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Bartonella quintana and Urban Trench Fever
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Contemporary Bartonella quintana infections have emerged in diverse regions of the world, predominantly involving socially disadvantaged persons. Available data suggest that the human body louse Pediculus humanus is the vector for transmission of B. quintana. Descriptions of the clinical manifestations associated with contemporary B. quintana infections have varied considerably and include asymptomatic infection, a relapsing febrile illness, headache, leg pain, “culture-negative” endocarditis, and, in human immunodeficiency virus–infected persons, bacillary angiomatosis. Laboratory diagnosis is most convincing when B. quintana is isolated in blood culture, but growth often takes 20–40 days; problems exist with both sensitivity and specificity of serological assays. On the basis of available information, use of doxycycline, erythromycin, or azithromycin to treat B. quintana infections is recommended. Treatment of uncomplicated B. quintana bacteremia for 4–6 weeks and treatment of B. quintana endocarditis (in a person who does not undergo valve surgery) for 4–6 months are recommended, with the addition of a bactericidal agent (such as a third-generation cephalosporin or an aminoglycoside) during the initial 2–3 weeks of therapy for endocarditis.

Bartonella quintana (formerly Rochalimaea quintana and Rickettsia quintana) is a fastidious gram-negative bacterium that has probably caused endemic and epidemic human disease since ancient times but has only episodically received widespread attention from the medical profession in the modern era. The first clear descriptions of human disease caused by B. quintana appeared during World War I, when trench fever affected an estimated 1 million people on the western and eastern fronts of Europe [1]. Military physicians described the nonspecific and highly variable clinical manifestations of the infection and performed elaborate experiments that identified the human body louse Pediculus humanus variety corporis as the principal vector of infection. Although early attempts to culture the causative agent failed, stained preparations of body lice that had fed on infected humans showed a small “Rickettsia-like” gram-negative organism [1]. After World War I, sporadic reports of trench fever appeared from Europe, Asia, and North Africa, followed by focal outbreaks of disease during World War II [2]. In the 1960s, Vinson [3] became the first to passage the agent of trench fever in axenic culture, when he isolated B. quintana from a patient in Mexico City. He subsequently fulfilled Koch’s postulates for this organism by inoculating volunteers and observing them develop a clinical illness consistent with trench fever.

The past decade has witnessed a dramatic increase in our awareness and understanding of the spectrum of human disease caused by members of the genus Bartonella. This renewed interest stems from the observation that B. quintana, along with the recently discovered and closely related species Bartonella henselae, can cause clinical disease in persons with advanced HIV infection [4]. In this population, B. quintana can cause cutaneous bacillary angiomatosis, chronic lymphadenopathy, bacteremia, and endocarditis [4, 5]. More recently, several investigators have described cases of B. quintana bacteremia, with and without endocarditis, in homeless persons without HIV infection, most notably in Seattle [6] and Marseille, France [7]. In this review, we summarize current information related to B. quintana–associated infections in persons not infected with HIV, with an emphasis on contemporary urban trench fever.

Ecology and Epidemiology of Disease Caused by B. quintana

Although little data exist regarding the incidence of B. quintana infection among specific populations, it is clear that B. quintana causes geographically widespread disease. Since the first descriptions during World War I, trench fever has appeared in every continent, except Australia and Antarctica [2]. Most recently, an epidemic of trench fever erupted in a refugee camp...
in Burundi [8]. Wherever it has appeared, disease caused by B. quintana has signaled social disruption and human hardship.

In Europe and North America, infection with B. quintana is associated with poverty, alcoholism, and homelessness. In the series of 10 patients with B. quintana bacteremia in Seattle, bacteremic patients were significantly more likely to be homeless (8 of 10) and to have chronic alcoholism (10 of 10) than were control patients who had negative blood cultures [6]. All 3 patients with B. quintana endocarditis described by Drancourt et al. [7] in Marseille were homeless and abused alcohol. As a follow-up to these reports, Jackson et al. [9] and Brouqui et al. [10] employed seroprevalence and case-control studies to further define the epidemiology of B. quintana infections in Seattle and Marseille, respectively. Jackson et al. [9] found serological evidence of prior B. quintana infection in 20% of patients at a downtown Seattle clinic serving many homeless patients but only a 2% seroprevalence among blood donors from the Seattle area at large. Among clinic patients, seropositivity was significantly associated with alcoholism. In Marseille, Brouqui et al. [10] found serological evidence of B. quintana infection in 16% of hospitalized homeless individuals, 1.8% of nonhospitalized homeless persons, and 0% of blood donors at large. Among a cohort of injection-drug users in Baltimore, Comer et al. [11] found a 10% prevalence of antibodies to B. quintana. In all of these studies, serological cross-reactivity between B. quintana and B. henselae may have confounded the results.

More recently, Koehler et al. [12] analyzed the molecular epidemiology of bartonella infections in HIV-infected patients with bacillary angiomatosis in San Francisco. These investigators identified homelessness and low income as risk factors for B. quintana infection. It is interesting that although B. henselae infections occurred at a steady rate throughout the 8-year study period, those caused by B. quintana clustered in the spring of 1993, simultaneous with the outbreak in Seattle. In 1997, Brouqui et al. [13] prospectively studied homeless patients presenting to the emergency department at the University Hospital in Marseille for blood culture or serological evidence of B. quintana infection. Ten (14%) of 71 patients had positive blood cultures, and an additional 7 had evidence of recent infection, as documented by seroconversion. In contrast, no blood donor at large or nonhomeless patient evaluated at an emergency department had evidence of bartonella infection.

Several lines of evidence support the role of the body louse as the principal vector of B. quintana infection. During World War I, Byam [1] showed that body lice from infected patients can induce trench fever in exposed humans. Vinson et al. [14] later confirmed these findings by inoculating body lice with B. quintana from pure culture and then allowing these lice to feed on volunteers. More recently, several epidemiological studies have demonstrated an association between B. quintana infection and recent louse exposure in homeless persons, providing indirect support for the role of lice in transmitting B. quintana in this setting [10, 12, 13].

Moreover, Roux et al. [15] and Rydkina et al. [16] recently used PCR analysis to detect B. quintana in lice gathered from multiple areas, including Marseille, several sites in Africa, Peru, and Moscow. In the above-mentioned prospective study of B. quintana infection in homeless patients presenting to the emergency department at the University Hospital in Marseille, Brouqui et al. [13] also gathered body lice for PCR analysis. PCR analysis revealed that body lice from 3 of 10 patients with positive blood cultures were positive for B. quintana, compared with 0 of 10 pools of lice gathered from patients with negative cultures. Although other ectoparasites, such as mites or fleas, might conceivably play a role in disease transmission, there is no direct evidence to support this possibility. Unlike for most other Bartonella species, there is currently no clear evidence to support the existence of an animal reservoir for B. quintana.

Multiple factors related to disease transmission and host susceptibility have likely contributed to the increased prevalence of B. quintana infection among urban homeless persons. Crowded and unsanitary living conditions promote close exposure to individuals potentially carrying B. quintana and predispose them to infestation with ectoparasites that may transmit the infection, in particular the body louse. After becoming infected, homeless individuals probably have an increased risk for progression of B. quintana infection to clinically significant disease. Host factors common in the homeless population, such as alcoholism and malnutrition, increase susceptibility to multiple infectious diseases and likely play a role [17–19].

Because homelessness and alcoholism are not new phenomena in our society, why was bacteremia due to B. quintana not detected in homeless persons before recent years? Increased diagnostic suspicion for bartonella infections and improved techniques for isolation in culture may have contributed to an increased detection of B. quintana infection. Increased microbiological vigilance, however, cannot entirely explain the emergence of trench fever in homeless persons. Although the blood culture techniques used to detect B. quintana bacteremia in Seattle were routinely in place several years before and after the outbreak in the spring of 1993, all 10 cases clustered within a 6-month period [6]. Since that time, only 4 additional patients have presented to Harborview Medical Center in Seattle with documented B. quintana bacteremia. Also of note, the seroprevalence of B. quintana among homeless persons in Marseille increased from 16% in 1994 to 30% in 1997, which suggests that there was an outbreak in the interim [13]; these investigators from France speculate that migration to Marseille from Eastern Europe or Russia, where trench fever is endemic, may explain the increase. Conceivably, increasing worldwide migration may lead to importation of trench fever from areas of endemicity to susceptible populations in other urban centers.

In theory, emergence of novel strains of B. quintana through horizontal acquisition of new virulence genes could explain the recent reappearance of trench fever. The unavailability of reliable B. quintana isolates from earlier outbreaks and the current
absence of defined virulence loci in Bartonella make it difficult to evaluate this possibility.

Clinical Manifestations in Immunocompetent Hosts

Descriptions of the clinical manifestations of B. quintana infection in the immunocompetent host have varied tremendously. During World War I, clinical experience suggested an incubation period for B. quintana that ranged from 3 to 38 days, whereas experiments that involved inoculating humans with B. quintana-infected blood or louse feces found a more narrow incubation period (range, 5–20 days) [1]. Military physicians noted either an abrupt or an insidious onset of symptoms and described 4 distinct patterns of illness: a single febrile episode, a short febrile period lasting roughly 5 days, a relapsing febrile illness occurring at 5-day intervals with asymptomatic intervening periods (so-called quintan fever), and a debilitating and persistent typhoidal illness, often lasting many months [1]. For soldiers with this last pattern of illness, xenodiagnosis with use of body lice that were initially free of infection allowed confirmation of chronic bacteremia [1]. Abrupt onset appeared to correlate with rapid resolution and an insidious onset with prolonged illness. Other frequent features of trench fever included a transient maculopapular rash, conjunctivitis, severe headache, myalgias, and, in chronic cases, splenomegaly. Pain was often most severe in the lower legs, causing soldiers to label the illness “shin bone fever.” Progression to death was extremely rare [1].

The recent descriptions of B. quintana bacteremia in urban homeless persons also reveal heterogeneous patterns of illness. In the cluster of 10 homeless patients with bacteremia in Seattle, 7 had fever at the time of initial evaluation, 3 reported weight loss, and 2 had endocarditis [6]. Distinct features of “classic” trench fever were absent. In contrast, Stein and Raoult [20] described a homeless man in Marseille who had a classic presentation of trench fever, manifested as an acute relapsing febrile illness with prominent bone pain in the legs. In the report of 3 homeless patients with B. quintana bacteremia from Marseille in that same year, all 3 patients had classic features of subacute bacterial endocarditis, including fever, weight loss, typical skin lesions, cardiac murmur, and valvular vegetations on echocardiograms [7]. Combining the Seattle and Marseille reports, all 5 patients with endocarditis had severe and progressive valvular damage, and all required valve replacement for cure [6, 7]. In a subsequent multicenter international study, Raoult et al. [21] reported 22 cases of endocarditis caused by Bartonella, 5 of which were confirmed to be due to B. quintana. Thirteen (59%) of the 22 patients with Bartonella endocarditis had pre-existing valvular disease, and 19 (86%) of 22 required valve replacement for cure. It is interesting that a disproportionate number of cases of Bartonella endocarditis have involved the aortic valve [7, 21, 22].

In the prospective study of homeless patients presenting to the emergency department at the University Hospital in Marseille that was reported by Brouqui et al. [13], patients with B. quintana bacteremia were more likely to have headache, leg pain, and thrombocytopenia than were those homeless patients who did not have bartonella infection. Otherwise, there was little to distinguish these groups. In contrast with the Seattle report [6], only 2 of 10 of these French patients with bacteremia were febrile. In agreement with older reports [7, 20], 5 of 10 patients maintained chronic bacteremia for weeks, although no patient developed endocarditis during the study. These findings suggest that although B. quintana clearly may cause acute and severe illness in homeless persons, it often produces a chronic and nonspecific illness that does not arouse clinical suspicion for bartonella infection. Moreover, the observation that the seroprevalence of B. quintana infection among urban homeless persons far exceeds the number of reported cases [9–11] suggests that infection may often be subclinical or cause nonspecific findings that mimic other diseases.

The origins of the highly variable clinical manifestations of B. quintana infections remain unclear. In experiments that involved inoculating humans, Vinson et al. [14] observed that a single clonal strain of B. quintana from culture produced widely variable clinical manifestations in different people, which suggested a role for host factors in determining the outcome of infection. Furthermore, use of restriction fragment length polymorphism techniques during the Seattle outbreak indicated that B. quintana isolates from all 10 patients were identical, but clinical manifestations varied considerably in the patients [6]. Unfortunately, very little is known regarding the mechanisms of protective immunity to bartonella infections, making it difficult to speculate on specific host factors that could alter clinical manifestations.

In addition, genetic variability in B. quintana itself may account for some of the contrasting clinical descriptions of trench fever from different periods and different geographic locations. It is noteworthy that endocarditis was rarely, if ever, described during the massive outbreak of trench fever during World War I [1] but has been found in a significant percentage of recent infections described in homeless persons [7, 21, 22]. One may speculate that multiple strains of B. quintana exist, each with unique virulence characteristics and the propensity to cause specific clinical syndromes. The small number of described cases and lack of a generally accepted method for strain typing make it difficult to test this hypothesis. Ultimately, detailed dissection of the relative roles of host and pathogen in determining the specific outcome of infection awaits the development of an animal model of disease and discovery of virulence genes in Bartonella.

Diagnosis

The diagnosis of B. quintana infection merits consideration in individuals from at-risk populations, such as urban homeless persons who develop an acute or chronic nonlocalizing illness that does not have a defined cause. Specific syndromes that
may suggest B. quintana infection include a relapsing febrile illness, “culture-negative” endocarditis, or lesions compatible with bacillary angiomatosis in an immunocompromised host. Confirming B. quintana infection requires specific culture, serological, or nucleic acid amplification techniques.

Although isolating B. quintana from blood is possible with use of standard BACTEC culture bottles (Becton Dickinson Diagnostic, Sparks, MD), growth is slow, often requiring 20–40 days, and carbon dioxide production is usually inadequate to trigger the automated growth sensor [23]. Recovery is enhanced in lysis centrifugation blood culture systems or by subculture of blood culture bottles onto fresh chocolate agar, followed by extended incubation under 5% carbon dioxide at 37°C. In some instances, acricline orange staining of BACTEC blood culture bottles after 8 days of incubation may enable earlier detection of growth, identifying appropriate samples for subculture [24]. Other studies have employed coculture with bovine endothelial cell lines [12]. Several methods can differentiate Bartonella species isolated in culture, including immunofluorescence assays that use species-specific mouse antisera [25]. DNA hybridization or restriction fragment length polymorphism analysis, and sequencing of the 16S rRNA or citrate synthase genes [26].

In the 1970s, Hollingdale et al. [27] reported the use of serological assays, including EIA and counterimmunoelectrophoresis, in the diagnosis of trench fever [27]. All patients in this series had elevated antibody titers, ranging from 1:20 to 1:640. Currently, several serological assays are available, including indirect immunofluorescence assay and ELISA-based techniques. To our knowledge, no previously reported large studies have evaluated the sensitivity or specificity of these assays, and significant serological cross-reactivity between B. quintana and B. henselae is known to exist [9]. In addition, infection with Coxiella burnetii may create false-positive results of serology for B. quintana [28], and B. quintana infection may induce cross-reactive antibodies in serological assays for Chlamydia [21]. Indeed, some cases of “culture-negative” endocarditis previously ascribed to Chlamydia species through serological assays were likely caused by Bartonella [21]. Overall, it appears that most immunocompetent patients with trench fever will have a positive serology, with endocarditis caused by B. quintana associated with particularly high titers. Specifically, in a series of 9800 serum samples prospectively tested for antibodies to Bartonella, 22 (85%) of 26 patients with titers $\geq$1:1600 had endocarditis [21].

Although nucleic acid amplification techniques have proved useful for diagnosing cat-scratch disease and bacillary angiomatosis (where biopsy material is often available for analysis), their use in the diagnosis of trench fever has been limited. Nevertheless, when suitable clinical material exists, such as valvular vegetations in cases of endocarditis requiring valve replacement, PCR amplification of the 16S rRNA or citrate synthase genes may confirm B. quintana infection [7].

**Therapy.** Unfortunately, sparse data exist to guide therapy for B. quintana infection, and the small number of sporadic cases makes clinical trials unlikely to occur in the near future. Furthermore, although 2 studies have reported in vitro measurements of antibiotic susceptibility in B. quintana, some indirect data suggest that results of in vitro susceptibility testing may not correlate with clinical efficacy [29, 30]. Therefore, we have based our therapeutic recommendations on reports of noncontrolled studies and information extrapolated from experience with HIV-infected patients with bacillary angiomatosis. In the Seattle outbreak of B. quintana bacteremia, most patients received treatment with a third-generation cephalosporin followed by a macrolide, with generally good results [6]. In a retrospective case-control study of bacillary angiomatosis in HIV-infected patients, prior treatment with trimethoprim-sulfamethoxazole, ciprofloxacin, penicillins, and first- or second-generation cephalosporins did not protect against infection with Bartonella [12]. In contrast, no patients previously treated with a macrolide or doxycycline developed bartonella infection. Clearly, care must be taken in extrapolating these findings for immunocompromised hosts to cases of trench fever in the immunocompetent patient.

On the basis of the limited available data, we recommend treatment of uncomplicated B. quintana bacteremia with a 4- to 6-week course of doxycycline (100 mg orally b.i.d.), erythromycin (500 mg orally q.i.d.), or azithromycin (500 mg orally q.d.). Patients with endocarditis should receive 4–6 months of therapy, with close monitoring for indications for valve replacement. Some authorities would recommend addition of a bactericidal agent, such as a third-generation cephalosporin or an aminoglycoside, in the initial 2–3 weeks of therapy for endocarditis.

**Conclusions and Future Direction**

In summary, contemporary B. quintana infections have emerged in multiple regions of the world and have predominantly involved socially disadvantaged persons, particularly homeless persons and chronic alcohol users. Available data suggest that the human body louse P. humanus serves as the vector for transmission of B. quintana. Reservoirs for B. quintana (other than humans) have not been identified. Descriptions of the clinical manifestations associated with contemporary B. quintana infections have varied considerably and include a relapsing febrile illness, headache, leg pain, thrombocytopenia, “culture-negative” endocarditis, and, in HIV-infected persons, bacillary angiomatosis. Results from several studies of the seroprevalence of B. quintana suggest that infection may occur as a subclinical illness or cause nonspecific findings that mimic other diseases. The cause of the highly variable clinical manifestations of B. quintana infections remains unknown but could involve specific host-related factors in humans, genetic variability of different strains of B. quintana, or both.

Laboratory diagnosis of B. quintana infections is most convincing when the organism is isolated in blood culture, but growth is slow, often requiring 20–40 days. Although serological studies can provide supportive evidence of a diagnosis, problems exist...
with both sensitivity and specificity of available assays. Recommendations for the treatment of B. quintana infection are hampered by lack of clinical studies and poor correlation of in vitro data with clinical responses. Nevertheless, on the basis of available information, we recommend using doxycycline, erythromycin, or azithromycin to treat B. quintana infections. We recommend treatment of uncomplicated B. quintana bacteremia for 4–6 weeks and treatment of B. quintana endocarditis (in a person who does not undergo valve surgery) for 4–6 months. For patients with endocarditis, it would be reasonable to add a bactericidal agent, such as a third-generation cephalosporin or an aminoglycoside, during the initial 2–3 weeks of therapy.

Despite advances in our understanding of contemporary trench fever, many questions remain unanswered. For example, what is the prevalence of B. quintana infection in urban areas outside of Seattle, Marseilles, and Baltimore? What environmental or social factors predispose homeless populations to epidemic outbreaks of B. quintana infection? Do animal reservoirs or vectors other than the body louse exist? What virulence mechanisms allow B. quintana to evade the immune system and establish chronic bacteremia? Potential strategies that could provide further insight into these questions include the following: establishing an urban hospital network that collects epidemiological and incidence data for those persons infected with B. quintana, attempting to isolate B. quintana from likely animal reservoirs, and developing an animal model to study host- and pathogen-specific factors related to the pathogenesis and natural history of B. quintana infection.

References