CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, Jan. 2002, p. 8–18 Vol. 9, No. 1
1071-412X/02/$04.00+0 DOI: 10.1128/CDLI.9.1.8–18.2002

Natural History of *Bartonella* Infections (an Exception to Koch's Postulate)

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"I have, on many occasions, examined normal blood and normal tissues using methods that ensure that such organisms are not overlooked, and I have never, in a single instance, found bacteria. I therefore conclude that bacteria do not occur in the blood or tissues of healthy animals or humans" (R. Koch, 1878 [12]).

"In Coaquet (Peru) was the origin of an infectious disease which covered them with warts, made them suffer and exhausted them. These warts, like bubons all over the body could be of the size of an egg and finish by spliting. Blood and other substances then came out" (Pedro Pizarro, 1571 [authors' translation of the first description of bartonellosis]).

The genus *Bartonella* contains numerous recently described species, many of which are new and emerging human pathogens. Until 1990, only two diseases were recognized to be caused by *Bartonella* species: Carrión's disease, due to *Bartonella bacilliformis*, and trench fever, due to *B. quintana* (47). More recently, *B. quintana* has also been associated with endocarditis and bacteremia in homeless people (29, 91) and with bacillary angiomatosis (BA), which was first described in 1983 (51, 52, 82, 93) and which is an AIDS-related disease. Another important cause of BA, however, is *B. henselae* (81). This organism is closely related to *B. quintana* and was first identified in 1990 by PCR amplification of the gene for bacterial 16S rRNA (82) and characterized as a new species in 1992 (77). *B. henselae* is now known to cause a number of other clinical syndromes in immunocompetent and immunocompromised patients. These include cat scratch disease (CSD), peliosis hepatis (74), relapsing bacteremia with fever, and endocarditis (39, 42). Other *Bartonella* species have recently been implicated as human pathogens. *B. clarridgeiae* is possibly another agent of CSD (56), *B. elizabethae* (24, 75) and *B. vinsonii* subsp. *berkhoffii* may cause endocarditis (85), *B. vinsonii* subsp. *arupensis* has been found in a patient with fever and a valvulopathy (97), and *B. grahamii* may cause uveitis (49).

People usually become infected with *Bartonella* species incidentally, as the organisms are normally found in the reservoir hosts of *Bartonella* species, which include animals such as cats and dogs that live in close contact with people. The *Bartonella* species are unique because of this specific association with mammalian reservoir hosts, in which they cause chronic bacteremia with no or few symptoms. This is contrary to the existing premise that cultures of blood from healthy individuals should be sterile. Cats can be infected and become bacteremic with *Bartonella* species such as *B. clarridgeiae* and *B. henselae*. Wild rats are the reservoirs of *B. grahamii*, *B. taylorii*, and *B. doshiae* and of the newly described species *B. tribocorum* (41), while dogs can be infected with *B. vinsonii* subsp. *berkhoffii* (9). Recently, *B. alsatica* has been isolated from healthy rabbits trapped in France (40) and *B. weissii* has been isolated from cattle and cats (10, 17). Arthropod vectors, including ticks, fleas, and lice, have been proposed for almost all the *Bartonella* species; and transmission of the organisms to people may also occur by scratches or bites from reservoir hosts, in particular, cats.

In this minireview we describe the presently recognized *Bartonella* species, their reservoirs and vectors, and the diseases that they cause. We also speculate on the possible natural history of the diseases caused by the *Bartonella* species.

BACTERIOLOGY

Members of the genus *Bartonella* are short, pleomorphic, gram-negative rods that are fastidious aerobic and oxidase-negative organisms within the α_2 subgroup of the class *Proteobacteria*. They have a close evolutionary homology with members of the genera *Brucella*, *Agrobacterium*, and *Rhizobium.* The *Bartonella* species grow on axenic medium at 37°C with 5% carbon dioxide but can also be grown in broth with fetal bovine serum and in tissue culture (60). Growth in axenic medium is hemin dependent (97), and agar should be enriched with rabbit and horse blood, which gives better growth than sheep blood. All *Bartonella* species grow slowly on blood agar, with primary isolates typically appearing after 12 to 14 days but sometimes requiring 45 days to be visible (70). In subcultures, colonies usually appear after only 3 to 5 days. *B. bacilliformis* grows best in vitro at 28°C, has polar peritrichous flagella, and is highly motile. *B. clarridgeiae* is also flagellated. The susceptibilities of *Bartonella* species to antibiotics has been evaluated (67, 68, 90); and the bacteria have been found to be very susceptible to beta-lactams (except oxacillin and cephalothin), aminoglycosides, macrolides (but not clindamycin), tetracyclines, and rifampin. There was considerable variability in the susceptibilities of isolates to the fluoroquinolones. Only the aminoglycosides (gentamicin, tobramycin, and amikacin) were found to be bactericidal.

The genus *Bartonella* contains 16 species, most of which have been reclassified from the genus *Rochalimeae* (*B. quintana*, *B. henselae*, *B. elizabethae*, and *B. vinsonii*) (11) and from the genus *Grahamella* (*B. talpae*, *B. peromysci*, *B. grahamii*, *B. taylorii*, and *B. doshiae*) (6) (Fig. 1). *B. bacilliformis* was first reported in 1909, and before recent taxonomic changes, it was

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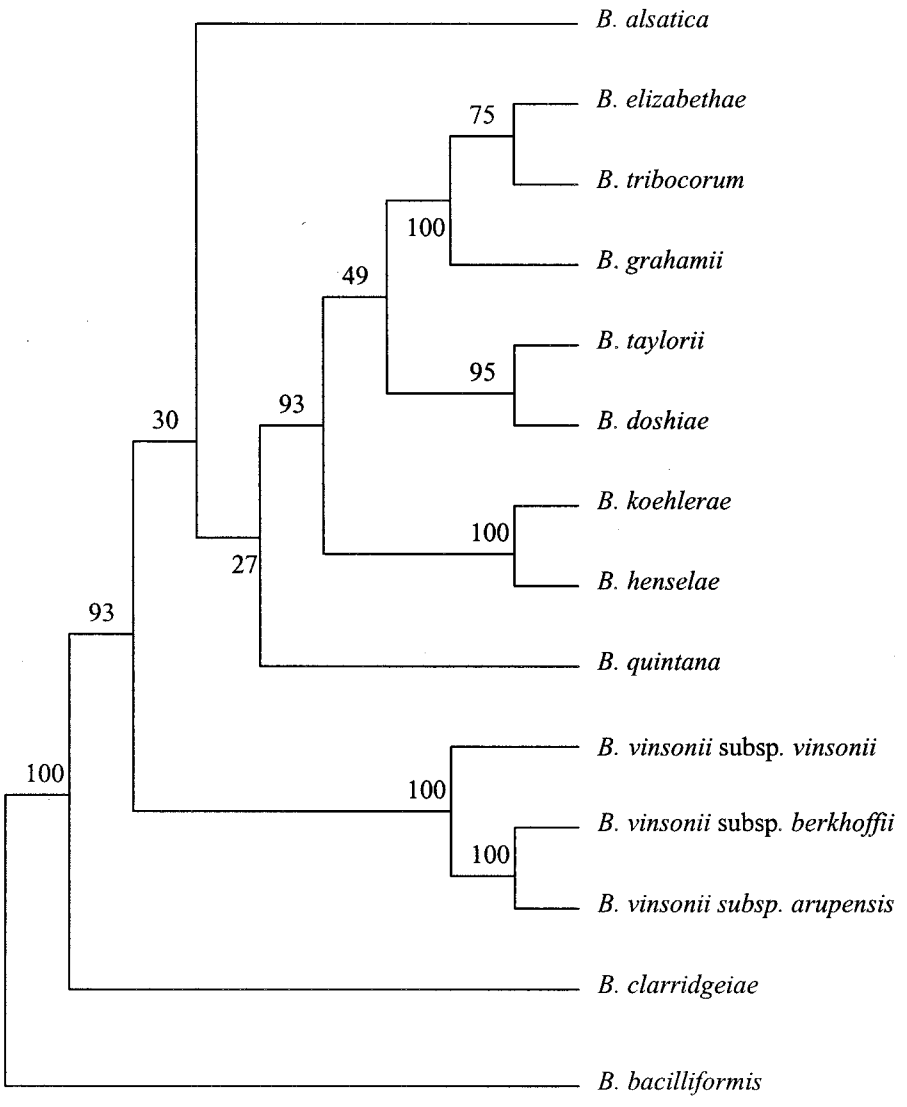

FIG. 1. Parsimony tree for *Bartonella* species derived from internal transcribed spacer sequences. The support of each branch, as indicated by 100 bootstrap samples, is indicated by the value at the node (adapted from reference 43).

the only member of the genus (Table 1). The *Bartonella* species are all closely related, having over 98% homology in the sequences of their 16S rRNA genes.

NATURAL HISTORY OF *BARTONELLA* INFECTIONS

As for many vector-borne disease agents, it seems that the *Bartonella* species also have a natural cycle. The cycle contains a reservoir host in which the *Bartonella* species cause a chronic intraerythrocytic bacteremia and a vector that transmits the bacteria from the reservoir hosts to new susceptible hosts. These could be the natural reservoir hosts, new competent reservoir hosts, or incidental hosts. There is usually a specific association between the natural host, the vector, and the *Bartonella* species which determines the spectrum of hosts (natural or incidental) possible and the geographic distribution of the organisms.

Natural infection in the host. Natural *Bartonella* infections begin with the inoculation of the bacteria, and this is usually associated with the feeding of the arthropod vector. Differences in the clinical presentations of individuals with primary infections may be due to several factors. The size of the inoculum may vary, and this could explain the differences in the severities of the clinical signs that might occur. Variations in strain virulence may also, however, contribute to differences in the intensity of illness (72). Host responses, modulated by immune responses to *Bartonella* infections, can vary and can induce variations in the intensities of clinical signs during initial infections.

With all other known bacteria, prolonged bacteremia is associated with signs of septicemia in the host. *Bartonella* bacteremias in the natural hosts, however, can be asymptomatic. This is contrary to our present understanding of bacteremia and goes against the idea originated by Koch that bacteria do

TABLE 1. Epidemiology of *Bartonella* species

Bartonella sp.	Yr of discovery (reference)	Yr of first cultivation (reference)	Reservoir (reference)	Vector (reference)	Current geographic distribution (reference)
B. bacilliformis	1909 (63)	1919 (63)	Humans (27, 63)	Phlebotomines (*L. verrucarum*) (2)	Peru (63), Ecuador and Columbia (2), Bolivia and Chile (33), and Guatemala (33)
B. quintana	1914 (59)	1961 (69)	Humans (69)	Human body lice (*Pediculus humanis corporis*) (69)	Worldwide (86)
B. talpae	1905 (6)		Moles		United Kingdom (6)
B. peromysci	1942 (6)		Mice (*Peromyscus* spp.) (6)		United States (6)
B. henselae	1950 (25)	1990 (89)	Cats	Fleas (*Ctenocephalides felis*)	Worldwide
B. clarridgeiae	1995 (22)	1995 (56)	Cats	Fleas (*Ctenocephalides felis*)	Cosmopolite (7, 38)
B. koehlerae	1999 (30)	1999 (30)	Cats (supposed reservoir) (30)	Fleas (supposed vectors) (30)	California (30)
B. vinsonii subsp. *vinsonii*	1946 (3)	1996 (3)	Voles (*Microtus pennsylvanicus*) (3)		Canada (38)
B. vinsonii subsp. *berkhoffii*	1995 (9)	1995 (9)	Dogs (9, 57)	Fleas and ticks	Cosmopolite
B. vinsonii subsp. *arupensis*	1999 (96)	1999 (96)	Cattle (96)		
B. elizabethae	1986 (24)	1993 (24)	Rats (5)	Fleas	
B. grahamii	1995 (6)	1995 (6)	Rats (*Clethrionomys glareolus*) (6)		United Kingdom (6)
B. taylori	1995 (6)	1995 (6)	Rats (*Apodemus* spp.) (6)		United Kingdom (6)
B. doshiae	1995 (6)	1995 (6)	Rats (*Microtus agrestis*) (6)		United Kingdom (6)
B. tribocorum	1998 (41)	1998 (41)	Rats (*Rattus rattus*) (41)		
B. alsatica	1999 (40)	1999 (40)	Rabbits (40)	Fleas or ticks (40)	France (40)
B. weissii	1999 (17)	1999 (17)	Deer, elk, beef, cattle (17)		United States, France (17)
B. birtlesii	2000 (4)	2000 (4)	Rats (*Apodemus* spp.) (4)		France (4)

not occur in the blood of healthy animals or humans (12). *Bartonella* may be the single bacterial genus capable of producing asymptomatic bacteremia in mammals and, thus, may be an exception to Koch's postulate. Using confocal microscopy, we have shown that *B. henselae* occurs within naturally infected asymptomatic cat erythrocytes (Fig. 2) (83) and that *B. quintana* occurs in human erythrocytes (unpublished data). As the *Bartonella* species are intraerythrocytic and, hence, might be less exposed to the immune system, their hosts may become adapted to the chronic bacteremia.

Recently, the kinetics of the colonization of *B. triborum* in rat erythrocytes has been reported (87). The organism multiplies until there are an average of eight *Bartonella* species per cell and thereafter remains in the cell for the life of the erythrocyte. It was suggested that this nonhemolytic intracellular colonization of erythrocytes is a bacterial persistence strategy that preserves the *Bartonella* species for potential transmission by arthropods. The host, then, could contaminate blood-feeding arthropods such as ticks, fleas (50), sand flies, or lice (14, 76), which could then subsequently infect a new host. The role of antibodies in the control of the multiplication of bacteria living in erythrocytes has been demonstrated in mice experimentally infected with *B. grahamii* (53), but in humans high antibody titers are associated with bacteremia (D. Raoult, unpublished data). Only *B. bacilliformis* has been reported to cause hemolysis (62).

Transmission between natural hosts. Evidence has accumulated that *Bartonella* species may be inoculated by arthropod vectors, through the bites and scratches of reservoir hosts, and perhaps, by needles and syringes in drug addicts (23). Arthropod vectors have been widely studied; and fleas have been shown to be infected with *B. henselae* (50), body lice have been shown to be infected with *B. quintana* (14), and ticks (61) have been shown to be infected with *B. henselae*, *B. quintana*, *B. washoensis*, and *B. vinsonii* subsp. *berkhoffii* (18).

Incidental infections caused by animal species. People are the incidental hosts of numerous *Bartonella* species. Infections can present in two clinical forms, depending on the immune status of the host. When the incidental host is immunocompetent, the infection is usually controlled locally by the immune system. The clinical manifestations of *Bartonella* infections are then local or regional. CSD results from *B. henselae* infection, and in immunocompetent people and immunocompetent mice, the disease usually presents as regional lymphadenopathy. Occasionally, visceral organ involvement has been described (31), but bacteremia has been reported only very rarely in immunocompetent hosts (89). *B. henselae* infections in immunocompromised hosts, however, result in bacteremia and other systemic conditions including BA and bacillary peliosis. *Bartonella* bacteremias in incidental hosts are manifested as systemic signs, and in people with existing heart valve abnormalities, the bacteremias may result in endocarditis, as reported with many other bacteria (15). Endocarditis due to *B. henselae* (75), *B. elizabethae* (24), *B. vinsonii* subsp. *berkhoffii* (85), and *B. vinsonii* subsp. *arupensis* (96) has been reported in patients with existing valve lesions.

Mammalian host specificity There is apparently a species-specific association between *Bartonella* species and their animal hosts or vectors (32, 44, 58). All *Bartonella* species appear to be associated mainly with a mammalian host. After the primary infection, which might or might not be symptomatic, an asymptomatic chronic bacteremia occurs in the natural mammalian host. The host is then a competent reservoir from which an arthropod vector can become infected and *Bartonella*

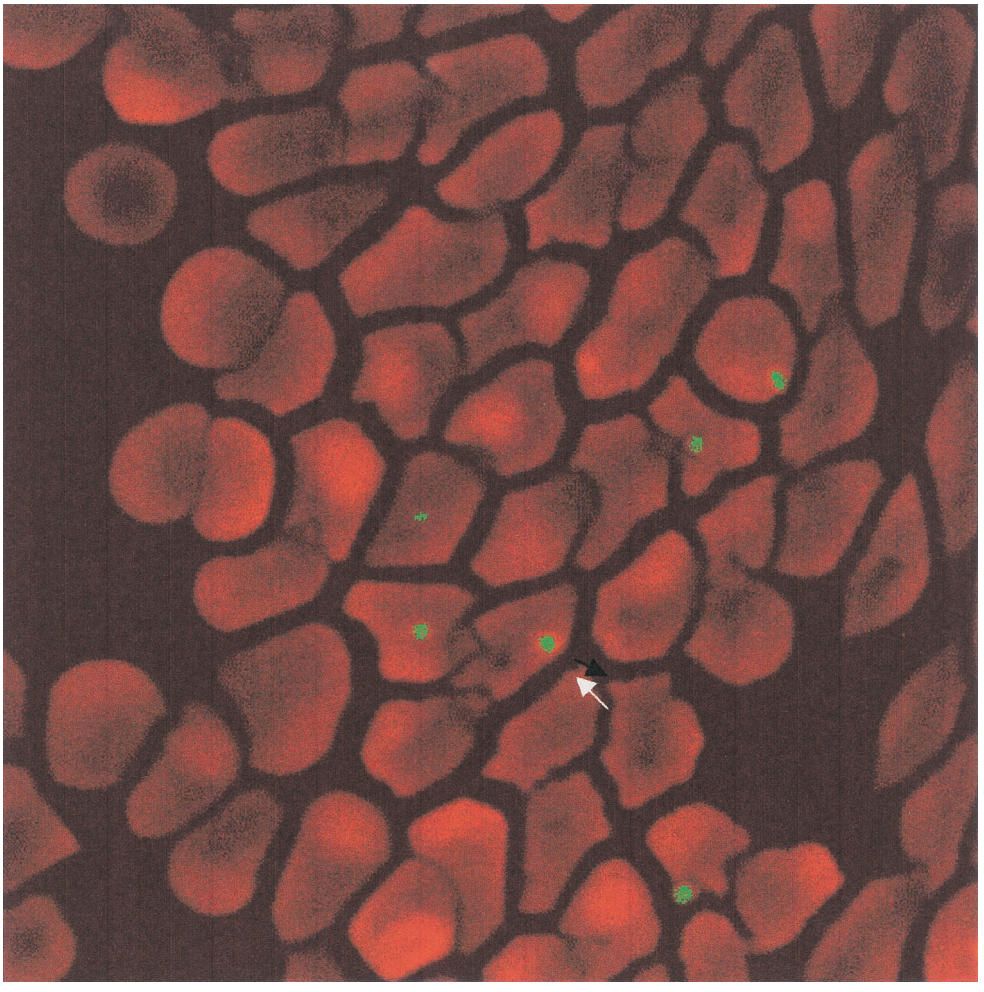

FIG. 2. Presence of *B. henselae* (arrow)within naturally infected cat erythrocytes, as seen by confocal microscopy.

species can be transmitted to other susceptible hosts. Analysis of the sequences of the 16S rRNA, *gltA*, and *groEL* genes of the *Bartonella* species shows that they are clustered into phylogenetically related groups (Fig. 1) (44). Each of the *Bartonella* species in each cluster has a particular mammal as a reservoir host. One cluster contains *B. bacilliformis*, the second contains *B. quintana*, and the third contains *Bartonella* species isolated from rodents of the New World (e.g., United States and Peru); the *Bartonella* species isolated from felines are found in an additional two clusters. The close relationships between the *Bartonella* species with the same mammalian reservoir support the hypothesis of a species-specific association (44). The geographic distributions of the different *Bartonella* species vary considerably, with *B. henselae* and *B. quintana* occurring worldwide and *B. clarridgeiae*, *B. elizabethae*, *B. weissii*, and *B. vinsonii* subsp. *berkhoffii* occurring in Europe and the United States. *B. vinsonii* subsp. *vinsonii* and *B. koehlerae* and have been found exclusively in the Americas, while *B. grahamii*, *B. taylorii*, B. *doshiae*, *B. tribocorum*, *B. birtlesii*, and *B. alsatica* have been found only in Europe. *B. bacilliformis* occurs only in a restricted area of South America (Peru, Colombia, and Ecuador). The geographic distributions of the *Bartonella* species may reflect the geographic distributions of their hosts or of their vectors. For example, in the case of *B. bacilliformis*, because of favorable climatic conditions, *Lutzomyia verrucarum*, the phlebotomine vector of the bacterium, occurs only in localized regions of South America (62). Continent-specific *Bartonella* species are mainly associated with rodents, and phylogenetic analyses show that there are marked genetic differences between *Bartonella* species associated with indigenous New World rodents and those associated with Old World rodents (6, 44, 65). The phylogenetic relationships between the *Bartonella* species isolated from *Rattus* species suggest that these rodents carried the organisms from the Old World to the New World during times of conquest, the intercontinental migration of populations, and commercial exchange. In rural areas, contact between *Rattus rattus* and rodents from the New World can occur. Where clusters of these rodents are found, the same species of *Bartonella* can be isolated from both New World and Old World rodents. Of course, the present classification could be contradicted in the future. The ubiquitous species *B. quintana* and *B. henselae* have hosts (people and cats, respectively) and vectors (body lice and cat fleas, respectively) with worldwide distributions.

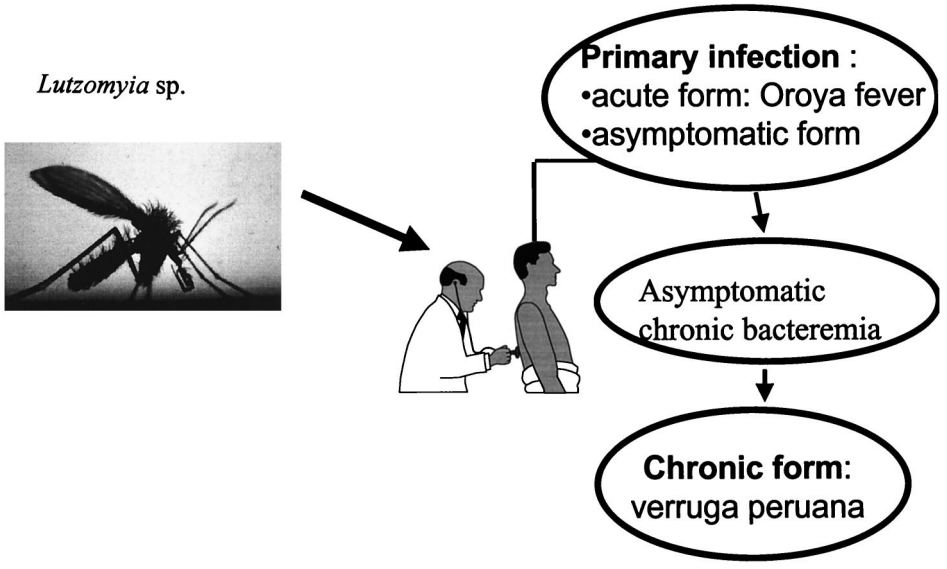

FIG. 3. Putative natural history of *B. bacilliformis* infection.

BARTONELLOSES IN PEOPLE

People are the hosts and reservoirs of *B. bacilliformis* and *B. quintana*; other mammals are the reservoirs for the other *Bartonella* species. There is usually a highly specific association between a *Bartonella* species and the mammalian species which is its reservoir. Sometimes, however, the organisms from animals may incidentally infect people, causing systemic diseases in those who are immunocompromised or who have preexisting heart valve abnormalities. In immunocompetent people, *Bartonella* species usually cause only localized disease.

Carrión's disease. Carrión's disease is caused by *B. bacilliformis*. Briefly, the epidemiological cycle of Carrión's disease begins when infected sand flies (*L. verrucarum*) transmit *B. bacilliformis* to susceptible people during feeding. The *Bartonella* organisms localize in the capillary endothelial cells, and this primary infection is asymptomatic in most cases (95). In some patients Oroya fever occurs when organisms enter erythrocytes and hemolysis occurs due to erythrophagocytosis by histiocytes and macrophages. In this acute stage of infection, the *Bartonella* species may be observed in erythrocytes. The level of erythrocyte parasitization can reach 100%, resulting in severe anemia and, occasionally, death. Death could also occur because of opportunistic infections (specifically, salmonellosis) following infection-induced immunosuppression. The fatality rate without treatment can be 40% (63). A chronic asymptomatic bacteremia which may last for up to 15 months (33) usually follows, and *B. bacilliformis* may be transmitted to sand flies that feed on patients during this time (Fig. 3). Seroepidemiological studies in areas of endemicity have shown that more than half the people infected with *B. bacilliformis* are asymptomatic. The majority of infected people are children or young adults (63). In the chronic stage of infection, people develop cutaneous eruptions, the verrugae of Carrión's disease. These individuals can, presumably, also serve as reservoirs for the bacteria. The disease has a very limited geographic distribution, with most cases having been reported in arid areas at 500 to 3,000 m above sea level in the Peruvian Andes between southwestern Colombia and central Peru. The disease has, however, also been reported to occur in Bolivia, Chile, and Guatemala and at high elevations in Colombia and Ecuador (33). Most of the suspected and confirmed cases of bartonellosis in Ecuador have been reported in an arid coastal province (63). The disease was apparently unknown in Colombia until an outbreak occurred in 1936, peaked between 1938 and 1940, and subsided after 1941 (2). Large epidemics of febrile anemia characterize the history of bartonellosis in Peru. For a long time it was reported that only people born in areas of endemicity developed the verruga peruana (Peruvian warts) of the chronic stage of the disease and that only foreigners developed the acute febrile form of the disease (63). A prospective study in the national hospital Cayetano Heredia in Peru, however, has shown that 58.8% of the 145 patients with Oroya fever were in fact born in areas of endemicity (63). People are still the only known reservoirs of *B. bacilliformis*, and they serve as sources of infection for sand flies, which are the vectors of the disease. The treatment of acute infection is based on tetracyclines and chloramphenicol. Interestingly, they are poorly effective in preventing or treating verruga peruana. This chronic stage is treated with streptomycin or rifampin (63).

***B. quintana* infections.** Trench fever or quintan fever is a recurrent fever caused by *B. quintana*, which is transmitted by human body lice. The lice cause pruritis and broken skin, through which *B. quintana*, present at high concentrations in the feces of infected lice, may enter the body. People are the only proven animal hosts for *B. quintana* and are probably the natural reservoirs of the organism. Although *B. quintana* is usually present in the blood of patients during the febrile stages of trench fever, infections may persist long after the disappearance of all clinical signs; this persistent bacteremia may facilitate the spread of the bacteria by lice. It has been shown that lice tend to migrate away from febrile hosts, and they may then spread the infection to people in close contact with the ill individual (59). The disease has an acute onset, with severe headache and pretibial pain. The acute signs usually

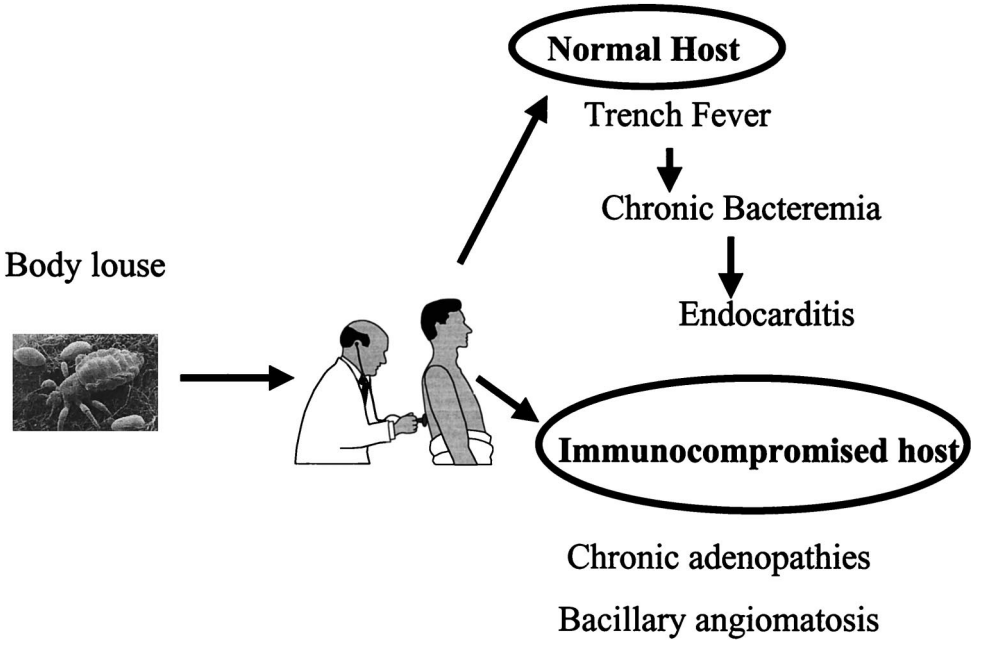

FIG. 4. Putative natural history of *B. quintana* infection.

resolve spontaneously, but in some patients they may recur after about 5 days. In some patients there may be six or more recurrences of the disease (59). In other patients relapses may occur many years after the initial illness or the patients may be bacteremic but have no clinical signs (14). The prolonged bacteremias that occur in patients with *B. quintana* infections may be associated with the development of endocarditis and bacillary angiomatosis (Fig. 4). Trench fever occurred in millions of troops in World War I, but with the introduction of louse control measures by armed forces, the disease was thought to no longer be a threat (69). Recently, however, the disease has reemerged, and an outbreak of bacteremia due to *B. quintana* (91) was reported in Seattle, Washington, in 1994. Infections were characterized by relapsing fever, and the major risk factors for acquiring these *B. quintana* infections included poor living conditions and chronic alcoholism. These are also the risk factors found in human immunodeficiency virus (HIV)-infected patients who develop BA (91) and endocarditis (75). Subsequent studies have shown that the seroprevalences of antibodies against *B. quintana* are high in homeless people in both the United States and Europe. In a 1997 study at the emergency departments of the university hospitals of Marseille, France (13), the blood of 14% of homeless people whose blood was sampled was found to be positive by culture, and half of these people had chronic bacteremia without fever (14). Serology showed that 30% had specific antibodies to *B. quintana*, and the DNA of the organism was detected in lice from three homeless patients (14). Trench fever responds favorably to tetracycline (69). However, chronic bacteremia is not controlled by doxycycline (D. Raoult, unpublished data).

Endocarditis. *B. quintana*, *B. henselae*, *B. elizabethae*, and two *B. vinsonii* subspecies, *B. vinsonii* subsp. *berkhoffii* and *B. vinsonii* subsp. *arupensis*, have been associated with endocarditis in patients with existing valvulopathies (34). In the largest series of *Bartonella* endocarditis cases reported, 13 of 22 patients had previously been diagnosed with a valvulopathy. *B. quintana* was the etiologic agent in five patients, and *B. henselae* was the etiologic agent in four patients. Patients with *Bartonella* endocarditis produce antibodies that react with *Chlamydia pneumoniae*, *Chlamydia psittaci*, and *Chlamydia trachomatis* (66). Cases of endocarditis caused by *B. vinsonii* subsp. *berkhoffii* (85) and *B. vinsonii* subsp. *arupensis* (96) have also been described, and in the latter study the organism was isolated from the blood of a rancher with preexisting cardiac valve disease. All together, these data suggest that previous valve lesions predispose an individual to endocarditis with nonhuman *Bartonella* species, with *B. quintana* endocarditis being more frequently diagnosed in patients without previous heart diseases. On the basis of retrospective analysis, prescription of an aminoglycoside appears to be critical in the outcome of endocarditis (D. Raoult, unpublished data).

CSD. CSD is usually a self-limiting regional lymphadenitis. At the inoculation site there is usually an erythematous papule, and later, the lymph nodes draining the site become enlarged and tender. They usually regress in size over a period of weeks or months, but the lymphadenitis may become suppurative in 10% of patients. Complications such as rash, hepatosplenomegaly, lytic bone lesions, and deep lymphadenitis can occur in 5% of patients, most often in children. In immunocompetent hosts, there is usually no bacteremia (16, 100). Serological studies have shown that the vast majority of cases of CSD are due to *B. henselae* (78). The first isolation of *B. henselae* from a patient with CSD lymphadenitis was made by Dolan et al. (26) in 1993. The organism was also isolated from the blood of an asymptomatic cat, indicating that domestic cats are reservoirs of *B. henselae* (79). CSD has been reported worldwide and seems to be the most common *Bartonella* infection in people today. Between 1 and 2% of people with CSD will

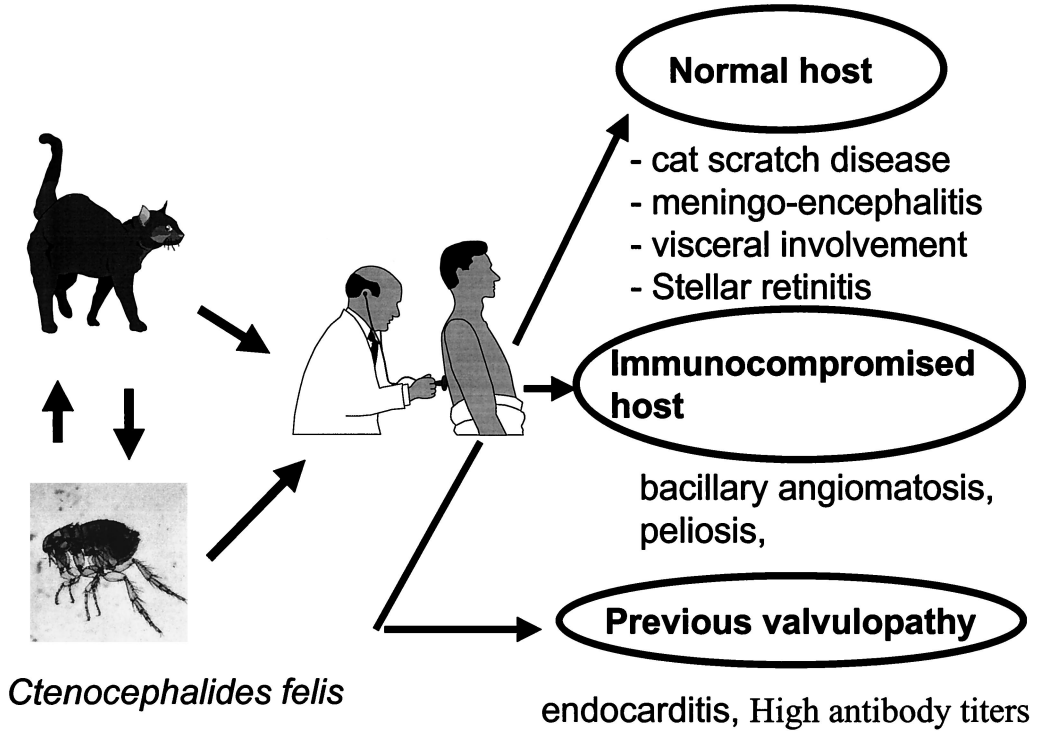

FIG. 5. Putative natural history of *B. henselae* infection.

suffer neuroretinitis, which includes disk edema and exudates of the macula (71). In the United States, Jackson et al. (45) studied epidemiological databases and estimated that approximately 24,000 cases of CSD occur each year, with a calculated incidence of 9.3/10,000 ambulatory patients per year. In various studies, the seroprevalence of antibodies to *B. henselae* in people has ranged from 3.6 to 6% (7). Although CSD may occur in people of any age, most patients are under 18 years of age (16), perhaps because children are more likely to have close and rough contact with cats. The incidence of CSD is seasonal, with most cases occurring in August to October in northern temperate areas (16). The prevalence of the disease also varies with the geographic location (45). Jameson et al. (46) reported that the prevalence of antibodies to *B. henselae* was higher in areas with warm humid climates, where there was a higher prevalence and intensity of cat flea infestations. Cats may infect humans either directly through scratches and bites or indirectly via the cat flea (*Ctenocephalides felis*), which is the arthropod vector (Fig. 5). Both the Houston and Marseille serotypes of *B. henselae* can cause CSD (28, 64). *B. clarridgeiae* may also cause some cases of CSD (56) (Table 2). No antibiotics have proved effective in the treatment of CSD. Together with the fact that few isolates were recovered by culture of pus from patients with CSD, this may be caused by the fact that clinical symptoms are related to the immune reaction rather than bacterial multiplication.

BA, peliosis hepatis, and immunodeficiency. BA and peliosis hepatis are vascular proliferative diseases that occur particularly in immunocompromised patients with *Bartonella* infections, mainly those infected with HIV (74) (94). In 1983, subcutaneous lesions named BA were observed in HIV-infected patients (93), and *B. henselae* DNA was later amplified from the lesions (82). At the same time, *B. henselae* was recovered from febrile patients with AIDS but without skin lesions (89). Subsequently, *B. quintana* has also been described as a causative agent of BA (51) (70). Among a series of 49 patients who were infected with *Bartonella* species identified by molecular biology-based techniques and who had clinical lesions consistent with BA (52), 53% were infected with *B. henselae* and 47% were infected with *B. quintana*. There are clinical and epidemiological differences between patients with BA due to *B. henselae* and *B. quintana*. Subcutaneous and lytic bone lesions are strongly associated with *B. quintana* infections, whereas peliosis hepatis was associated exclusively with *B. henselae* infections (52). Patients with *B. henselae* infections were more likely to be exposed to cats and their fleas, while those infected

TABLE 2. Conditions caused by *Bartonella* species in people

Bartonella sp.	Condition
B. grahamii	Uveitis
B. elizabethae	Endocarditis
B. vinsonii subsp. *berkhoffii*	Endocarditis
B. vinsonii subsp. *arupensis*	Fever in a patient with valvulopathy
B. henselae	CSD, BA, peliosis hepatis, endocarditis, bacterema, neuroretinitis
B. clarridgeiae	CSD (based on serology only)
B. bacilliformis	Carrion's disease (acute Oroya fever and chronic verruga peruana)
B. quintana	BA, endocarditis, trench fever, chronic bacteremia

with *B. quintana* were more likely to be homeless and exposed to lice. In a study of 37 patients with BA in the literature (35), the presence of lymphadenopathy was significantly associated with *B. henselae* infections but not with *B. quintana* infections. Neurological disorders were significantly associated with *B. quintana* infections. Epidemiological risk factor analysis revealed that cat exposure was specified by 25 of the 37 patients and cat contact was recorded by 11 (84.6%) of the 13 *B. henselae*-infected patients. *Bartonella* infections of the central nervous system have also been proposed as a cause of meningitis and neuropsychiatric deterioration in HIV-infected patients with antibodies to *Bartonella* species in their cerebrospinal fluid and serum (88). HIV-infected patients with BA or peliosis hepatis can present with concomitant *Bartonella* bacteremia, and bacteremia can also occur in immunocompromised patients in the absence of focal BA (92). BA responds dramatically to macrolide antibiotics (51, 52).

BARTONELLA SPECIES IN ANIMALS

Rodents. Numerous rats and mice are known to have intraerythrocytic *Bartonella* bacteremias. *B. talpae* was first observed in 1905 in the erythrocytes of moles and other rodents (6), and in 1995, three new *Bartonella* species were isolated from the blood of small woodland mammals in the United Kingdom (6). *B. grahamii* was isolated from the blood of *Clethrionomys glareolus* rats, *B. taylori* was isolated from the blood of *Apodemus* rat species, and *B. doshiae* was isolated from the blood of *Microtus agrestis* rats. In a recent survey, *Bartonella* species were found in the blood of intradomiciliary animals and *Phyllotis* mice in the Huayllacallàn Valley in Peru (5). Erythrocyte-associated bacteria were observed in blood smears from only one mouse, but two *Bartonella* species were isolated from *Rattus norvegicus*. One was indistinguishable from *B. elizabethae*, and the second was a distinct new *Bartonella* species. Ellis et al. (32) analyzed whole-blood specimens from 325 *R. norvegicus* rats and 92 *R. rattus* rats trapped in Portugal and at 13 different sites in the United States. *Bartonella* species were isolated from the blood of 63 *R. norvegicus* rats and 11 *R. rattus* rats. The overall prevalence of *Bartonella* bacteremias in both species was 18%, with the prevalence of *Bartonella* species in *R. norvegicus* rats being significantly high in California (45%); Los Angeles, California (56%); and Portugal (100%). The prevalence of *Bartonella* bacteremias in *R. rattus* rats did not differ from the overall prevalence except in California, where the prevalence was 60%. Two isolates were identical to *B. elizabethae*, and all 63 *Bartonella* species isolated from *R. norvegicus* rats were closely related and clustered with *B. elizabethae* and *B. grahamii*. *B. tribocorum* was obtained from the blood of wild *R. norvegicus* rats in eastern France (41), and it was observed that intraerythrocytic *Bartonella* bacteremias are lifelong in experimentally infected rats (87). It is not known how the *Bartonella* species carried by rodents can be transmitted to people, but 61% of *Xenopsylla cheopis* collected from rats have been found to be infected with *Bartonella* species, including *B. elizabethae* (7). Also, the pathogenicities of most rodent *Bartonella* species are not known, although one patient with a *B. elizabethae* infection and another patient with a *B. grahamii* infection have been described (49).

Felines. Domestic cats are most commonly infected with *B. henselae*, although they may also be infected with *B. clarridgeiae*, *B. koehlerae*, and *B. weissii* (7). The prevalence of blood culture-positive cats is high worldwide and is up to 41% in California (50). Transmission electron microscopy (54) and confocal microscopy (Fig. 2) (83) have shown that *B. henselae* occurs within the erythrocytes of bacteremic cats, and such infections can persist for up to a year (54). The cat flea (*C. felis*) can transmit *B. henselae* between cats and is probably the main vector of the organism (21).

Other felines can be infected with bartonellas, with *B. henselae* having been isolated from a cheetah (*Acinonyx jubatus*) (48) and a strain named *B. henselae* Humboldt having been isolated from four mountain lions in California (99). Antibodies to *B. henselae* have been found in 30% of captive wild felids (98) and in free-ranging Florida panthers (*Puma concolor coryi*), mountain lions, and cougars (84).

There are conflicting reports on the clinical signs that might be seen in cats experimentally infected with *B. henselae*. Three studies have reported that cats show clinical signs including swelling at the site of inoculation, fever, lethargy, anorexia, myalgia, behavioral and/or neurological changes, and lymphadenopathy (36, 55, 72). Reproductive failures and delayed conceptions have been reported in female cats inoculated with *B. henselae*. Infections were not spread by sexual contact, and kittens from pregnant queens were free of infection (37). In other studies, cats infected with *B. henselae* have shown no clinical signs (1, 80); therefore, there might be variations in the pathogenicities of *B. henselae* strains for cats.

Canids. *B. vinsonii* subsp. *berkhoffii* was first isolated from a female domestic dog with endocarditis (9). Subsequently, the organism has been found in another dog with endocarditis (57) and it has been implicated in granulomatous lymphadenitis, granulomatous rhinitis, peliosis hepatis, myocardial inflammation, cardiac arrhythmias, syncope, and sudden death in dogs (8). The organism may also be found in healthy dogs, with one dog having had a persistent infection for 16 months (57). In this dog, *B. vinsonii* subsp. *berkhoffii* was isolated in 8 of 10 blood cultures performed over the 16-month period and the dog had antibodies at titers of $\geq$1:64 against *B. vinsonii* subsp. *berkhoffii* but not against *B. clarridgeiae* or *B. henselae*. A seroepidemiological study has identified tick exposure as a risk factor for the presence of *B. vinsonii* antibodies in dogs (73). Recent studies in California have implicated coyotes as the wildlife reservoir of *B. vinsonii* subsp. *berkhoffii*, with 76% of animals being seropositive and bacteremia being present in 28% of animals (19, 20).

Rabbits. Of 9 of 30 (30%) wild rabbits (*Oryctolagus cuniculus*) from eastern France that were culture positive for *B. alsatica* (40), 2 that were sent for postmortem examination had no gross abnormalities and also appeared normal by histopathology.

Ungulates. In recent studies in the United States, the prevalences of *Bartonella* bacteremias have been determined to be 15% in elk (*Cervus elaphus*), 90% in mule deer, 0% in 84 bighorn sheep (*Ovis canadensis*), and about 50% in domestic cattle (*Bos taurus*) (10). Analyses of partial sequences of the citrate synthase genes of the isolates showed they were all closely related to one another and also to *B. weissii*.

CONCLUSION

The available data on the *Bartonella* species have expanded rapidly in recent years as this group of organisms has been found to be responsible for a growing spectrum of emerging and reemerging diseases. We now have new insights into the natural history of the *Bartonella* species and can see that these bacteria have adapted to their mammalian reservoir hosts in unique ways. They cause chronic intraerythrocytic infections, with up to half of the reservoir host populations being bacteremic at any one time. This bacteremia is the source of the vector infection. The *Bartonella* bacteremias, however, result in few (and, if present, very subtle) clinical signs in their specific reservoir hosts, and this contradicts Koch's observation that the blood of healthy humans or animals is free of bacteria.

ACKNOWLEDGMENT

We acknowledge J. M. Rolain for photography with confocal microscopy.

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