Current Knowledge of Bartonella Species

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Bartonella species are now considered emerging pathogens. Of the 11 currently recognized species, four have been implicated in human disease, although only two have been encountered in Europe. Bartonella quintana infections are now being diagnosed among the urban homeless and deprived, manifesting as trench fever, and Bartonella henselae has been shown to be the causative agent of cat scratch disease. Both species also cause a variety of HIV-associated infections, including bacillary angiomatosis. However, perhaps the most significant presentation of bartonellae infection is culture-negative endocarditis. The epidemiologies of Bartonella infections are poorly understood; most Bartonella henselae infections are probably acquired from infected cats, either directly by contact with a cat or indirectly via fleas. No animal reservoir has been implicated for Bartonella quintana; however, infection can be transmitted via the human body louse. Diagnosis of Bartonella infections can be made using histological or microbiological methods. The demonstration of specific antibodies may be useful in some instances, although certainly not in all. Cultivation of Bartonella is difficult, as the bacteria are extremely fastidious. Polymerase chain reaction-based or immunological methods for the detection of bartonellae in infected tissues have proven useful. Clinical relapse is often associated with Bartonella infections despite a wide range of prescribed regimens. Only aminoglycosides display in vitro bactericidal activity against intracellular Bartonella species; therefore, they are recommended for treatment of Bartonella infections.

Human infections due to Bartonella species are widely considered emerging diseases. They include long-recognized diseases such as Carrion's disease (classic bartonellosis), trench fever, and cat-scratch disease and newer clinical manifestations such as bacillary angiomatosis, peliosis hepatitis, septicemia, endocarditis, chronic lymphadenopathy, and neurologic disorders. New molecular biology techniques, mainly based on 16S rRNA gene amplification and analysis, have allowed recognition of the role of Bartonella (formerly Rochalimaea) species in a number of these pathological conditions. The association of Bartonella henselae infection with bacillary angiomatosis is an example.

The availability of specific techniques to diagnose Bartonella infections has led to the description of new Bartonella species and recognition of a broadened disease spectrum due to these microorganisms. The most striking pathological feature of Bartonella infection is the apparent ability of these bacteria to produce angioproliferative lesions in immunocompromised patients, such as those infected with HIV. Capillary and endothelial cell proliferations are characteristic histologic findings of bacillary angiomatosis, peliosis hepatitis, and classic bartonellosis. Bartonellae are the only known bacteria with the ability to produce angiogenic tumors in humans, although Agrobacterium species, which belong to the same phylogenic group as Bartonella species, produce tumors in plants.

The present review focuses on the epidemiological and clinical aspects of infection due to the Bartonella species presently recognized as human pathogens: Bartonella bacilliformis, Bartonella quintana, Bartonella henselae, and Bartonella elizabethae.

**History of Bartonella**

Before recent taxonomic proposals, Bartonella bacilliformis was the only member of the genus...
Bartonella. This bacterium, first recognized in Peru in 1909 by Alberto Barton, infected the erythrocytes of patients with bartonellosis (or Carrión’s disease). Reports of this disease, which presents as one of two distinct manifestations, are limited to the Andean region of South America and predate Columbus. Bartonella quintana was recognized during World War I as the causative agent of trench fever, but culture of the organism was not reported until 1966 (1). Trench fever afflicted several thousand troops during the war (2, 3), but it is likely that trench fever-like syndromes were recognized much earlier (4). Bartonella vinsonii has been isolated only once, from a field vole on Grosse Island in the St. Lawrence Seaway, Canada, in 1943 (5); however, a recent report details the isolation of a subspecies of Bartonella vinsonii from an apparently healthy dog and from one with endocarditis (6).

The two former Grahamella species were also first described more than 50 years ago: Bartonella talpae was observed in the blood of moles captured near Cambridge, UK, in 1905, and Bartonella peromysci was isolated from a deer mouse in New England, USA, in 1942. However, unlike Bartonella vinsonii, the precise identity of these two species is unclear, as their original characterizations were vague and representative strains no longer exist. The remaining six Bartonella spp. have all been described within the last five years, although the medical syndromes now attributed to Bartonella henselae have been recognized for much longer.

The identification and characterization of Bartonella henselae as an organism of medical importance resulted from a protracted search that began with the recognition of cat scratch disease in France in 1950 (7) and was ultimately resolved following study into the etiology of an AIDS-related disease, bacillary angiomatosis, which was first observed in 1983 (8). Bacillary angiomatosis was initially characterized by multiple skin lesions that were considered infectious because histological examination of biopsy material revealed Warthin-Starry-staining bacilli. Furthermore, the lesions resolved with antibiotic treatment (9). However, it was not until 1990 that these bacteria were identified. Relman et al. (10) used polymerase chain reaction (PCR) to amplify bacterial 16S rRNA gene fragments directly from biopsy material taken from four patients with bacillary angiomatosis. The nucleotide base sequences of these amplification products were identical for all four patients; thus, all four were infected by the same organism. When this sequence was compared with those available for other bacteria, it was found to be very similar to, but distinct from, that of Bartonella quintana.

Concurrent with this work, peliosis hepatitis, a disease previously reported in patients suffering from wasting diseases or in association with the use of anabolic steroids, was first characterized in AIDS patients (11), at about the same time a previously uncharacterized bacterium was isolated from five HIV-infected patients with bacteremia (12). Subsequent collaboration demonstrated that the agents of all three syndromes were indistinguishable by comparison of partial 16S rRNA gene sequences (13). Isolation and subculture of the organism from the lesions of patients with bacillary angiomatosis were subsequently achieved (14), and following its characterization, the organism was confirmed as a new species and named Rochalimaea henselae (15).

Following the isolation and identification of Bartonella henselae, specific methods for detection of the bacterium were developed, which led to increased medical awareness of its potential pathogenicity. The species has subsequently been implicated in other clinical syndromes occurring among immunocompetent as well as immunocompromised patients, including cat-scratch disease. Interestingly, improved diagnosis of bacillary angiomatosis led to the implication of Bartonella quintana in several cases reviewed recently (16). The spectrum of modern illnesses associated with both organisms continues to increase.

Bartonella elizabethae has been isolated only once, from the blood of an immunocompetent patient suffering endocarditis (17). Three other newly described species, Bartonella grahamii, Bartonella taylorii, and Bartonella doshiae, were characterized following their isolation from the blood of small mammals in the UK in 1994 (18). The sixth new species, Bartonella clarridgeiae, was isolated from an American cat and was first described in 1996 (19).

Bacteriology

Following recent taxonomic proposals (18, 20), the genus Bartonella presently includes the 11 validated species as described above. A second serogroup (Marseille) has been identified among Bartonella henselae isolates (21), and a subspecies of Bartonella vinsonii, berkhoffii, has been described re-