as the CSD agent. However, its potential for transmission of hepatitis viruses, HIV, and prions is a major contemporary concern, even if the source patients are well screened. Its use in the era of other methods of diagnosis is no longer warranted.

Among the *Bartonella* spp., CSD has been associated nearly exclusively with *B. henselae.* Evidence indicating the central role of *B. henselae* includes the serologic response of people with CSD to *B. henselae* antigens[59]; the identification of *B. henselae* in CSD lymphadenitis by culture,[61] PCR-based DNA amplification,[62,63,154–157] and immunocytochemistry[158]; detection of *B. henselae* in CSD skin test antigens by PCR[64]; and the recovery of *B. henselae* isolates from the blood of healthy cats (which can be persistently bacteremic)[51,53,159] and from cat fleas.[51]

In the United States an estimated 12,500 to 25,000 CSD cases occur annually.[60,160] Of interest, veterinary care personnel do not have evidence of notably higher levels of infection than the general population.[161] It is reasonable to ascribe the vast majority of CSD cases to *B. henselae* on the basis of the numerous lines of evidence developed in recent years. Yet it remains possible that other agents can, very rarely, cause "typical" CSD cases, such as was reported with *Afipia felis* and *Bartonella grahamii*.[162–164] CSD is the most commonly recognized manifestation of human infection with *Bartonella*.

Typical Cat-Scratch Disease

"Typical CSD" represents 88% to 89% of CSD cases overall. A primary cutaneous papule or pustule develops approximately 3 to 10 days after an animal contact (most commonly a kitten or feral cat with flea infestation) at a site of inoculation (usually from a scratch) (Fig. 234.9A),[165–167] and it may last for 1 to 3 weeks. Regional lymphadenopathy ipsilateral to the inoculation site (usually head, neck, or upper extremity) that develops in 1 to 7 weeks (see Fig. 234.9B and C), is the most prominent and common

FIG. 234.6 Diverse manifestations of bacillary angiomatosis (BA) caused by *Bartonella henselae* or *Bartonella quintana* in severely immunocompromised AIDS patients. In severely immunocompromised patients with AIDS, infection with *B. henselae* or *B. quintana* can manifest as BA, a vascular proliferative process. Cutaneous lesions are most common, but deeper soft tissue, musculoskeletal, or visceral masses can occur. Diagnosis is often delayed due to the diversity of clinical appearances and broad differential diagnoses in this patient population. (A) Magnetic resonance imaging shows a 7 × 4 × 5-cm lobulated, highly vascular, soft-tissue mass *(arrow)* anterior to the femoral vessels, 8 months before diagnosis of BA. (B) Cutaneous BA on the lower leg (pretibial region) of an AIDS patient (CD_4^+ cell count 20/mm^3). The lesion is protuberant, without erythema, firm and dry, with a collarette of hyperkeratotic skin covered with serous crust. (C) 3.5 × 3.5-cm pedunculated, vascular cutaneous BA lesion on the thigh of a woman with AIDS, systemic symptoms, and inguinal adenopathy. (D) Cutaneous BA, presenting with numerous, painful angiomatous nodules within an indurated, erythematous plaque that developed over the biopsy site of the right thigh mass in the patient shown in (A). *B. quintana* was cultured from the cutaneous lesions. (E) Cutaneous BA in a man with AIDS and multiple comorbid opportunistic infections. Reddish-purple dome-shaped papules, 0.2 to 1 cm in diameter, were noted on the face, trunk, and upper extremities and were initially thought to represent Kaposi sarcoma, but histopathology demonstrated BA. (F) A man with AIDS presented with a 4-month history of a painful, 5 × 3-cm firm, erythematous nonpulsatile right wrist mass *(left image);* a radiograph showed a bony defect in the distal radius *(right image, arrows).* Histopathology confirmed BA. *(Images A, B, and D reprinted with permission from Koehler JE, Quinn FD, Berger TG, LeBoit PE, Tappero JW. Isolation of* Rochalimaea *species from cutaneous and osseous lesions of bacillary angiomatosis.* N Engl J Med. *1992;327:1625–1631. Image C reproduced with permission from Koehler JE, Glaser CA, Tappero JW.* Rochalimaea henselae *infection. A new zoonosis with the domestic cat as reservoir.* JAMA. *1994;271:531–535. Image E reproduced with permission from Cockerell CJ, Whitlow MA, Webster GF, Friedman-Kien AE. Epithelioid angiomatosis: a distinct vascular disorder in patients with the acquired immunodeficiency syndrome or AIDS-related complex.* Lancet. *1987;2:654–656. Image F reproduced with permission from Koehler JE, LeBoit PE, Egbert BM, Berger TG. Cutaneous vascular lesions and disseminated cat-scratch disease in patients with the acquired immunodeficiency syndrome [AIDS] and AIDS-related complex.* Ann Intern Med. *1988;109:449–455.)*

manifestation (>90% of typical cases) and the one that usually prompts medical evaluation. Even at the time of such presentation, an inoculation site (scratch, bite, or primary papule or pustule) can be detected in more than two-thirds of patients when actively sought. One-third to 60% of patients may have low-grade fever lasting several days. One-fourth of patients report malaise or fatigue, and approximately 10% report headache or sore throat. Transient rash occurs in approximately 5% of patients. Erythema nodosum (erythematous nodules on the lower legs) has been described as a another rare dermatologic manifestation of CSD in immunocompetent patients.[168] Transient, mild leukocytosis, with increased neutrophils and sometimes eosinophils, as well as elevated erythrocyte sedimentation rate, can occur.

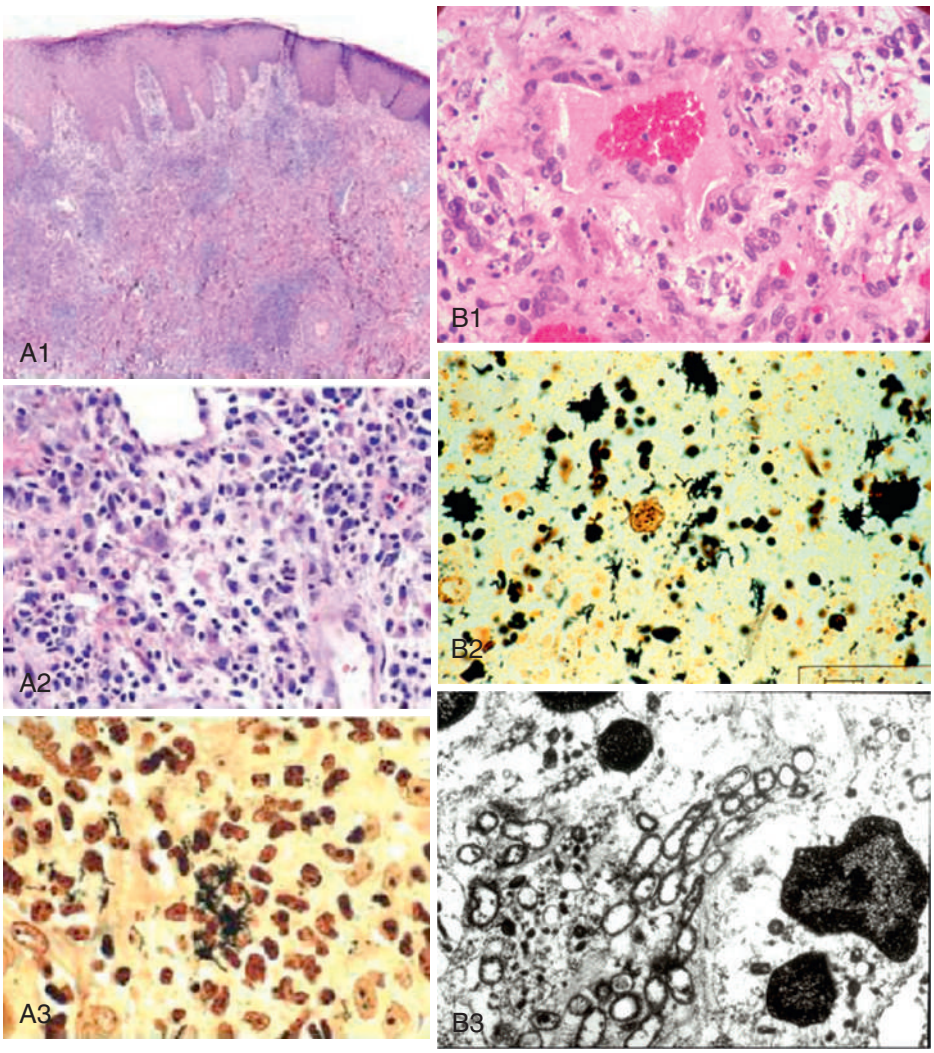

FIG. 234.7 Histopathologic manifestations of cutaneous cat-scratch disease (CSD) and bacillary angiomatosis (BA) in patients with compromised immunity and infection with *Bartonella henselae*. (A) Chronic CSD (cutaneous) in a moderately immunocompromised host (5 years postcadaveric kidney transplant; patient's clinical lesion shown in Fig. 234.5B). (A1) Histopathology (hematoxylin and eosin stain [H&E]) demonstrates poorly formed granulomas. Epidermal hyperplasia is observed at low magnification, with an underlying dense inflammatory infiltrate that extends throughout the dermis and into the subcutis. (A2) At higher magnification, the inflammatory infiltrate is noted to be composed of histiocytes, lymphocytes, neutrophils, and plasma cells. (A3) Warthin-Starry silver staining shows clumped and solitary rods *(black-stained organisms),* consistent with *Bartonella* spp. (B) BA (cutaneous) in a severely immunocompromised patient with AIDS. (B1) H&E staining of a biopsied cutaneous BA lesion demonstrates a dermal vessel. The vessel is lined with protuberant endothelial cells surrounded by myxoid connective tissue containing neutrophils and amphophilic granular material in close proximity to the vascular lumen. (B2) Warthin-Starry staining of cutaneous BA tissue reveals multiple clumps of tangled, dark silver-staining bacillary organisms (bar = 10 μm). (B3) transmission electron micrograph of cutaneous BA lesion tissue shows multiple trilaminar cell-walled bacillary organisms. *(Images in A reprinted with permission from Koehler JE, Duncan LM. Case records of the Massachusetts General Hospital. A 56-year-old man with fever and axillary lymphadenopathy.* N Engl J Med. *2005;353:1387–1394. Images in B reprinted and modified with permission from Koehler JE, Tappero JW. Bacillary angiomatosis and bacillary peliosis in patients infected with human immunodeficiency virus.* Clin Infect Dis. *1993;17:612–624.)*

Nearly half of typical CSD patients have a single lymph node involvement, another 20% have multiple node involvement at one site, and the remaining one-third have node involvement at multiple sites. Up to one-sixth of patients with typical CSD develop lymph node suppuration. Ultrasonography may assist in the assessment of lymph node size and suppuration,[53,169] and it can be used to direct needle aspiration of pus (usually done to relieve discomfort). Node enlargement usually persists for 2 to 4 months but may last considerably longer; spontaneous resolution is the rule, regardless of whether the patient is treated with antibiotics. The histopathology of nodes includes a mixture of nonspecific inflammatory reactions, including granulomata and stellate necrosis (see Fig. 234.9D and E). However, out of 100 cases evaluated with molecular confirmation of *B. henselae* infection, 43 lacked microabscesses, the classic diagnostic feature of CSD; in addition, sometimes PCR-positive CSD lymph nodes demonstrated features mimicking other infectious lymphadenopathies. This underscores the importance of *B. henselae* molecular testing.[170] Bacilli are best demonstrated by Warthin-Starry and possibly Dieterle or Steiner silver staining. Uncommonly, hypercalcemia may complicate CSD lymphadenopathy as a result of endogenous overproduction of active vitamin D associated with granuloma formation.[171]

Musculoskeletal Manifestations of Cat-Scratch Disease

Although previously considered to be uncommon in CSD, some musculoskeletal manifestations actually occur in greater than 10% of cases, as defined in an 11-year surveillance study involving 913 patients with compatible clinical presentation and confirmatory PCR or serologic test, or both, for *B. henselae*.[172] Myalgia occurred in 5.8% of surveyed patients, had a median duration of 4 weeks, and was often severe. Arthropathy (arthralgia or arthritis, or both) occurred in 5.5%, involving mainly the medium and large joints, for a median of 5.5 weeks, and was characterized as moderate to severe in intensity in more than half of these patients. In a small proportion chronic symptoms persisted for more than 1 year and could be debilitating. Age older than 20 years

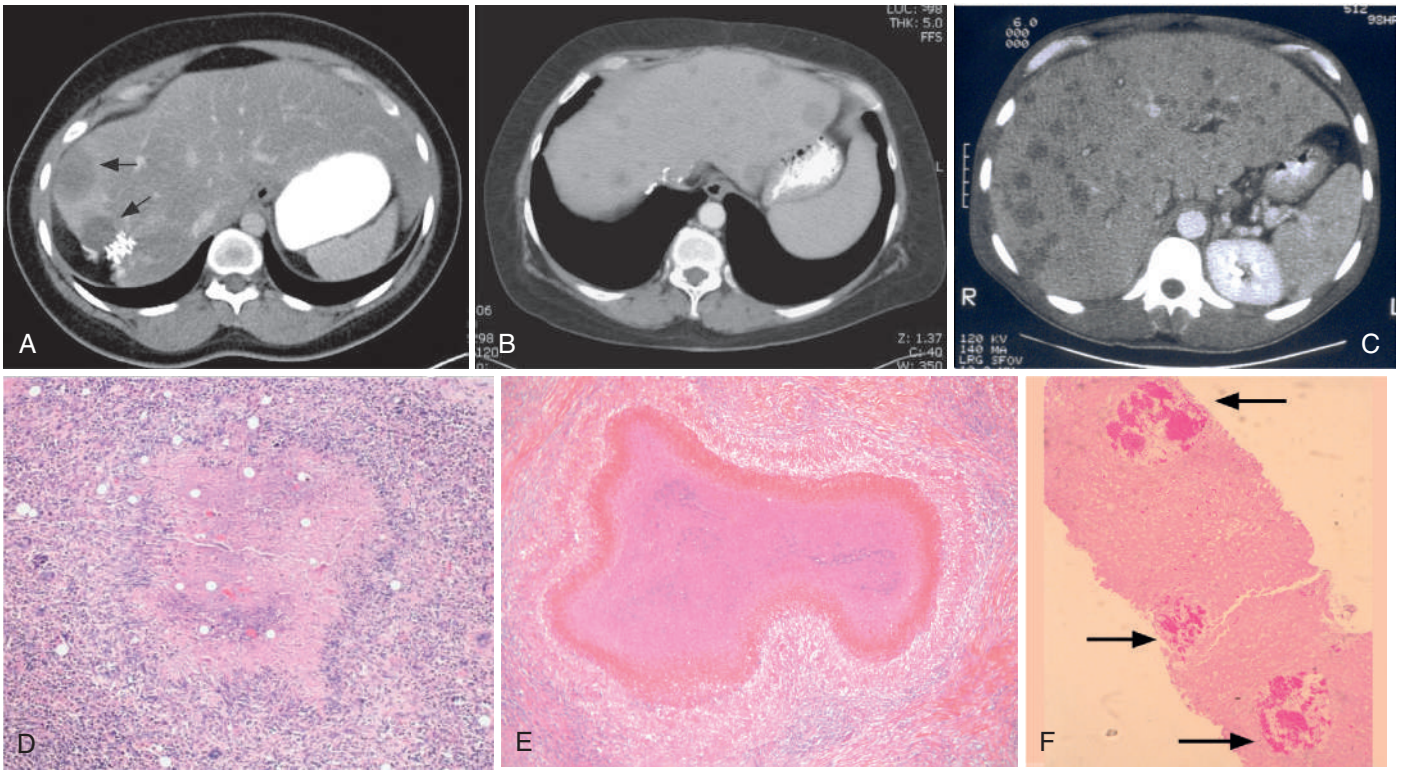

FIG. 234.8 Hepatic manifestations of *Bartonella henselae* occur often when infection disseminates in either immunocompetent or immunocompromised patients, but histopathologic characteristics differ markedly depending on host immune status. Although hepatic lesions caused by *B. henselae* infection can have a similar appearance on CT imaging, biopsy and histopathologic examination reveal markedly different manifestations, depending on the immune status of the host. Histopathology of hepatic lesions from immune competent hosts typically demonstrates necrotizing granulomatous lesions with few *B. henselae* bacilli, whereas hepatic lesions from severely immunocompromised patients usually reveal bacillary peliosis (BP) hepatis with numerous bacilli. In patients with moderate immunosuppression, such as solid-organ transplant recipients, the spectrum of pathology is quite variable, from granulomatous hepatitis to BP hepatis. (A) Abdominal CT scan showing several hypodense liver lesions *(arrows)* in an immunocompetent patient. (B) Abdominal CT scan showing discrete hypodense masses in a liver transplant patient. (C) Abdominal CT scan showing multiple hypodense liver lesions in a patient with advanced AIDS and disseminated *B. henselae* infection; biopsy demonstrated BP hepatis. (D) Resected liver lesion in an immunocompetent patient with granulomatous hepatitis due to *B. henselae* infection, documented by molecular diagnostics. Histopathology shows necrotizing granulomatous inflammation with giant cells and characteristic palisading histiocytes. (H&E, 100×). (E) Hepatic granuloma in a moderately immunocompromised host (2.7 years post–liver transplant); H&E histopathology on the resected liver lesion shows a necrotizing granuloma with palisading histiocytes and central coagulative necrosis. (F) *B. henselae* BP hepatis in an immunocompromised host (6 years after combined pancreas-kidney transplant). Transjugular liver biopsy stained with H&E showed numerous randomly distributed, cystic, blood-filled spaces *(arrows)* between areas of normal parenchyma. *(Images A and D reproduced with permission from VanderHeyden TR, Yong SL, Breitschwerdt EB, Maggi RG, Mihalik AR, Parada JP, Fimmel CJ. Granulomatous hepatitis due to* Bartonella henselae *infection in an immune competent patient.* BMC Infect Dis. *2012;12:17. Images B and E reproduced with permission from Thudi KR, Kreikemeier JT, Phillips NJ, Salvalaggio PR, Kennedy DJ, Hayashi PH. Cat scratch disease causing hepatic masses after liver transplant.* Liver Int. *2007;27:145–148. Image C reproduced with permission from Koehler JE, Tappero JW. Bacillary angiomatosis and bacillary peliosis in patients infected with human immunodeficiency virus.* Clin Infect Dis. *1993;17:612–624. Image F reproduced with permission from Freed MM, Ramirez-Valle F, Chandran S. Fever, hepatosplenomegaly and a skin nodule in a kidney-pancreas transplant recipient.* Am J Transplant. *2012;12:2556–2558.)*

increased the risk of having any of these symptoms, and female gender also was associated with increased risk of arthropathy.[172] Less commonly, tendonitis, neuralgia, and osteitis were identified, each at a rate of less than 1%. A review of 47 patients with skeletal manifestations associated with CSD found a median age of 9 years. The most frequently involved sites were the vertebral column (42%) and the pelvic girdle (27%).[173]

Atypical Manifestations of Cat-Scratch Disease

The nonspecific nature and rarity of many of the atypical manifestations can result in a delay of accurate diagnosis until a history of cat exposure, a positive serology, or suggestive findings on histopathology prompt specific evaluation for *B. henselae* infection.[165] "Atypical" manifestations of CSD[174] include Parinaud oculoglandular syndrome, self-limited granulomatous hepatitis/splenitis,[175] atypical pneumonitis,[176] osteitis,[173,177] and neurologic syndromes (predominantly encephalopathy and neuroretinitis). A syndrome of prolonged FUO in children also has been described.[178] Because of the insidious and nonspecific nature of the fever and abdominal pain of CSD hepatitis/splenitis, diagnosis may be delayed until a history of cat exposure prompts serologic testing and ultrasonographic or CT abdominal imaging, which usually demonstrates multiple hypodense lesions (see Fig. 234.8A).[146,179–181] Histopathologic examination usually demonstrates necrotizing granulomatous inflammation with giant cells and palisading histiocytes (see Fig. 234.8D).

Encephalopathy Complicating Cat-Scratch Disease

Encephalopathy, a dramatic but infrequent manifestation, was first reported within a few years of the description and naming of CSD. Encephalopathy probably occurs in 2% to 4% of all diagnosed CSD cases, although estimates range widely from 1% to 7%.[182] In a state-wide study to systematically identify the etiology of encephalitis in California, *Bartonella* was identified as the most common bacterial cause of encephalitis (7/203 total cases).[183] All patients required ICU care, and brain MRI scans and CSF analyses were normal. Currently, a history of cat exposure and presence of anti–*B. henselae* antibodies in serum provide the best evidence for diagnosis of CSD encephalitis. Adolescents and adults may represent a greater proportion of cases of CSD encephalopathy than they do of CSD overall.[184] Although encephalopathy usually follows the development of lymphadenopathy, it also has been reported to precede lymph node involvement or to occur in its absence. Persistent, generalized headache is a common part of the

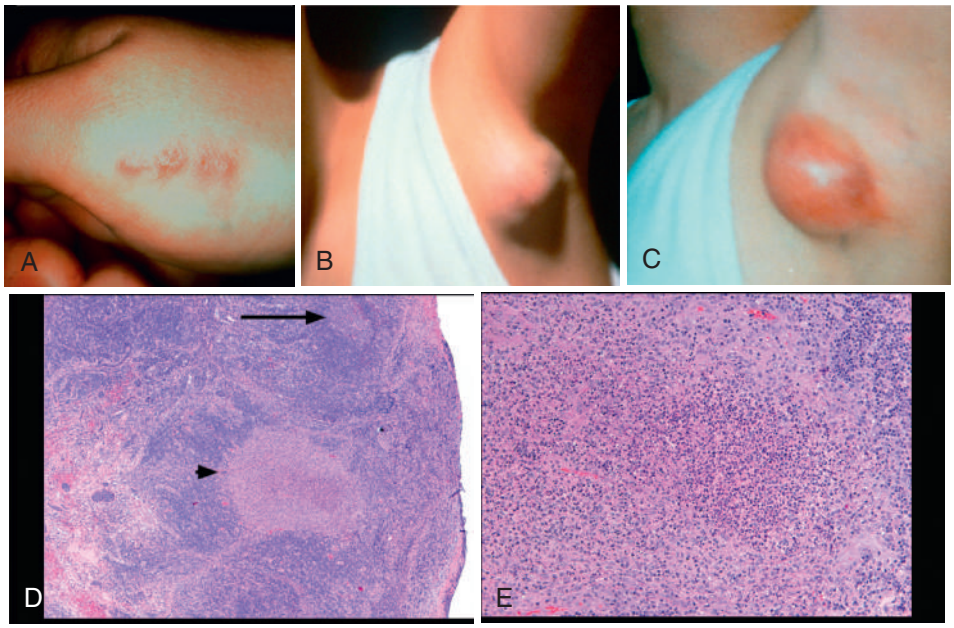

FIG. 234.9 Clinical and histopathologic features of typical cat-scratch disease (CSD) in the immunocompetent host. In an immune competent host, the typical presentation of CSD involves (A) a cutaneous lesion at the site of inoculation (7–10 days after a cat scratch and before development of ipsilateral lymphadenopathy), and (B and C) progressive regional lymphadenopathy. (D) Shows the typical H&E-stained histopathologic appearance of suppurative granulomatous lymphadenitis of CSD in a low-power view, with a large, ovoid, pale-appearing granuloma *(arrowhead),* in contrast to a normal germinal center *(arrow).* (E) A higher-power view of a granuloma shows eosinophilic epithelioid histiocytes and small lymphocytes forming the rim, with a necrotic central core that contains numerous neutrophils. *(Image A courtesy Dr. Timothy Berger, University of California–San Francisco. Images B and C reproduced with permission from Dr. Anna Sander from Katzenkratzkrankheit und andere* Bartonella*-Infektionen. In: Hofmann F.* Handbuch der Infektionskrankheiten*. 8th ed. Landsberg, Germany: ecomed Verlagsgesellschaft AG; 2004 (Ergänzungslieferung). Images D and E reproduced with permission from Dr. Linda Ernst, North Shore Medical Group, Evanston, IL, published in Florin TA, Zaoutis TE, Zaoutis LB. Beyond cat scratch disease: widening spectrum of* Bartonella henselae *infection.* Pediatrics*. 2008;121:e1413–e1425.)*

history, but fever is an inconsistent finding. Patients may become restless, and combativeness occurs often. Nearly half of patients develop seizures that range from focal to generalized and from brief and self-limited to status epilepticus. Short-term anticonvulsant therapy may be required, as well as supportive therapy when there is obtundation or coma. Concurrent acute neurologic manifestations can be present transiently (e.g., nuchal rigidity, pathologic reflexes, pupillary dilatation). When they occur, neurologic deficits, such as aphasia, cranial nerve palsy, paresis, hemiplegia, and ataxia, also are usually self-limited, although time to resolution may span weeks to months to as long as 1 year. However, persistence of cognitive impairment and of seizures has been reported uncommonly.[185–187]

Laboratory studies, such as cerebrospinal fluid (CSF) analysis and culture, generally do not add specific diagnostic findings to the clinical picture of CSD encephalopathy but can exclude other processes. Elevations of CSF protein concentration and leukocytes occur in only approximately one-third of patients but do not necessarily coincide in the same patients; lymphocytes predominate and hypoglycorrhachia is rare. CSF cultures have been consistently negative, even after the identification of *B. henselae* as the causative agent of CSD. Studies of the brain with CT or magnetic resonance imaging, or both, are usually normal, but a few cases of persistent structural abnormalities have been reported.[186,187] Electroencephalography during the acute phase of CSD encephalopathy commonly reveals diffuse slowing, yet another nonspecific feature that resolves with clinical recovery.

The pathogenesis of CSD encephalopathy and other central nervous system (CNS) manifestations associated with CSD remains unclear. It is unknown whether these rare complications are attributable to direct invasion of the CNS by *B. henselae* or to other mechanisms, such as vasculitis or host immune response. At autopsy of a patient who died from CSD meningoencephalitis, there was marked cerebral edema with no gross evidence of acute meningitis. Microscopic examination revealed multiple granulomatous lesions, as well as meningitis and encephalitis.[188] Warthin-Starry silver stain of the brain and liver revealed pleomorphic rod-shaped bacilli consistent with *B. henselae*. Analysis of brain tissue with PCR confirmed the presence of *B. henselae* DNA.[188] Autopsy of another rare case of a 6-year-old child who died from disseminated CSD with encephalitis demonstrated intracerebral histologic findings of perivascular lymphocytic infiltrates and microglial nodules.[189]

Ocular Manifestations of Cat-Scratch Disease

Ocular manifestations of CSD include Parinaud oculoglandular syndrome (an atypical form of CSD lymphadenitis), neuroretinitis, vascular-occlusive events, retinitis, choroiditis, and optic nerve granuloma.[190–192] Up to half of the 11% or 12% of CSD cases that are atypical represent Parinaud oculoglandular syndrome, a self-limited granulomatous conjunctivitis with ipsilateral, usually preauricular, lymphadenitis (Fig. 234.10).[193,194] After its description in 1970,[192] neuroretinitis remained solely a clinical diagnosis for years, but development of a serologic test for anti–*B. henselae* antibodies has facilitated diagnosis.[59] Neuroretinitis associated with CSD[192,195,196] subsequently has been associated with *B. henselae* infection by serology.[109,190] *B. grahamii* neuroretinitis was identified in a single patient by PCR amplification and sequence analysis of DNA in the intraocular fluid of an HIV-seronegative patient with bilateral neuroretinitis and behavioral changes.[197] *B. elizabethae* has been implicated as the pathogen in another patient with neuroretinitis, although only by serologic antibody studies.[198]

Neuroretinitis often manifests with a sudden loss of visual acuity, usually unilaterally, and sometimes preceded by an influenza-like syndrome or development of unilateral lymphadenopathy. The most striking retinal manifestation is papilledema associated with macular exudates in a star formation (Fig. 234.11), first associated with CSD in 1984.[195] Although this manifestation is characteristic of CSD neuroretinitis, other types of inflammation/infection also can cause this finding. In a retrospective study of 24 CSD patients with 35 affected eyes,[190] isolated foci of retinitis or choroiditis were the most common ocular manifestation, identified in 83% of eyes and 83% of patients. Optic disk swelling was the second most common finding (46% of

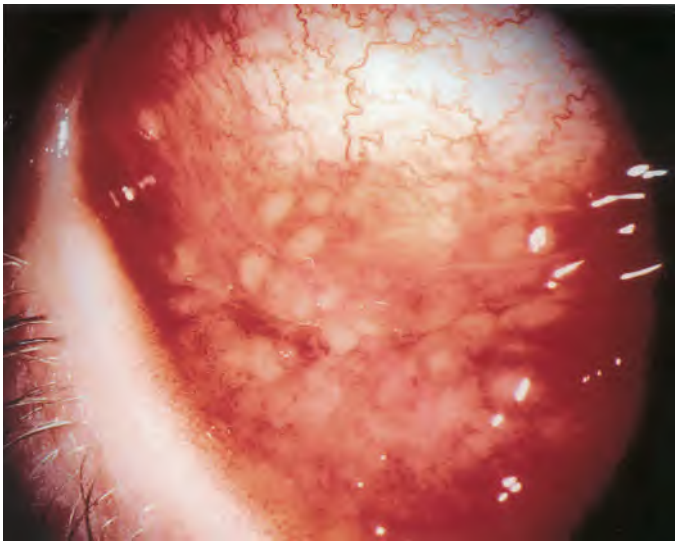

FIG. 234.10 Atypical cat-scratch disease: Parinaud oculoglandular syndrome, a granulomatous conjunctivitis, is associated with ipsilateral regional lymphadenopathy (usually preauricular and, less commonly, submandibular).

FIG. 234.11 Atypical cat-scratch disease (CSD): neuroretinitis is one of the more common complications of CSD. The striking papilledema associated with stellate macular exudates is among the most common manifestations of CSD neuroretinitis.

eyes and 63% of patients), followed by a macular star (43% of eyes and 63% of patients), and vascular-occlusive events (14% of eyes and 21% of patients). Final visual acuity was 20 of 25 or better in 26 of 35 eyes (74%) and was similar in both treated and untreated patients.[190] Although patients with neuroretinitis or retinochoroiditis can have concomitant anterior segment inflammation, the association of isolated uveitis (without optic disk edema or focal retinochoroiditis) with *Bartonella* infection is not as well established; in one study,[199] 17 of 51 patients with uveitis had positive *Bartonella* serology, compared to 1 of 101 controls; however, the presence of *Bartonella* could not be confirmed with PCR testing of surgical specimens (lens mass, intraocular fluid) obtained from 33 patients.[199] Unlike many other causes of neuroretinitis, *B. henselae* neuroretinitis usually spontaneously resolves with a favorable visual outcome, although prospective follow-up of some recent, well-documented cases reveals that some have mild residual visual deficits.[109,196] The utility of antimicrobial or corticosteroid therapy, or both, continues to be debated.[196]

Differential Diagnosis of Cat-Scratch Disease

The differential diagnosis of typical CSD includes many causes of (unilateral) lymphadenopathy, among which are typical or atypical mycobacterial infection, tularemia, plague, brucellosis, syphilis, sporotrichosis, histoplasmosis, coccidioidomycosis, toxoplasmosis, infectious mononucleosis syndromes, lymphoma, and other neoplasms.[200] In SOT recipients, posttransplant lymphoproliferative disease also would be included in the differential diagnosis. In the inguinal area tender adenopathy in the absence of a genital lesion suggests *Staphylococcus aureus*, CSD, lymphogranuloma venereum, and, in the febrile patient with tick exposure, tularemia. The diagnosis of CSD can be overlooked if the clinician fails to obtain an adequate history, especially in patients with atypical CSD syndromes, but also in adults with typical CSD who are seen by internists lacking experience with diagnosing CSD (in contrast to pediatricians). In elderly adults (older than 60 years) manifestations tend to be less typical, further confounding the diagnosis.[201] With domestic cats representing the largest category of companion animals in the United States, obtaining an accurate history regarding animal exposure is critical when evaluating a patient with findings consistent with CSD. Fortunately, spontaneous resolution occurs in most cases of CSD, whether typical or atypical.

Bartonella Infections in Solid-Organ Transplant Recipients

Background/Risk Factors for Acquisition of *Bartonella* in Solid-Organ Transplant Recipients

SOT recipients represent an important emerging population that develops serious and potentially life-threatening *Bartonella* infections; the majority of cases have been reported since 2012. When *Bartonella* was first identified in the United States in the 1990s, the infections occurring in immunocompromised individuals were almost exclusively identified in patients with late-stage HIV infection. As increasingly active antiretroviral agents were identified, the incidence of *Bartonella* infections in HIV-infected individuals decreased dramatically, whereas the incidence increased substantially in SOT recipients. In addition to the temporal difference in recognition of *Bartonella* infections in these two immunocompromised populations, the infecting *Bartonella* sp. also differs: in AIDS patients with *Bartonella* infection in the 1990s, approximately half were infected with *B. henselae* and the other half with *B. quintana*.[43] In contrast, SOT recipients almost always are infected with *B. henselae*,[129] presumably because SOT recipients are housed, not homeless, and thus often exposed to pet cats (*B. henselae*) but not to body lice (*B. quintana*). Indeed, most SOT recipients with *Bartonella* infection either owned a cat or had exposure to cats.[129] One patient had a potential donor-derived *Bartonella* infection.[65] This patient developed a localized liver infection 2 months after liver transplantation and did not have a history of cat exposure. The donor serum IFA IgG for *B. henselae* was 1:64 (lowest positive titer).

The recent numerous reports of *Bartonella* infection in SOT recipients provides documentation of the increasing frequency and wide spectrum of disease manifestations in this patient population.[112,129–133,150–152] In a review of 29 SOT recipients with *B. henselae* infection, 28% of patients had typical CSD with regional lymphadenopathy, and 72% had disseminated disease, which included BA (cutaneous, lymph node), hepatic or splenic BP, granulomatous or suppurative tissue reaction (liver, lymph node, bone, lung, or bone marrow), endocarditis, and bilateral chorioretinitis.[129] Representative of the typical distribution of SOTs, two-thirds of the patients had received a kidney transplant, one-fourth a liver transplant, and one patient each had received a lung and heart transplant.[129] Of note, eight patients were receiving trimethoprim-sulfamethoxazole (TMP-SMX) (for *Pneumocystis* prophylaxis) when the *Bartonella* infection occurred, providing further evidence that this agent is not an acceptable treatment for bartonellosis.

Clinical Features of *Bartonella* Infection in Solid-Organ Transplant Recipients

As noted earlier for HIV-infected patients, the clinical manifestations in SOT recipients depend on the degree of immunocompromise (see

Fig. 234.4 and Table 234.2). Prominent clinical features included fevers (93% of patients) and lymphadenopathy (41%),[129] emphasizing the importance of considering *B. henselae* infection when evaluating an SOT recipient with FUO or lymphadenopathy. The majority of patients (69%) had abnormal findings on CT scan, including lymphadenopathy, splenomegaly, hepatomegaly, and low-attenuation hepatic and splenic lesions (see Fig. 234.8B), a lytic bone lesion, or a lung nodule.[129]

Cases of ocular bartonellosis in transplant recipients also have been reported; in one case the ocular disease was manifested as panuveitis and retinal detachment, and the patient also was found to have endocarditis and ring-enhancing cerebral lesions, emphasizing that ocular manifestations should prompt workup for disseminated *Bartonella* infection in an immunocompromised host.[131]

Diagnosis of *Bartonella* Infections in Solid-Organ Transplant Recipients

Histopathologic examination, serologic testing, and PCR testing for *B. henselae* provided important methods for establishing the diagnosis of *Bartonella* infection.[129] PCR testing on tissue (lymph node, liver, bone marrow, lung) or serum was positive in 12 of 14 patients in whom it was performed.[129] Serologic testing was positive in 6 of 6 of CSD patients and 17 of 21 patients with disseminated disease who underwent testing, providing reassurance that most SOT recipients are capable of mounting an antibody response to *Bartonella* infection.[129] Serologic testing should be performed in a validated reference laboratory, and because serology may be negative initially, acute and convalescent serologic testing is important and may increase the diagnostic accuracy.[129,132,133,150] Note that a negative *Bartonella* serology does not exclude the diagnosis, as reported in two SOT recipients with cutaneous BA but negative acute and convalescent serologies.[130]

Pathologic Findings and Relation to Duration of Time Posttransplant

Granulomatous or suppurative inflammation (see Figs. 234.7A1–A3 [cutaneous] and 234.8E [hepatic]), the histopathology characteristic of CSD, occurs more often than BA/BP (see Fig. 234.8F [hepatic]) in SOT recipients with *Bartonella* infection.[129] Patients with BA/BP developed infection on average 3 years earlier posttransplant than patients with granulomatous or suppurative inflammation. Similarly, patients with disseminated bartonellosis developed disease approximately 3 years earlier after transplantation than patients who had typical CSD. These findings may reflect a greater degree of immunosuppression closer to the time of transplantation. A clear relationship between a specific immunosuppressive regimen and development of disseminated disease or BA/BP was not identified, possibly due to the limited number of patients and retrospective nature of the study.[129]

Prognosis for Solid-Organ Transplant Recipients With *Bartonella* Infection

The majority of SOT recipients with *Bartonella* infection responded to antibiotic therapy, but several patients experienced a relapse of CSD[129] or BA,[130] and two patients died from endocarditis.[129] In another patient, who presented 2 years postrenal transplantation with fever, lymphadenopathy, and pauciimmune necrotizing glomerulonephritis, antimicrobial therapy was unsuccessful, and the patient ultimately required retransplantation. However, experience in treatment of other immunocompromised hosts has demonstrated that the short treatment duration (1 week of azithromycin) would be of insufficient duration to cure an immunocompromised host.[151]

CELLULAR AND MOLECULAR PATHOGENESIS ASSOCIATED WITH *BARTONELLA* INFECTIONS

In cats and other mammalian hosts, *Bartonella* appears to be a nearly perfectly adapted parasite, capable of causing long-term or cyclic, high-grade, intraerythrocytic bacteremia, largely in the absence of illness in its cognate host.[51,57,66,202–205] Each *Bartonella* spp. has adapted to, and infects, only one or a few mammalian reservoir hosts.[206] Elucidation of the mechanisms of this host-pathogen relationship is a focus of current research. Fundamental knowledge about the pathogenic mechanisms of *Bartonella* spp. in humans is growing, primarily focused on entry mechanisms into endothelial cells and erythrocytes, induction of angiogenesis (e.g., in lesions of BA), and mechanisms of *Bartonella* survival in the mammalian host and arthropod vector. The pathogenic mechanisms of *Bartonella* spp. involve complex host-pathogen interactions. In vitro studies demonstrate that *B. henselae* can invade a diverse repertoire of host cells, including endothelial cells, monocytes, macrophages, dendritic cells, hematopoietic progenitor cells, and epithelial cells.[207–212] Pathogenic mechanisms have been reviewed in detail elsewhere.[207,208,213,214]

Adhesion to host cells is an important initial step in infection of the host, and a number of surface proteins and structures have been implicated in this adhesion process. The *B. quintana* variably expressed outer membrane proteins (Vomps) and the *B. henselae* ortholog, *Bartonella* adhesion A (BadA) protein, are nonfimbrial, nonpilus, outer membrane trimeric autotransporter adhesion (TAA) proteins that play an important role in attachment to host cells.[215,216] The Vomps in *B. quintana* are encoded by a family of four genes and are necessary for infection of the host.[217] Each Vomp is expressed on the *B. quintana* surface, and each has a unique region that mediates binding to different host cell substrates or to other *Bartonella* bacilli (autoaggregation).[215] The Vomps also undergo phase variation during prolonged bloodstream infection, which can facilitate persistence in the mammalian host.

During endothelial cell invasion by *B. bacilliformis,* the bacterium induces rearrangement of the host cytoskeleton.[218] Entry of *B. henselae* into endothelial cells in vitro can occur via two mutually exclusive pathways in vitro.[211] One route of entry involves uptake of a single or a small group of bacteria into *Bartonella*-containing vacuoles (BCVs). BCVs appear to avoid lysosomal fusion and, instead, accumulate in the perinuclear space.[210,211] The second route of entry involves bacterial aggregation on the cell surface, followed by engulfment and internalization of the bacterial aggregate by a unique structure, the invasome.[207,208,211] Invasome-mediated uptake is dependent on *Bartonella* effector proteins (Beps), which are translocated into endothelial cells via the VirB/D4 type IV secretion system (T4SS), and bidirectional signaling through integrin receptors.[207–209,219]

Adherence and invasion of erythrocytes by *Bartonella* spp. are likely specific to each species' cognate host(s), and establishment of high-density bacteremia is important to ensure continuous transmission.[206,207] There is in vitro evidence that human-specific *B. bacilliformis* and *B. quintana* can invade human erythrocytes[220,221]; host specificity for the *Bartonella* spp., designated lineage 4 (which includes most modern *Bartonella* spp., including *B. henselae, B. quintana, B. vinsonii,* and *Bartonella tribocorum*), is governed by the Trw T4SS and is essential for erythrocyte attachment and invasion.[206,207,208] *B. bacilliformis,* the sole representative of an ancestral lineage, does not have a Trw T4SS but does have a unipolar tuft of flagella that confer motility and may participate in erythrocyte attachment and invasion.[207,208,222] Of interest, the *Bartonella* Trw system has been investigated for use in genetic engineering, given its potential for facilitating cellular entry and DNA integration.[223] Erythrocyte invasion by *B. bacilliformis* and *B. henselae* may involve an extracellular deformin protein and proteins encoded by the invasion-associated locus *(ialAB)*.[207,208,222,224–227] Deformin may induce invaginations of the erythrocyte membrane, which could serve as points of entry for *Bartonella*.[207,208] After entry into erythrocytes in vitro, *B. bacilliformis* can replicate within, and occasionally escape from, the erythrocytes.[220] In an elegant in vivo study by Schülein and colleagues,[228] *Bartonella* infection of erythrocytes was followed over time by confocal imaging and flow cytometry, demonstrating the replication of *Bartonella* in erythrocytes during bloodstream infection.

B. bacilliformis has been demonstrated to stimulate endothelial cell proliferation both in vitro and in vivo, possibly through a stimulatory factor shed from, or actively secreted from, the bacterium.[229–231] Several in vitro studies indicate that the proliferative effects of *B. henselae* and *B. quintana* may be partially mediated by the adhesins BadA and Vomp, which are required for bacterial attachment to endothelial cells.[215,216,232,233] BadA also may promote angiogenesis through activation of hypoxia inducible factor-1 and nuclear factor kappa B, which induces the secretion of vascular endothelial growth factor (VEGF), and interleukin-8 (IL-8), respectively.[207,232] In *B. quintana* expression of the Vomp is associated

with induction of VEGF expression from human macrophage and epithelial cell lines.[233]

Another family of important virulence factors in *B. henselae* and *B. quintana* is that of the hemin binding proteins (Hbps), porin-like outer membrane proteins that bind hemin and play a role in heme acquisition, which is crucial for *Bartonella* growth.[234] Overexpression of one protein in the *B. henselae* Hbp family, HbpC, results in increased resistance to heme toxicity, implicating HbpC in protection of *B. henselae* from the toxic levels of heme present in the gut of the arthropod vectors that transmit *Bartonella* spp.[235] In contrast, other members of the *B. henselae* Hbp family are hypothesized to maintain a heme reservoir and increase the efficiency of heme uptake when the *Bartonella* bacteria occupy their other niche, the mammalian bloodstream, where iron and hemin are extremely scarce.[235] In addition, *B. henselae* Hbp knockdown mutants have a decreased ability to counteract reactive oxygen species, have decreased capacity to invade endothelial cells, and are more rapidly cleared in flea feces.[236] These findings highlight the role Hbps have in facilitating endothelial cell invasion by *B. henselae,* resistance against oxidative stress, and survival of *B. henselae* in the flea vector.

Probably the most important and most studied virulence factors are the *Bartonella* Beps.[237] The *B. henselae* and *B. quintana* Beps are translocated into the host cell by the VirB/VirD T4SS, where the Bep target processes in the host and modulates it to the advantage of the invading bacterium. The *B. henselae* and *B. quintana* BepAs are necessary and sufficient to inhibit vascular endothelial cell apoptosis by causing elevated intracellular levels of cyclic adenosine monophosphate (cAMP), resulting in expression of cAMP-responsive genes.[238] This BepA activity may contribute to the endothelial cell proliferation observed in the focal lesions of verruga peruana and BA. BepC is important for invasome formation, inducing uptake of *Bartonella* at the host cell surface; it also effects host cell fragmentation.[237] It has been proposed that BepE, which protects endothelial cells from BepC-mediated cell fragmentation, is necessary for infection of the reservoir host dendritic cells during intradermal inoculation.[239] Further study of Beps will likely provide novel insight into the pathogenesis mechanisms used by *Bartonella* to survive and persist in the reservoir host.

Immune evasion and attenuation of the host inflammatory response are important strategies adopted by *Bartonella* for survival in the host. The invasion of erythrocytes provides a sequestered niche to protect *Bartonella* from the adaptive and innate immunity of the reservoir host.[207] Multiple studies have demonstrated that the helper T-1 response, which stimulates the production of interferon-γ and tumor necrosis factor-α, probably plays a central role in the elimination of *B. henselae*.[207,240,241] The inflammatory response elicited by *B. henselae* in CSD leads to the formation of B-cell–rich suppurative granulomas, which appear to be mediated by the effect of the organism on dendritic cells.[212] However, *Bartonella* also can attenuate the host immune response and promote persistence of infection by stimulating IL-10 production. IL-10 is known to suppress the function of multiple immune cells, including helper T cells, monocytes, macrophages, and dendritic cells. This mechanism was suggested by an investigation of the immune response in homeless people with chronic asymptomatic *B. quintana* bacteremia, which identified a specific increase in IL-10 secretion with a concomitant dampening of the inflammatory response.[242] *B. quintana* also may dampen the immune response by blocking Toll-like receptor 4, thus inhibiting the downstream inflammatory response.[243]

LABORATORY DIAGNOSIS OF *BARTONELLA* INFECTIONS

The major impediments to diagnosis of *Bartonella* infections are (1) omission of *Bartonella* from the differential diagnosis because of the nonspecific manifestations and the widely varying presentations as the result of host immune status; (2) failure to obtain a history of risk factors for *Bartonella* infection; and (3) the extremely fastidious nature of *Bartonella* spp., resulting in a subsequent lack of a reproducible, sensitive, specific, and widely available diagnostic tests.

To include *Bartonella* infection in the differential diagnosis, a crucial initial step is obtaining a history of cat and flea exposure (*B. henselae*), homelessness and body louse exposure (*B. quintana*), or exposure to an area endemic for *B. bacilliformis*. Diagnostic approaches that are available at many clinical and reference laboratories include serology, direct PCR-based DNA detection assays, and sometimes culture. However, to ensure the most reliable results, testing for *Bartonella* infection should be performed in Clinical Laboratory Improvement Amendments (CLIA)-approved laboratories, using well-validated tests, such as IFA testing or PCR using broad-range bacterial or *Bartonella*-specific 16S ribosomal DNA (rDNA) primers at established reference laboratories. Use of validated tests is particularly important for diagnosis of patients presenting with atypical symptoms or with a potential new presentation of *Bartonella* infection. Laboratories with extensive experience include, but are not limited to, the Centers for Disease Control and Prevention (CDC),[59] University of Washington Molecular Diagnostics Laboratory (UW-MDL),[244] and Unité des Rickettsies in Marseille, France.[245]

If direct isolation of *Bartonella* is not possible (generally impractical because of the highly fastidious nature of *Bartonella*), a diagnosis of *Bartonella* infection can be achieved by PCR amplification of DNA extracted directly from involved tissues or blood, in the absence of additional manipulation of samples, and using appropriate PCR controls and a low number of PCR cycles. Amplification of *Bartonella*-specific DNA also may identify the infecting *Bartonella* spp. Although isolation or molecular identification of a *Bartonella* spp. provides a definitive diagnosis, when these are not possible, fulfillment of two or more positive criteria among epidemiologic, serologic, and histologic tests can provide a presumptive diagnosis. Analysis of serum antibodies using IFA testing is the most widely available laboratory test for diagnosis of *Bartonella* infection, with the caveat that there is extensive cross-reactivity among the different *Bartonella* spp., the IgM assay lacks sensitivity, and many late-stage AIDS patients never develop anti-*Bartonella* antibodies. Additional diagnostic approaches include direct examination of blood smears *(B. bacilliformis)* or histopathologic materials stained with H&E or Warthin-Starry silver stain (typically for CSD and BA/BP). Although serologic testing remains the mainstay of diagnosis for most *Bartonella* clinical syndromes, molecular diagnostics are increasingly used. A detailed discussion of diagnostic techniques for *Bartonella* is available in other reference sources.[246,247]

Direct Examination of Blood Smears and Histopathologic Specimens

Giemsa-stained blood films are commonly used in endemic locales of South America to detect *B. bacilliformis* in patients with Oroya fever. A wide morphologic range is seen in such smears, with the organisms appearing as red-violet rods or rounded forms, occurring singly or in groups, and associated with erythrocytes. Bacillary forms are most typically seen, measuring 0.25 to 0.5 × 1.0 to 3.0 μm; rounded organisms measure approximately 0.75 μm in diameter. The cells are often curved and may show unipolar or bipolar enlargement and granules. Although *B. bacilliformis* bacteria appear to be adherent to erythrocytes by light microscopy, they have also been observed within erythrocytes when viewed by electron microscopy.[248] Except for *B. bacilliformis,* blood smears rarely detect *Bartonella* during bacteremia in humans. The low titers of bacteremia associated with *B. henselae* and *B. quintana* during human infection make direct observation of bacteria in blood smears difficult; however, direct immunofluorescence[249] and acridine orange staining[12,33] may occasionally be positive.[249]

Bartonella spp. are gram negative, are not acid fast, and stain poorly or not at all in tissue, except by silver deposition stains (e.g., Warthin-Starry stain). *B. henselae* and *B. quintana* are demonstrable by Warthin-Starry staining in BA/BP; *B. henselae* bacilli may be observed by silver staining during the early stages of lymphadenopathy in CSD but typically not during the later granulomatous stage of inflammation. Species-specific direct detection of organisms in tissue by immunocytochemical labeling also has been described,[97,158,250] but reagents for such labeling are not widely available and not well characterized.

Specimen Collection and Handling for Culture

Isolation of *Bartonella* spp. is most commonly attempted from blood and tissue. The time interval from collection to processing should be minimized. If storage of specimens is necessary, the specimens should be immediately frozen. A controlled study of the effects of blood collection

and handling methods showed that blood specimens from *B. henselae*–infected cats, collected in either ethylenediaminetetraacetic acid (EDTA) or Isolator (Alere Isolator Microbial Tubes; Abbott, Abbott Park, IL) blood-lysis tubes, yielded good recovery and that blood collected in tubes containing EDTA could be plated after 26 days of storage at −65°C with no loss of culture sensitivity.[251] Whenever possible, specimens should be collected before antimicrobial therapy, especially before receiving even a single dose of a tetracycline or macrolide. Growth of *B. henselae* also is inhibited by concentrations of sodium polyanethol sulfonate (SPS) that are used in blood culture media.[246] Lytic blood culture systems (e.g., Isolator Tubes) combine the advantageous effects of neutralizing SPS toxicity by hemoglobin freed from erythrocytes, in addition to releasing intracellular *Bartonella* organisms.

Culture of *Bartonella* Species

All *Bartonella* spp. can be cultured on cell-free media, unlike members of the order Rickettsiales. Recovery of *Bartonella* spp. (except *B. quintana* and *B. koehlerae*) is optimized by using freshly prepared (<7 days old) heart infusion agar and 5% fresh defibrinated rabbit blood plates, poured with double the usual agar volume.[43,252] Various other formulations of blood or chocolate agar will support *B. henselae* growth, with the best results dependent on media freshness, presence of a hemin or hemoglobin source, and adequate moisture. *B. quintana,* and especially *B. koehlerae,* are probably the most fastidious *Bartonella* spp. and grow optimally on chocolate agar. Note that *Bartonella* isolation from humans requires more than 7 days of incubation before colonies can be detected on agar.[43,103] Therefore routine bacterial culture protocols rarely allow *Bartonella* spp. to be detected, and sensitivity is further compromised by prior antibiotic exposure.[43] Protocols designed to yield other slowly growing organisms (e.g., *Histoplasma capsulatum* or *Mycobacterium avium* complex on noninhibitory media) also can result in recovery of *Bartonella* spp. if incubation time is prolonged (at least 14–28 days). Cultures are not recommended to diagnose cases of CSD; the sensitivity is at best only 20% compared with PCR assays.[253] Attempted isolation of *Bartonella* spp. may be useful in the settings of (1) FUO after cat or body louse exposure; (2) fever, lymphadenitis, neuroretinitis, or encephalitis of unknown origin in the immunocompromised patient; (3) endocarditis without recovery of typical pathogens (i.e., culture negative); and (4) BA/BP. The highest yield of *Bartonella* spp. from blood culture is in patients with BA/BP (50%)[43] and homeless individuals with body louse exposure.[107]

Ideally, inoculated plates should be incubated at 35° to 37°C under conditions of 5% to 10% carbon dioxide (CO_2) and greater than 40% humidity; this environment can be created in a candle jar.[10] The candle jar should be soaked in a bleach solution, cleaned thoroughly, and then wiped with 70% ethanol before inoculated plates are placed in the candle jar. Because adequate ambient moisture is critical, and isolation of *Bartonella* spp. from human blood or tissue rarely occurs before 8 days of incubation, the candle jar should not be opened until 8 days after inoculation and then only weekly thereafter. This also decreases the likelihood of contamination of the rich agars during the prolonged (up to 4 weeks) incubation time before *Bartonella* is detected.[10,43,103] Note that *B. bacilliformis,* and possibly some strains of *B. clarridgeiae,* have a lower optimal temperature (25°–30°C) for growth. It is ideal to perform all culture and screening of inoculated plates in a biosafety cabinet to further reduce chances of agar contamination. As an alternative to candle jars, plates can be sealed after 24 hours of incubation with plastic film or shrink wrap to preserve moisture content of the media and reduce contamination.

Although *Bartonella* spp. usually grow best on solid or semisolid media, there are alternative approaches to plating blood collected in an EDTA tube or Isolator tube directly onto agar. These include broth-based blood culture systems, chemically defined fluid media,[254] or eukaryotic cell coculture systems.[10,255] The sensitivity of a shell vial culture assay may be slightly better than that of agar plate techniques.[245] In the automated, continuously monitored blood culture systems, *Bartonella* spp. rarely produce turbidity or convert enough oxidizable substrate for these CO_2 detection–based systems to indicate growth. However, several isolates of *Bartonella* have been detected initially using BACTEC (Becton Dickinson, Sparks, MD) or resin-containing media, followed by acridine orange staining at the termination of a 7- or 14-day incubation period, with subsequent recovery of *Bartonella* colonies after subculture to solid media.[11,12,33,95] Another CO_2 detection–based blood culture system, BacT/Alert (bioMérieux, Durham, NC), yielded a positive growth algorithm in several cases of *B. henselae* bacteremia.[256] Although Gram stains of the broth and routine 72-hour subcultures proved negative, acridine orange and Warthin-Starry staining demonstrated bacilli, and *B. henselae* was ultimately subcultured on semisolid media.[256] Extended incubation of blood culture vials also resulted in recovery of *B. quintana* in prosthetic valve endocarditis.[257]

Bartonella spp. have been isolated from liver, spleen, lymph node, and skin after homogenization, either by direct plating of tissue homogenate or aspirate[10,17,53,61,109] or by cocultivation with various cell lines.[10,13] *B. henselae* and *B. quintana* grow in endothelial cell cultures as elongated pleomorphic organisms visible in Gimenez-stained preparations 72 hours after inoculation of the cell cultures. The cocultivation method is not practical for most microbiology laboratories, although it may result in recovering isolates not cultured in cell-free media. In the absence of coculture, more than 1 month of incubation often is necessary to yield colonies from tissue specimens.[53,61] Isolation of *Bartonella* spp. from potentially contaminated biopsy sites (e.g., skin) can be facilitated by using selective media that exploits the observation that *Bartonella* spp. infecting humans are instrinsically resistant to nalidixic acid and cefazolin. These two antibiotics can be incorporated into chocolate agar (nalidixic acid, 20 µg/mL and cefazolin, 2 µg/mL).[217]

Identification of *Bartonella* Species

The primary isolate of a given *Bartonella* spp. can have several morphologic colony types, for instance, *B. henselae*: (1) irregular, raised, whitish, rough, and dry in appearance (characterized as "cauliflower," "molar tooth," or "verrucous"), with agar pitting and strong adherence to the agar or (2) flat, circular, moist in appearance, and less adherent. Both are often present in the same primary culture (Fig. 234.12A).[43] Colony heterogeneity varies by species. *B. henselae* typically displays a greater proportion of rough colonies, and primary cultures of *B. quintana* colonies are virtually always

FIG. 234.12 Appearance of colonies from primary isolation of *Bartonella henselae* and *Bartonella quintana* from biopsied tissue of cutaneous bacillary angiomatosis (BA) lesions from AIDS patients. (A) Primary isolation of *B. henselae* from a cutaneous BA lesion reveals colonies that are predominantly uniform in size, elevated, rough, gray, and deeply embedded in the chocolate agar. (B) Primary isolation of *B. quintana* from a cutaneous BA lesion on chocolate agar reveals colonies that are flat, round, smooth, shiny, opaque, of heterogeneous size, and demonstrating neither a rough appearance nor pitting of the agar. *(Images A and B reproduced with permission from Koehler JE, Sanchez MA, Garrido CS, et al. Molecular epidemiology of* Bartonella *infections in patients with bacillary angiomatosis-peliosis.* N Engl J Med. *1997;337:318.)*

uniformly smooth, although very heterogenous in size (see Fig. 234.12B).[43] Serial *B. henselae* subcultures on agar tend to have a progressively increasing proportion of smooth colonies. *B. bacilliformis* colonies are flat, small, and translucent or slightly white. Gram-stained *Bartonella* from colonies appear as small, gram-negative, slightly curved rods, sometimes resembling *Campylobacter* or *Helicobacter*. Twitching motility of *B. henselae* is evident in wet mounts. *B. bacilliformis, B. clarridgeiae, B. ancashensis*, and *B. rochalimae* bacteria possess polar flagella.

A preliminary identification of *B. henselae* or *B. quintana* can be made if the following are observed: (1) a prolonged incubation time of >7 days before the appearance of colonies, (2) a Gram stain appearance of small curved gram-negative bacilli, and (3) negative catalase and oxidase reactions.[247,252] Isolates should be referred to a laboratory experienced with *Bartonella* spp. for confirmatory identification; definitive diagnosis requires molecular testing (discussed later).

The use of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) has been proposed as a potentially useful tool for rapid identification of *Bartonella* spp. from a positive clinical culture. This technique permits bacterial identification based on unique patterns of peptidic spectra. In a proof-of-concept study, successful identification of 36 of 39 "blind-tested" *Bartonella* strains was demonstrated.[258] Subsequently, peptide mass reference spectra were constructed from *Bartonella* and other zoonotic pathogens and added to a reference database, the MALDI-TOF MS Biotyper System (Bruker, Billerica, MA), for research purposes.[259] Test results are rapid (within minutes); limitations of this testing modality include the lack of available MALDI-TOF MS technology at most clinical laboratories and that testing requires isolation of a positive culture from a clinical specimen.[258,259]

Molecular Methods for *Bartonella* Identification and Characterization

Numerous PCR assays, some using real-time DNA detection technology,[128,260,261] have been developed and become increasingly important for direct detection of *Bartonella* spp. in pus, skin lesions, tissue, blood, or serum. *Bartonella* DNA is rarely detected in sera from CSD lymphadenitis patients[262]; however, in the majority of patients with CSD, a *B. henselae* gene fragment specific for the citrate synthase, heat shock protein, or the *groEL* or 16S rRNA gene can be amplified from lymph node tissue by PCR.[63,155–157,261] Amplification of rRNA gene segments with universal primers, followed by direct nucleotide sequence analysis of the amplification products, is used in a number of reference laboratories to identify and speciate *Bartonella* isolates.[157] Improved detection of *Bartonella* DNA in histologic or other material, such as sera from culture-negative endocarditis, has been reported using nested PCR amplification techniques.[263,264]

PCR testing of excised cardiac valves has become one of the most important modalities for diagnosis of *Bartonella* culture-negative endocarditis.[99,100,101,113] In the case of an AIDS patient with aortitis of unknown etiology, broad-range bacterial 16S rRNA gene primers were used to detect *B. quintana* from DNA extracted from a paraffin-embedded sample of biopsied aortic tissue; the result was subsequently confirmed by serologic testing.[244] PCR amplification from a variety of tissues also has proved useful for the diagnosis of both regional and disseminated bartonellosis in SOT recipients.[129] A direct blood PCR-based method also identified *B. bacilliformis* in a subset of patients that had clinically suspected Carrión disease with a negative thin blood smear.[265] Use of PCR in the diagnosis of *B. bacilliformis* from dried blood spots also has been reported.[266]

PCR-based typing techniques have proven useful for epidemiologic characterization of *Bartonella* isolates, and some studies suggest a greater diversity of restriction fragment length polymorphism (RFLP) types in the blood of bacteremic HIV-infected people than in the CSD lesions of immunocompetent hosts.[267,268] Strain typing can be performed using PCR-based RFLP,[267–269] pulsed-field gel electrophoresis (PFGE), multilocus sequence typing (MLST),[270] repetitive extragenic palindromic PCR (REP-PCR),[20,271] enterobacterial repetitive intergenic consensus PCR (ERIC-PCR),[54] and multilocus variable-number tandem-repeat analysis (MLVA).[272] When these and other techniques are compared with PFGE, the latter tends to be less reliable than other typing methods for *Bartonella* spp. that have been studied.[270,273]

Serologic Testing for Detecting Infection With *Bartonella* Species

For *B. bacilliformis*, early testing using a simple sonicated lysate as antigen in an IgG immunoblot assay was reported to have 70% and 94% sensitivity in people with acute and chronic infection, respectively, but with suboptimal specificity.[274] An IFA had 82% and 93% sensitivity in people with acute and chronic infection, respectively, but at the expense of substantial cross-reaction with other *Bartonella* spp.[275] IFA also detected IgM in patients with early acute *B. bacilliformis* infection. When used in the endemic region to assess patients with syndromes compatible with *B. bacilliformis* disease, the low specificity of these tests may be relatively less important than for the geographically widespread *Bartonella* spp. An enzyme-linked immunosorbent assay for detecting *B. bacilliformis* infection in endemic areas used recombinant *B. bacilliformis* Pap31 protein,[276] resulting in a sensitivity of 84.5% and a specificity of 94% in 302 sera from at-risk Peruvian patients.[277]

A number of IFA[59,278–280] and enzyme immunoassays (EIAs) [252,281,282] have been described for *B. henselae* and *B. quintana* diagnosis. They most commonly have been used to demonstrate anti-*Bartonella* antibodies in people with CSD[59,278,280–282] or endocarditis[13,96–98] and in some cases of retinitis.[109] The CDC developed an IFA that uses *B. henselae* or *B. quintana* bacteria cocultivated with Vero cells on slides and then fixed.[59,278] This is the most widely adopted test for diagnosis of *Bartonella* infection, but preparation of slides, dilution of serum, and time-consuming reading of immunofluorescence on each slide affect the ability to make rapid, reproducible, and cost-effective diagnosis of *B. henselae* and *B. quintana*. In general, the sensitivity of this IFA is highest in the setting of CSD (≈84%,[59] and up to 95% when using the strictest clinical criteria for CSD[278]). The sensitivity is substantially lower among late-stage AIDS patients with culture-proven bartonellosis (≈75%).[103] In SOT recipients, this IFA appears to be at least 80% sensitive in the setting of disseminated disease and even higher in patients with regional lymphadenitis.[129] The *Bartonella* IFA sensitivity and specificity vary substantially for different commercial laboratories in the United States.

Depending on the laboratory, an IFA IgG titer of 1:64 for *B. quintana* or *B. henselae* indicates possible infection, and a titer greater than 1:256 strongly suggests recent or acute infection.[278] A fourfold rise in titer between acute and convalescent specimens is definitive.[283] For patients with culture-negative endocarditis, a very high serologic titer (IFA IgG ≥1:1024 in US laboratories or ≥1:800 at Unité des Rickettsies in France) provides supportive evidence of *Bartonella* endocarditis and has a high positive predictive value.[96] However, IFA assays performed only one time for a particular subject appear to be variably, and sometimes suboptimally, sensitive and specific.[280,281,284] Some patients with CSD can have low or negative titers that subsequently increase as late as 3 weeks after presentation[278]; thus obtaining repeat serology 3 to 4 weeks after presentation can increase the IFA sensitivity. It is important to note that the *Bartonella* IFA IgM is frequently negative, even in documented acute infection, and cannot be relied on to diagnose acute *Bartonella* infection. Also of importance, IFA tests often show extensive cross-reactivity between antibodies to *B. quintana* and *B. henselae,* and often other *Bartonella* spp.[278] Furthermore, in some of these assays there may be serologic cross-reaction with antibodies to *Chlamydia* spp. and *Coxiella burnetii,* two other potential agents of "culture-negative endocarditis" in humans; however, the *Bartonella* titer usually is much higher than the cross-reacting genus titer.[13,96,279,284] Despite the challenges in interpretation outlined earlier, serology, typically IFA, remains the mainstay of diagnosis for most clinical syndromes of bartonellosis.

EIA and IFA methodologies that use partially,[97,252,285] highly purified,[286] or recombinant[276,287] antigen preparations ultimately may prove more species sensitive and specific. In addition, the use of specific fractions or purified proteins may enhance the standardization, interpretation, and efficiency of serological testing for *Bartonella*.[288]

Antimicrobial Susceptibility Testing of *Bartonella* Isolates

It is important to note that in vitro susceptibility testing of *Bartonella* isolates is often not relevant to the in vivo patient treatment response, and thus there is a well-demonstrated lack of correlation between the in vivo and in vitro susceptibilities. In addition, susceptibility testing

methods have not been standardized for *Bartonella* due to its extremely fastidious nature. In vivo, *B. henselae* and *B. quintana* infections respond rapidly to erythromycin, doxycycline, and rifampin. If required, antimicrobial susceptibility testing can be performed by incorporation of antimicrobial agents into either blood or chocolate agar and then testing by the agar dilution technique.[15,289] *Haemophilus* test medium with a broth microdilution technique also has been described, but the Etest (bioMérieux, France) may be the most practical means to assess in vitro susceptibility of *B. quintana* and *B. henselae* isolates.[290–292] Testing in other types of systems also has been reported.[293–296] In vitro, *B. henselae* isolates appear to be susceptible to many antibacterial agents tested but are intrinsically resistant to nalidixic acid and cefazolin, which can be useful for preparing selective agar.[217] *B. quintana* has a similar susceptibility pattern to *B. henselae* in vitro. In summary, *Bartonella* infections in patients are most reliably responsive to tetracycline, macrolide, and rifamycin classes.

TREATMENT AND PREVENTION OF *BARTONELLA* INFECTIONS

Consensus recommendations for treatment of *Bartonella* spp., based on the best available evidence at the time, were published in 2004.[297] However, the increasing identification of small vessel vasculitis, glomerulonephritis, and renal compromise associated with *Bartonella* endocarditis necessitate great caution in, or avoidance of, using gentamicin (or other potentially nephrotoxic antimicrobials) as an adjunct antimicrobial in the first 2 weeks of doxycycline treatment of *Bartonella* endocarditis, although suggested in previous guidelines (see later).[114,115,117]

Treatment of *Bartonella bacilliformis* Infections

For acute *B. bacilliformis* infection in South America (Oroya fever), oral ciprofloxacin with ceftriaxone for 14 days is recommended for first-line treatment,[39,297–299] although some reports of intrinsic and in vivo fluoroquinolone resistance suggest that fluoroquinolones may not provide optimal treatment.[300–302] Alternative antibiotic options for Oroya fever include chloramphenicol (adults: 500 mg orally [PO] or intravenous [IV] every 6 hours; children: 50 to 75 mg/kg/day PO or IV divided into four doses) for 14 days, coadministered with a β-lactam antibiotic (e.g., amoxicillin-clavulanate).[297,298] Parenteral therapy can be substituted for severe illness or if oral intake or bowel absorption is impaired. Currently, in Peru the primary agent of choice in the treatment of eruptive-phase lesions (verruga peruana) is oral azithromycin for 7 to 14 days (<14 years of age, <45 kg: single dose of 10 mg/kg/day; ≥14 years of age, >45 kg: single dose of 500 mg/day).[298] Alternative agents include rifampin for 21 to 28 days or ciprofloxacin for 14 days.[85,297–299]

Treatment of *Bartonella* Infections in the Immunocompromised Host

For immunocompromised patients with HIV infection, periodically updated guidelines for prevention and treatment of opportunistic infections in adults and adolescents have been developed under the auspices of the National Institutes of Health, CDC, and Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America.[303] This information can be accessed online at https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/329/bartonellosis. For *B. henselae* or *B. quintana*, in vitro susceptibilities often do not predict in vivo response to therapy, as noted earlier in "Antimicrobial Susceptibility Testing of *Bartonella* Isolates." Indeed, in contrast to in vitro sensitivities, CSD and BA/BP have developed in, and *Bartonella* has been cultured from, HIV-infected patients or SOT recipients while receiving ongoing therapy with TMP-SMX, β-lactam antibiotics, or fluoroquinolone antibiotics.[43,121,129,303] Thus these antibiotics are not recommended for empirical treatment of *B. quintana* or *B. henselae*. In contrast, therapy with rifampin, tetracyclines, or macrolides (even a single dose) dramatically reduced culture recovery of *B. quintana* or *B. henselae* from blood and BA/BP lesions. In addition, treatment or prophylaxis with a macrolide appears to protect against development of *Bartonella* infections.[43] In particular, the routine use of rifabutin, clarithromycin, or azithromycin for the prevention of *M. avium* complex infections in people with late-stage AIDS appears to have reduced the incidence of *Bartonella* infections.[103]

On the basis of observed clinical effectiveness in immunocompromised patients with culture-proven *Bartonella* infections, the recommended initial agent of choice to treat *Bartonella* infections is doxycycline (100 mg PO or IV every 12 hours) or erythromycin (adults: 500 mg PO or IV every 6 hours; pediatric: 40 mg/kg/day in four divided doses, maximum total daily dose, 2 g/day) for a minimum of 3 months.[43,297,303–305] For severe illness, rifampin can be added to doxycycline, although interactions with antiretroviral therapy or immunosuppressants should be considered. Azithromycin (500 mg PO daily) or clarithromycin (500 mg PO twice a day) is recommended as an alternative treatment.[303] In addition, azithromycin can be considered for patients at risk for antibiotic nonadherence.[303]

In SOT recipients with disseminated bartonellosis, treatment regimens consisting of doxycycline, or macrolides (azithromycin, erythromycin, or clarithromycin), or a combination of doxycycline and a macrolide has been clinically effective.[129] However, due to the poor tolerability of erythromycin and potential drug-drug interactions with antiretroviral and immunosuppressive agents, doxycycline is often preferred over erythromycin in transplant recipients and HIV-infected individuals.

Relapse occurs frequently in immunocompromised patients; to prevent relapse, immunocompromised patients should receive at least a 3-month course of initial therapy with doxycycline or a macrolide for any manifestation of *Bartonella* infection. For immunocompromised patients with widely disseminated disease (e.g., BA/BP), an initial treatment duration of 6 months should be considered. If relapse occurs after initial treatment of 3 to 6 months, treatment should be extended for a minimum of another 3 months. If subsequent relapse occurs, chronic suppressive therapy with doxycycline or erythromycin should be considered. HIV-infected patients starting antiretroviral therapy should be treated for *Bartonella* until the CD_4^+ cell count is >200/mm^3 for 6 months or longer.[303]

Treatment of *Bartonella* Bacteremia and Endocarditis

In World War I trench fever (*B. quintana* bacteremia without endocarditis) appeared to spontaneously resolve without antibiotic treatment, although many soldiers experienced one or more relapses before ultimate resolution.[7,8] Treatment of modern-day trench fever was studied in an open, randomized trial enrolling homeless patients in France.[106] One group received doxycycline for 4 weeks plus gentamicin for the first 2 weeks, and the other group did not receive antimicrobial therapy. Clearance of *B. quintana* occurred in 7 out of 7 treated but only 2 of 9 untreated patients. One patient in the treatment group developed increased creatinine.[106] The current recommendation for treating isolated *Bartonella* bacteremia in immunocompetent individuals (after endocarditis has been ruled out) is with 4 weeks of doxycycline plus gentamicin in the first 2 weeks.[106,297]

For confirmed *Bartonella* endocarditis, parenteral therapy is indicated initially. Some published guidelines recommend IV gentamicin for the first 2 weeks, in combination with 6 weeks of doxycycline (100 mg PO or IV every 12 hours).[297,306] This recommendation is based largely on retrospective, observational data suggesting improved outcomes of patients with *Bartonella* endocarditis who received an aminoglycoside.[98] However, it is important to note that before *Bartonella* endocarditis is suspected and diagnosed, it usually has been present for many months or even a year, and thus renal failure is frequently present at presentation in patients with *Bartonella* endocarditis (or develops shortly thereafter), as the result of small vessel vasculitis and/or deposition of immune complexes in the kidneys. In one study 44% of patients with *B. quintana* and 50% of patients with *B. henselae* endocarditis had renal failure.[99] In addition, the number of reports of *Bartonella* endocarditis-associated vasculitis and glomerulonephritis has increased dramatically recently, prompting caution about the use of any nephrotoxic antibiotics for *Bartonella* endocarditis treatment.[114–117] Furthermore, in a recent meta-analysis the combination of gentamicin and doxycycline was not significantly more effective than other regimens.[307] There are reports of successful therapy for endocarditis with rifampin-containing regimens, most commonly paired with doxycycline for adults (doxycycline 100 mg PO or IV every 12 hours), or a macrolide for children.[101,115] Thus rifampin,

which has excellent intracellular penetration, can be added to doxycycline for 6 weeks (adults: 300 mg PO or IV every 12 hours; pediatric: 10 mg/kg PO or IV every 12 hours, maximum dose 600 mg/day), and is the preferred substitute for gentamicin, which penetrates cells poorly.

Relapsing infection is the hallmark manifestation of *Bartonella*, and treatment of *Bartonella* endocarditis is often extended beyond 6 weeks of antibiotic therapy. Because anti-*Bartonella* antibody titers are often very high in patients with endocarditis, obtaining titers diluted to end point every 6 to 8 weeks to ensure a decrease may be useful for determining duration of therapy. For HIV-infected and other immunocompromised patients, ≥3 months of treatment is appropriate,[297] as well as in immunocompetent patients when fever or bacteremia is persistent or recurrent.[109] Valve surgery is required for *Bartonella* endocarditis in the majority of cases.[98]

Treatment of Cat-Scratch Disease

There have been anecdotal reports of the utility of various agents[308,309] in the treatment of CSD. However, in the immunocompetent host, only azithromycin has been demonstrated to accelerate the resolution of typical CSD lymphadenopathy in a placebo-controlled, double-blind study.[169] The value of antibiotic therapy for CSD in immunocompetent patients remains uncertain because of the usually benign outcome of most manifestations[308] and the risk of adverse drug reactions and potential for generation of antimicrobial resistance. If antimicrobial treatment is contemplated for treating extensive CSD lymphadenitis, oral azithromycin (adults: 500 mg on day 1 and then 250 mg PO once daily on days 2–5; pediatric: 10 mg/kg PO on day 1 [maximum dose 500 mg] and 5 mg/kg [maximum dose 250 mg] PO once daily on days 2–5) should be the agent of first choice.[297] Limited data in children with hepatosplenic CSD has shown favorable clinical outcomes with rifampin therapy.[175] Due to the risk of developing rifampin resistance with monotherapy, combining rifampin with azithromycin for 14 days is the preferred treatment if rifampin is used.

Treatment of Neuroretinitis, Encephalopathy, Osteomyelitis, and Parenchymal Cat-Scratch Disease

Although the utility of antibiotic therapy in altering the course of neurologic and ophthalmologic manifestations of CSD has not been studied rigorously, two-agent therapy for neuroretinitis appears to accelerate resolution in comparison with untreated historical control cases. The agents used in such cases have usually been erythromycin or doxycycline (with or without combined rifampin) or, alternatively, azithromycin or clarithromycin.[109,190] Currently, treatment with 4 to 6 weeks of oral doxycycline (adults: 100 mg PO or IV every 12 hours) or azithromycin (pediatric: 10 mg/kg PO on day 1 [maximum dose 500 mg] and then 5 mg/kg [maximum dose 250 mg] PO once daily thereafter) plus rifampin therapy (adults: 300 mg PO or IV every 12 hours; pediatric: 10 mg/kg PO or IV every 12 hours [maximum dose 600 mg/day]) is recommended for neuroretinitis.[297] Systemic corticosteroid therapy is often administered by ophthalmologists as an adjunct to antimicrobials; no definitive advantage or disadvantage to such an approach has been demonstrated. For other neurologic manifestations of CSD, the combination of doxycycline and rifampin also is recommended for HIV-infected patients[303] and immunocompetent individuals.[297] For immunocompetent patients with CSD and bony or parenchymal (liver, spleen) involvement, initial parenteral therapy for several weeks may be advantageous, and oral therapy is then often continued for 4 to 6 weeks total.

Prevention of *Bartonella* Infections

Prevention of *B. bacilliformis*, *B. henselae,* and *B. quintana* infections is probably best achieved by avoiding the locales or circumstances in which one is exposed to the arthropod vectors harboring *Bartonella*. Eradication of body louse infestation reduces the risk of *B. quintana* infection.[303] Prevention of *B. henselae* (and possibly *B. koehlerae)* infection entails avoidance of interactions with cats that might result in scratches, bites, or licks and exposure to cat fleas or flea feces.[303] Feral cats, cats that are allowed outdoors, cats with fleas, and kittens (<12 months of age) all have a higher risk of being infected with *B. henselae*.[310] The role of cat fleas in the direct transmission of *B. henselae* to humans is not known. However, treatment of pet cats for flea infestation is extremely important because flea feces carry large numbers of *B. henselae* organisms, and infected flea feces can readily contaminate the claws of cats, resulting in transmission of *B. henselae* to humans during a scratch. Human cat owners or contacts who are immunosuppressed should be especially careful to avoid cat scratches and to eliminate cat fleas from their cats and home. Antibiotic therapy does not durably eliminate bacteremia in cats implicated in CSD transmission or cats with demonstrated *B. henselae* bacteremia,[51,311–313] and thus treatment of pet cats with antibiotics is not recommended.[303] Direct contact with cat feces or urine does not appear to present a risk for *B. henselae* infection in humans. In general, removal of cats from the household of immunocompetent or immunocompromised humans is unnecessary as long as the flea control and contact precautions described earlier are maintained.[303]

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The complete reference list is available online at Expert Consult.

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235 *Klebsiella granulomatis* (Donovanosis, Granuloma Inguinale)

Bradley P. Stoner and Hilary E.L. Reno

SHORT VIEW SUMMARY

Definition
- Donovanosis is a chronic ulcerative sexually transmitted infection caused by the intracellular bacterium *Klebsiella granulomatis.*

Epidemiology
- Donovanosis is generally restricted to developing countries in tropical locations; it is rare in developed countries.

Microbiology
- *K. granulomatis* is a gram-negative encapsulated intracellular bacterium that demonstrates bipolar densities on staining.

Diagnosis
- The diagnosis is confirmed by visualizing Donovan bodies on microscopic examination of biopsy specimens or crush preparation smears prepared from active ulcerative lesions.

Therapy
- The treatment of choice is azithromycin, 1 g weekly (or 500 mg daily) for at least 3 weeks or until lesions have healed and complete epithelialization has occurred.

Donovanosis is a chronic, progressive ulcerative disease of the skin and subcutaneous tissues that is caused by the encapsulated, gram-negative bacterium *Klebsiella* (formerly *Calymmatobacterium*) *granulomatis.* The infection is also commonly referred to as granuloma inguinale, but because this term can easily be confused with lymphogranuloma venereum (caused by the invasive L-serovars of *Chlamydia trachomatis*), many experts now recommend *donovanosis* as the preferred term. McLeod[1] is credited with providing the first description of donovanosis based on his work in India in 1881; this was followed by the discovery of the causative organism by Donovan[2] in 1905. Donovanosis is uncommon in developed, nontropical settings, and cases are sporadically reported from Papua New Guinea, South Africa, India, Brazil, and Australia.[3]

BIOLOGY OF CAUSATIVE ORGANISM

K. granulomatis is an encapsulated intracellular pleomorphic gram-negative bacillus (dimensions approximately 1–2 µm long by 0.5–0.7 µm wide) that resides in cytoplasmic vacuoles of large mononuclear cells.[4] The bacteria are described as having bipolar densities when stained (Donovan bodies), which give the appearance of closed safety pins on microscopic examination. The bacteria multiply intracellularly and are subsequently released on rupture of mature intracytoplasmic vacuoles leading to infection of surrounding cells. Ultrastructurally the organisms are described as having a clearly defined capsule and the absence of flagella, along with small surface projections resembling pili or fimbriae and electron-dense granules (35–45 µm in diameter) in the cell periphery.[5] These granules had previously been thought to represent evidence of bacteriophage infection; however, this hypothesis remains controversial.[6]

In the 1940s investigators reported successful culture of the organism in chick embryo yolk sacs[7] and subsequently in egg yolk–based media and defined liquid media.[8] However, no pure isolates were stored for further study, hampering further characterization of the organism. In the 1990s renewed efforts to isolate the bacterium from clinical specimens were successful using human monocyte cultures[9] and Hep-2 cell monolayers.[10] In 1999 detailed molecular analyses of *Calymmatobacterium granulomatis* phylogeny ultimately resulted in its proposed reclassification as a *Klebsiella* species.[11,12]

GEOGRAPHIC DISTRIBUTION AND EPIDEMIOLOGY

Donovanosis is a relatively rare disease in developed countries. In the United States, it is estimated that less than 100 cases occur annually, although epidemiologic tracking is difficult because it is not a nationally reportable condition. Donovanosis is recognized as a cause of genital ulcer disease in parts of India, Papua New Guinea, the Caribbean, and South America (particularly Brazil) and has been identified in Zambia, Zimbabwe, South Africa, Southeast Asia, and among Aboriginals and Torres Strait Islanders in Australia.[3,13] The fact that these are all tropical locations raises the possibility of ecologic tropism, that is, preferential organismal survival and infectivity in tropical environments, although this has not been proved. The reported incidence has decreased significantly in recent years in Australia,[14] Papua New Guinea,[15] India,[16] South Africa,[17] India, and Jamaica,[18] owing to either greater recognition of donovanosis as a public health problem and the implementation of appropriate measures for prevention and control or general improvements in living standards and health service provision in endemic areas. Still, cases of donovanosis continue to be encountered in parts of the world remote from these endemic regions (e.g., metropolitan France[19]) as a result of immigration to developed countries or alternatively through increased global travel to predominantly tropical areas.[20] In most cases the disease is considered to be sexually acquired: infection rates of 52% have been reported among steady sex partners of individuals with donovanosis.[21] However, the possibility of nonsexual transmission remains a controversial hypothesis. In the 1960s Goldberg[22,23] postulated that the causative organism may be a gastrointestinal tract commensal and that the vagina may be infected through autoinoculation. Nonsexual transmission is further suggested by lesions in very young children and the occurrence of infection in extragenital sites (e.g., mastoiditis and meningitis).[24] However, the age distribution in endemic areas, the common co-occurrence of other sexually transmitted infections, and the high frequency of genital tract lesions support the assertion that donovanosis is predominantly transmitted through sexual contact.

CLINICAL MANIFESTATIONS

The primary lesion of donovanosis begins as a small indurated nodule or painless papule that develops at the site of exposure following an incubation period estimated to be between 3 and 40 days based on epidemiological observations.[25] The lesion soon ulcerates to form a painless, exuberant, beefy red, granulomatous ulcer with rolled edges that bleeds easily on contact (Fig. 235.1). Multiple smaller lesions may coalesce into large areas of ulceration, and new ulcers may appear via autoinoculation. The disease extends into subcutaneous tissues and may become progressively more destructive (Fig. 235.2). Spontaneous healing may result in scar formation and tissue deformities (Fig. 235.3). In severe cases, lymphatic blockage may occur resulting in lymphedema

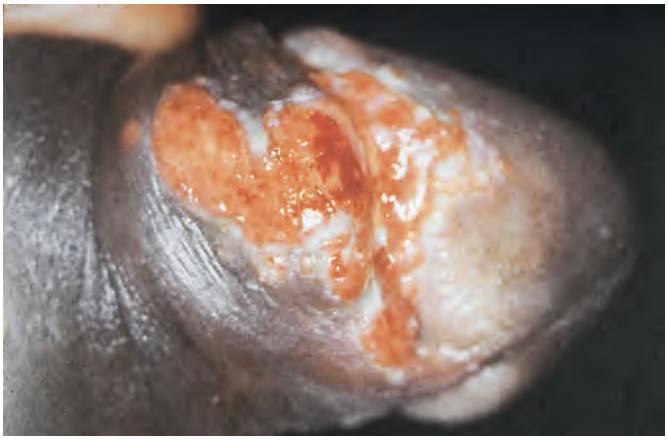

FIG. 235.1 Early lesion of donovanosis.

FIG. 235.2 Extensive active lesions of donovanosis.

FIG. 235.3 Late lesions of donovanosis showing extensive scarring and subcutaneous spread.

and external genital elephantiasis.[26] The prepuce, coronal sulcus, and penile shaft are commonly reported sites of infection in men. In women the labia and fourchette are commonly involved sites, and vaginal wall and cervical lesions may also occur. Subcutaneous inguinal spread may lead to pseudobubo formation without lymph node involvement. Hypertrophic lesions have been reported during pregnancy,[27] raising concern that pregnancy may exacerbate disease outcomes.[28] However, increases in diagnoses during pregnancy may simply reflect the detection of asymptomatic disease during routine prenatal pelvic examination. Rectal lesions may be associated with receptive anal intercourse,[29] and oral lesions have been reported in association with orogenital contact.[30]

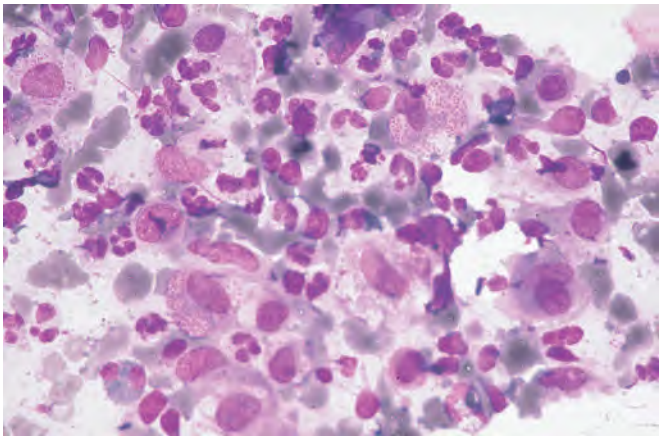

FIG. 235.4 Scraping from an active lesion of donovanosis showing typical Donovan bodies in large mononuclear cells (Giemsa stain, ×100).

Systemic disease is rare but appears to be more common in women with primary lesions of the cervix.[31] Hematogenous spread of infection is rare but has been documented, resulting in the formation of pelvic granulomas, bone and joint involvement, and lymphadenitis.[32] Constitutional symptoms are generally absent except in cases with coinfection with other sexually transmitted agents, secondary bacterial infection, or extensive spread. Donovanosis should be distinguished from other causes of genital ulcer disease, regional lymphadenopathy, and genital elephantiasis. The lesions most likely to resemble donovanosis clinically include cases of pseudogranulomatous chancroid, ulcerating genital warts, primary and secondary syphilis, and squamous cell carcinoma. Multiple infectious agents have been isolated from a single ulcerative lesion, raising the possibility of coinfection with other sexually transmitted pathogens.[17,33] Early reports suggested a link between donovanosis and squamous cell carcinoma of the external genitalia.[34] This hypothesis remains unproven; however, more recent case reports of donovanosis with malignant transformation again raise this concern.[35,36] The possible coexistence of donovanosis and oncogenic human papillomavirus may be one explanation for this phenomenon. There have been no confirmed cases of congenital donovanosis infection, but two cases have been described in infants younger than 6 months presenting with Donovan body–positive external auditory canal polyps, otitis media, and mastoiditis.[37] The infants in these two cases were born to mothers with human immunodeficiency virus infection with genital donovanosis lesions.

DIAGNOSIS

Clinical evaluation provides the basis for a presumptive diagnosis of donovanosis: classic-appearing, slow-growing, relatively painless, bright red hypertrophic lesions that bleed easily on contact.[4] Wherever possible, confirmation of the diagnosis should be obtained through histologic examination of clinical specimens from active lesions. These may include punch biopsy specimens or scrapings taken from the edges of active lesions or crush preparation smears of granulation tissue taken by scalpel or forceps after cleaning with physiologic saline.

Although biopsy specimens are mandatory to exclude malignancy, crush preparation smears are adequate in most cases for diagnosis of acute active disease.[38] Ideally the smear preparations should be made immediately with fresh moist tissue and should be fixed and stained with Giemsa, Leishman, or Wright stain before being examined microscopically.[4,39] Although the use of rapid Giemsa techniques may provide an immediate definitive diagnosis,[40] most experts prefer standard Giemsa or silver stains for histologic examination of fixed, embedded tissue specimens.[4] The demonstration of typical bipolar-staining intracellular Donovan bodies in stained smears obtained from lesions (Fig. 235.4) remains the gold standard for diagnosis of donovanosis. Donovan bodies may also been detected in Papanicolaou-stained smears obtained from women with cervical lesions.[41–43]