

Human bartonellosis: seroepidemiological and clinical features with an emphasis on data from Brazil - A Review

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Bartonellae are fastidious Gram-negative bacteria that are widespread in nature with several animal reservoirs (mainly cats, dogs, and rodents) and insect vectors (mainly fleas, sandflies, and human lice). Thirteen species or subspecies of Bartonella have been recognized as agents causing human disease, including B. bacilliformis, B. quintana, B. vinsonii berkhoffii, B. henselae, B. elizabethae, B. grahamii, B. washoensis, B. koehlerae, B. rochalimaea, and B. tamiae. The clinical spectrum of infection includes lymphadenopathy, fever of unknown origin, endocarditis, neurological and ophthalmological syndromes, Carrion's disease, and others. This review provides updated information on clinical manifestations and seroepidemiological studies with an emphasis on data available from Brazil.

Key words: *Bartonella* - infection - epidemiology - serology - Brazil

Members of the genus *Bartonella* are small, fastidious Gram-negative rod-shaped bacteria that parasitize mammalian erythrocytes and endothelial cells. Until 1993, *Bartonella bacilliformis* was the only recognized *Bartonella* species pathogenic to humans, responsible for Carrion's disease, which occurs in regions of Colombia, Ecuador and Peru. After molecular studies, four species belonging to the genus *Rochalimaea* were moved to the genus *Bartonella*, and at present, there are more than 23 recognized species (Brenner et al. 1993, Birtles et al. 1995) (Table I).

Several *Bartonella* species have been recovered from a wide range of wild and domesticated mammals throughout the world with a high diversity of geographic distributions, animal reservoirs, and arthropod vectors such as sandflies, the human body louse, the cat flea and, potentially, ticks (Podsiadly et al. 2007, Wikswó et al. 2007, Billeter et al. 2008). Contact with animals and vectors seem to be the most important mode of transmission, although recent studies have shown the ability of *Bartonella* to survive in stored blood for more than 35 days with the potential for transfusion-associated infection (Magalhães et al. 2007).

Thirteen species or subspecies of *Bartonella* have been recognized as agents causing human disease, including *B. bacilliformis*, *B. quintana*, *B. vinsonii* subsp. *berkhoffii*, *B. henselae*, *B. elizabethae*, *B. grahamii*, *B. washoensis*, *B. koehlerae*, and more recently, *B. rochalimaea* and *B. tamiae*, among others (Table I) (Regnery et al. 1992a, Birtles et al. 1995, Ellis et al. 1999, Kerkhoff et al. 1999, Chang et al. 2000, 2001, Jacomo et al. 2002, Holmberg et al. 2003, Kosoy et al. 2003, 2008, Bown et

al. 2004, Avidor et al. 2004, Castle et al. 2004, Jardine et al. 2005, Mediannikov et al. 2005, Chomel et al. 2006a, b, Diederer et al. 2007, Ereemeeva et al. 2007, Li et al. 2007, Wikswó et al. 2007). Phylogenetic analysis using *groEL* sequences (*groEL* is a highly conserved heat-shock chaperonin protein) has distinguished four groups of *Bartonellae*: (1) two human pathogens *B. henselae* and *B. quintana*; (2) four rodent isolates, *B. elizabethae*, *B. tribocorum*, *B. grahamii* and *B. taylorii*; (3) a cluster including the *B. vinsonii* subspecies (*B. vinsonii* subsp. *vinsonii*, *arupensis* and *berkhoffii*); and (4) *B. birtlesii* and *B. weissi*. *B. washoensis*, *B. alsatica*, *B. doshaiae*, *B. bacilliformis*, and *B. clarridgeiae* did not reliably cluster with any other *Bartonella* species (Zeaiteer et al. 2002).

Bartonellae have pathogenic characteristics such as the ability to invade red blood cells and cause lysis of those cells, the ability to cause persistent bacteremia, and the ability to induce small vessel endothelial cell proliferation (Benson et al. 1986, Garcia et al. 1990, Battierman et al. 1995, Kordick & Breitschwerdt 1995, Brouqui & Raoult 1996, Resto-Ruiz et al. 2003). The pathologic response varies with immune status. In immunocompetent human individuals (IHI), the response is granulomatous and suppurative, whereas in immunodeficient patients, it is predominantly vasculoproliferative (Resto-Ruiz et al. 2003). This article reviews the current seroepidemiological studies of *Bartonella* infections as emerging infectious diseases and discusses presently identified clinical manifestations, emphasizing data available from Brazil.

Seroepidemiologic studies

The number of seroepidemiologic studies has grown significantly during the last ten years but more publications in human populations need be made available from the Southern Hemisphere (Table II). In Brazil, in 2001, a study of 457 Brazilian healthy adults from Piau, a small town in the state of Minas Gerais, showed 13.7 and 12.8% seroprevalence for *B. henselae* and *B. quintana*, respectively (cut off titer of 1:64). No correlation was

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TABLE I

Bartonella species associated and potentially associated with human disease, their distribution and vectors

| Species | Diseases | Distribution | Vector ^b |
|--|--|--|---|
| <i>B. bacilliformis</i> | Carrion's disease | South America | Sandflies (<i>Lutzomyia verrucarum</i>) |
| <i>B. rochalimaea</i> | bacteremia, fever, cutaneous lesions and splenomegaly | Peru | unknown (possibly <i>L. verrucarum</i>) |
| <i>B. quintana</i> | endocarditis, trench fever, CSD, BA, peliosis hepatis | South America, Europe, USA, Africa | human body louse (<i>Pediculus humanus corporis</i>), cat fleas, gerbil fleas, <i>Ixodes pacificus</i> ticks |
| <i>B. henselae</i> | CSD, ocular manifestations, encephalopathy, aseptic meningitis, acute hemiplegia, dementia, acute psychiatric symptoms, FUO, hepatosplenic abscesses, asymptomatic bacteremia, osteomyelitis, BA, peliosis hepatis, erythema nodosum, other skin lesions | South America, Europe, USA, Africa, Asia | cat flea (<i>Ctenocephalides felis</i>), <i>Ixodes ricinus</i> ticks, <i>I. pacificus</i> ticks, <i>Rhipicephalus sanguineus</i> ticks (dogs) |
| <i>B. elizabethae</i> | endocarditis | Europe, USA, Asia | rat fleas (genera <i>Rattus</i> and <i>Mus</i>), wild rodent fleas |
| <i>B. clarridgeiae</i> | CSD, sepsis, endocarditis | Europe, USA, Asia | cat flea (<i>C. felis</i>), rodent fleas, dog ectoparasites(?), gray foxes ectoparasites(?) |
| <i>B. clarridgeiae</i> -like | fever and splenomegaly | Peru | unknown |
| <i>B. koehlerae</i> | endocarditis, CSD | USA | Cat and rodent fleas |
| <i>B. vinsonii</i> subsp. <i>berkhoffii</i> | endocarditis, arthralgia/myalgia/headache/fatigue | Europe, USA | <i>I. pacificus</i> ticks, coyote ticks(?) gray foxes ectoparasites(?) |
| <i>B. washoensis</i> | fever and myocarditis | USA | <i>I. pacificus</i> ticks, ground squirrels |
| <i>B. tamiae</i> | fever | Thailand | unknown |
| <i>B. grahamii</i> | neurorretinitis | Europe, Canada, Asia | vole fleas, other wild rodents fleas(?) |
| <i>B. doshiae</i> | CSD | Europe | rat fleas (genera <i>Rattus</i> and <i>Mus</i>) |
| <i>B. taylorii</i> | unknown | Europe | gerbil fleas, vole fleas |
| <i>B. alsatica</i> ^a | unknown | Europe | vector unknown |
| <i>B. bovis</i> | unknown | Europe, Africa, North America | ticks |

a: *B. alsatica* has been isolated from the blood of wild rabbits; *b*: so far ticks have not been shown experimentally to transmit *Bartonella* spp to human beings; voles and gerbils are wild rodents; BA: bacillary angiomatosis; CSD: cat scratch disease; FUO: fever of unknown etiology.

found with job exposure, living in a rural area or sex, but individuals over 40 had a tendency toward higher seroprevalence (Costa et al. 2005). Another study was conducted in 2005 in 125 consecutive outpatient clinically asymptomatic HIV-positive patients in Jacarepaguá, a semi-rural area of Rio de Janeiro city, in which *Bartonella* sp. seroprevalence was 41.6% (cut-off titer of 1:20). These individuals were young (mean age 37 ± 10 years) and none were intravenous drug users. The only iden-

tified risk factor for *Bartonella* infection was breeding cats, which had an odds ratio of 3.6. No differences were found in CD4 cell count, sex, age, exposure to dogs, rodents, ticks, fleas or lice (Lamas et al. 2006).

From the data presented in Table II and those discussed above, it is clear that *Bartonella* largely circulates among human populations (Jackson et al. 1996, Brouqui et al. 1996, 1999, 2005, Comer et al. 1996, 2001, Rotily et al. 1996, Noah et al. 1997, Blanco et al. 1998, 1999,

TABLE II
Bartonella human seroprevalence in selected populations in the last decade (1996-2007) by country
 and chronological order of publication

| Country | Number of individuals | Population/ <i>Bartonella</i> species | Positive (%) | Reference |
|--|-----------------------|---|----------------------|-------------------------------|
| USA | 192 | clinic patients (homeless, alcoholic, HIV-negative) | 20 | Jackson et al. (1996) |
| | 199 | age- and sex-matched blood donors/ <i>B. quintana</i> | 2 | |
| USA | 630 | IVDU from Baltimore/ <i>Bartonella</i> spp., <i>B. elizabethae</i> , <i>B. henselae</i> , <i>B. quintana</i> | 37.5, 22.9, 1.4, 1.6 | Comer et al. (1996) |
| USA | 351 | veterinarians, vet technicians, other individuals attending a conference/ <i>B. henselae</i> and <i>B. quintana</i> | 7.1 | Noah et al. (1997) |
| USA | 146 | children with FUO/ <i>B. henselae</i> | 4.8 | Jacobs et al. (1998) |
| USA | 204 | IVDU from New York/ <i>B. elizabethae</i> , <i>B. henselae</i> , <i>B. quintana</i> | 46, 10, 2 | Comer et al. (2001) |
| USA | 200 | clinic patients/ <i>B. elizabethae</i> , <i>B. quintana</i> , <i>B. henselae</i> | 12.5, 9.5, 3.5 | Smith et al. (2002) |
| USA | 382 | HIV-positive patients with fever/ <i>Bartonella</i> spp. | 17 | Koehler et al. (2003) |
| France | 71 | homeless patients/ <i>B. quintana</i> | 30 | Brouqui et al. (1996) |
| France | 57 | adult homeless with cutaneous infestation/ <i>B. quintana</i> | 54 | Guibal et al. (2001) |
| | 53 | blood donors/ <i>B. quintana</i> | 2 | |
| France, Eastern Europe and Northern Africa | 930 | homeless mainly from France/ <i>B. quintana</i> | 7.5 | Brouqui et al. (2005) |
| Germany | 270 | healthy adults/ <i>B. henselae</i> | 30 | Sander et al. (1998) |
| Greece | 500 | healthy adults/ <i>B. henselae</i> , <i>B. quintana</i> | 19.8, 15 | Tea et al. (2003) |
| Greece | 63 | healthy children/ <i>Bartonella</i> spp. | 15.9 | Antoniou et al. (2002) |
| Italy | 508 | healthy children/ <i>B. henselae</i> | 61.6 | Massei et al. (2004) |
| Spain | 83 | cat owners | 28.9 | Blanco Ramos Jr et al. (1998) |
| | 85 | blood donors/ <i>B. henselae</i> | 5.9 | |
| Spain | 147 | HIV-positive IVDU | 14 | Ramos AJ et al. (2002) |
| | 94 | HIV negative IVDU/ <i>Bartonella</i> spp. | 15 | |
| Spain | 146 | healthy individuals/ <i>Bartonella</i> spp. | 24.7 | Garcia-Garcia et al. (2005) |
| Sweden | 498 | blood donors/ <i>B. elizabethae</i> , <i>B. grahamii</i> , <i>B. henselae</i> , <i>B. quintana</i> | 14.1, 2.6, 1.2, 0.2 | McGill et al. (2005) |
| United Kingdom | 200 | blood donors/ <i>B. henselae</i> , <i>B. quintana</i> | 1.5 | Harrison and Dosh (1999) |
| Jordan | 482 | children/ <i>B. henselae</i> , <i>B. quintana</i> | 11, 4.1 | Al-Majali and Al-Qudah (2004) |
| Japan | 233 | veterinary professionals/ <i>B. henselae</i> | 15 | Kumasaka et al. (2001) |
| Japan | 159 | patients with cardiovascular disease, veterinary students/ <i>B. henselae</i> | 3.1 | Kikuchi et al. (2002) |
| | 129 | | 10.1 | |
| Japan | 151 | homeless, blood donors/ <i>B. quintana</i> | 57 | Seki et al. (2006) |
| | 200 | | 51 | |
| Thailand | 163 | healthy individuals/ <i>B. henselae</i> | 5.5 | Maruyama et al. (2000) |
| New Zealand | 140 | healthy blood donors/ <i>B. henselae</i> | 5 | Zarkovic et al. (2007) |
| Brazil | 437 | adult healthy individuals/ <i>B. henselae</i> , <i>B. quintana</i> | 13.7, 12.8 | Costa et al. (2005) |
| Brazil | 125 | HIV-seropositive asymptomatic adults/ <i>B. henselae</i> | 40.8 | Lamas et al. (2006) |
| Chile | 181 | children and adolescents | 13.3 | Ferrés et al. (2006) |
| | 107 | adult cat carers/ <i>B. henselae</i> | 10.3 | |

| Country | Number of individuals | Population/ <i>Bartonella</i> species | Positive (%) | Reference |
|---------|-----------------------|---|--------------|--------------------------|
| Ecuador | 213 | serosurvey of close contacts of cases of Carrion's disease/ <i>B. bacilliformis</i> | 18.5 | Amano et al. (1997) |
| Peru | 544 | children and adults in an area with an outbreak of Carrion disease/ <i>B. bacilliformis</i> | 77.5 | Kosek et al. (2000) |
| Peru | 690 | children and adults in endemic area/ <i>B. bacilliformis</i> | 45 | Chamberlin et al. (2002) |

FUO: fever of unknown etiology; IVDU: intravenous drug user.

Jacobs & Schutze 1998, Sander et al. 1998, Harrison & Doshi 1999, Maruyama et al. 2000, Guibal et al. 2001, Kumasaka et al. 2001, Antoniou et al. 2002, Kikuchi et al. 2002, Ramos et al. 2002, Smith et al. 2002, Tea et al. 2003, Koehler et al. 2003, Al-Majali & Al-Qudah 2004, Massei et al. 2004, Garcia-Garcia et al. 2005, McGill et al. 2005, Ferres et al. 2006, Seki et al. 2006, Ehrenborg et al. 2007, Zarkovic et al. 2007). *B. bacilliformis* serology performed in endemic areas is notably high (Amano et al. 1997, Kosek et al. 2000, Chamberlin et al. 2002). *B. henselae* seropositivity has a close association with cat ownership and/or cat care (for example, veterinary professionals) (Rath et al. 1997, Chang et al. 2002, 2006, Schattner et al. 2003, Podsiadly et al. 2007). *B. quintana* seropositivity is linked to homelessness, alcoholism, infestation, and animal exposure (Spach et al. 1995b, Stein & Raoult 1995, Brouqui et al. 1996, Abbott et al. 1997, Guibal et al. 2001, Boulouis et al. 2005). *B. henselae* and *B. vinsonii* subsp. *berkhoffii* have been isolated in blood of IHI with frequent animal and arthropod contact (Breitschwerdt et al. 2007a, b).

In relation to *Bartonella* spp. infections in animals, pets, especially cats, represent a large reservoir for human infection (Skerget et al. 2003, Chomel et al. 2006a, b). Cats are the main reservoir for *B. henselae*, *B. clarridgeiae* and *B. koehlerae* (Regnery et al. 1990, Groves & Harrington 1994, Lawson & Collins 1996, Gurfield et al. 1997, Heller et al. 1997, Chomel et al. 1999, Zanutto et al. 2001). Although they are well-adapted hosts to Bartonellae, several clinical and experimental studies have shown cats may become ill with the infection (Regnery et al. 1996, Kordick et al. 1999, O'Reilly et al. 1999).

Dogs can be infected with *B. vinsonii* subsp. *berkhoffii*, *B. henselae* (Tsukahara et al. 1998), *B. clarridgeiae*, *B. washoensis* (Chomel et al. 2003), *B. elizabethae*, *B. quintana*, and *B. bovis*. The role of dogs as an important reservoir for *Bartonella* spp. (Honadel et al. 2001, Henn et al. 2005, 2006) is less clear than that for cats because domestic dogs are more likely to be accidental hosts, at least in tropical regions. However, dogs may be sentinels for human infections because they may become ill (Chomel et al. 2006a, b, Henn et al. 2007). Transmission of *B. henselae* by cat fleas is well-understood, though new potential vectors (ticks and biting flies) have also been identified (Chomel et al. 2006a, b, Podsiadly et al. 2007, Wikswow et al. 2007, Billeter et al. 2008).

Transmission of *B. quintana* from a cat to a human individual has been documented by molecular biological methods (MBM) and the putative mode of transmission

was a cat bite (Breitschwerdt et al. 2007b). Although human transmission by ticks has not been proven, several recent studies have identified *Bartonella* DNA in ticks attached to humans (Adelson et al. 2004).

Seroprevalence in cats varies from 14 to 50 % across studies, and it has been reported that cats may have persistent and asymptomatic bacteremia (Koehler et al. 1994, Baneth et al. 1996, Bergmans et al. 1997, Chomel et al. 1999, 2002, 2006a, b, Hjelm et al. 2002, Fabbi et al. 2004). A study by Shlessarenko et al. (1996) on the seroprevalence of cats in the city of São Paulo, Brazil, revealed 46% sero-reactivity to *Bartonella* spp.

B. koehlerae has been isolated from cats and cat fleas, and has been linked to human disease (Rolain et al. 2003, Avidor et al. 2004, Chomel 2006a). *B. koehlerae* and *B. clarridgeiae* have also been detected by MBM in cat fleas (Rolain et al. 2003). *B. quintana* was thought, until recently, to have only humans as a reservoir species, but recent publications have shown that it is also present in dogs (La et al. 2005), cats, cat fleas (Rolain et al. 2003), and even monkeys (O'Rourke et al. 2005).

In dogs, *B. quintana* and *B. clarridgeiae* have been shown to cause endocarditis (Kelly et al. 2006). *B. vinsonii* subsp. *berkhoffii* has been shown to cause endomyocarditis and arrhythmias (Breitschwerdt et al. 1995, 1999), and its seroprevalence in dogs has been reported as high (Solano-Gallego et al. 2004, Henn et al. 2006). Coyotes seem to be its wild reservoir (Chang et al. 2000). A recent study in Brazil (Diniz et al. 2007) analyzed the serological and molecular prevalence of *Bartonella* spp. in sick dogs: 4/197 (2%) were seroreactive to *B. henselae* and 3/197 (1.5%) to *B. vinsonii* subsp. *berkhoffii*. DNA amplification showed co-infection with both species.

B. elizabethae has been isolated from the blood of *Rattus rattus* and from the rat flea *Xenopsylla cheopis*. Despite the association of *B. elizabethae* with rodents, Hjelm et al. (2002) found a seroprevalence of 25% in 292 cats studied in Sweden. Other *Bartonella* species that are less important in causing human disease have been identified in ground squirrels (*B. washoensis*), and wild felids have been shown to be naturally infected with *B. henselae* variants (Chomel 2006a, b). A recent study in Brazil (Filoni et al. 2006) showed a prevalence of 95% (20/21) of *B. henselae* in wild felids from different biomes. *B. bovis* (previously *weisii*) has been identified in cattle from Europe, North America and Asia, but no role in human disease has been established to date (Bermond et al. 2002, Raoult et al. 2005, Maillard et al. 2006).

Clinical manifestations

The clinical spectrum of *Bartonella* infections has continually expanded. Besides classical diseases such as Carrion's (Ricketts 1949) and cat-scratch disease (CSD) (Wear et al. 1983), others, such as relapsing bacteremia, endocarditis, and trench fever occur today mainly in socio-demographic niches such as poor urban areas and refugee camps (Stein & Raoult 1995).

Bacillary angiomatosis (BA) and hepatic peliosis, classically associated with Acquired Immunodeficiency Syndrome (AIDS) (Regnery et al. 1995) is seen less frequently today, possibly due to earlier recognition of HIV serostatus and a reduced number of individuals with CD4 lymphocyte cell counts below 50 cells/mm³.

Bartonella infections that deserve detailed discussion based on their increasing number of reports include blood culture negative infective endocarditis and fever of unknown origin. In addition, for several decades atypical manifestations of CSD such as meningoencephalitis, retinitis, dissemination with hepatosplenic abscesses and osteomyelitis have been reported, and it is likely that many such manifestations still go unrecognized (Stevens 1952, Adams & Hindman 1954, Selby & Walker 1979, Miller & Bell 1980, Johnson et al. 1985, Wear et al. 1985, Katner et al. 1986, Greenbaum et al. 1986, Lewis & Tucker 1986, Margileth et al. 1987, Chrousos et al. 1990, Apalsch et al. 1993, Golden 1993, Tappero et al. 1993, Bernini et al. 1994, Waldwogel et al. 1994, Hadley et al. 1995, Whitman & Krafte-Jacobs 1995, Wong et al. 1995, Riviello & Ruoff 1998, Walter & Eppes 1998, Arisoy et al. 1999, Hulzebos et al. 1999, Maggiore et al. 1999, Robson et al. 1999, Ventura et al. 1999, Azevedo et al. 2000, Krause et al. 2000, Hmaimess et al. 2004, Baylor et al. 2007, Stockmeyer et al. 2007). The onset of signs and symptoms of bartonellosis generally occur about one to two weeks after exposure, but this delay can range from 1-4 weeks, depending on the syndrome presented, and may last several months (Carithers 1985).

Lymphadenopathy - Lymphadenopathy, usually of lymph nodes draining the site of inoculation (axillary, epitrochlear, neck, and jaw nodes being most frequently affected) of the bacteria, is the most constant feature of CSD. More than 85% of cases have single lymph node chain involvement, and 2-4 nodes may be enlarged. Nodes may be tender and have inflammatory signs (erythema, tenderness, warmth) and suppurate in 13 to 48% of cases (Daniels & McMurray 1954, Carithers 1985). They may reach several centimeters in diameter and may persist for about two weeks to several months. Lymphadenopathy is associated with an inoculation papule in most cases, but the papule may go unrecognized when the patient is brought to the physician's attention three or more weeks after contact with a cat. It is unassociated with fever in about 40% of cases (Carithers 1985). CSD is an important cause of lymphadenopathy of the head and neck (Ridder et al. 2002).

Cat scratch disease affects children and young adults more often, but many cases may go undiagnosed in older adults. Exposure to cats, often young, is the rule. Seasonality is different in the Southern (December and

January, summer school vacation and exposure to pets; Huarcaya et al. 2002) and Northern hemispheres (late fall and early winter, September to February; Spaulding & Hennessy 1960, Carithers 1985, Zangwill et al. 1993, Hamilton et al. 1995).

A few reports of generalized lymphadenopathy and of mediastinal masses due to *Bartonella* infection have been published (Katner et al. 1986, Tolan et al. 1990, Apalsch et al. 1993). However, the most common manifestation associated with lymphadenopathy is conjunctivitis, characterizing Parinaud oculoglandular syndrome. In this case, enlarged nodes are pre-auricular and there is a characteristic granulomatous lesion on the ipsilateral conjunctiva; its frequency in large series of CSD is around 5% (Carithers 1985, Margileth 1992). Most often, the conjunctivitis is painless and does not present discharge. More information about ocular manifestations will be presented in the next section. Cases of CSD have been confirmed in Brazil, as observed by testing of biological samples in the reference laboratory in Fiocruz (unpublished observation). A case of CSD caused by *B. quintana* that was associated with cat contact deserves mention since it is one of the first observations of the possibility of cat-related infection with *B. quintana* (Azevedo et al. 2000).

Ocular manifestations - The ocular manifestation of CSD was initially reported as a chronic ulcerative conjunctivitis associated with lymphadenopathy, named Parinaud oculoglandular syndrome (POGS), as noted above. Several reports have since confirmed the association between POGS and cat exposure. It was only in 1970, when Sweeny and Drance described a possible association between neuroretinitis and cat-scratch disease, that intra-ocular changes secondary to CSD began to be considered. These findings were confirmed by Gass (1977), and in the last two decades, several studies have been published regarding intra-ocular manifestation of CSD. Intra-ocular changes secondary to *B. henselae* infection include neuroretinitis, sub-retinal lesions, retinitis, intermediate uveitis, inflammatory masses, and angiomas lesions. Other findings are occlusive events, retinal serous detachment and optic neuritis. Despite the variety of ocular manifestations, neuroretinitis, small foci of retinitis, and angiomas lesions are the most common ocular findings in CSD. Neuroretinitis is the second most common ocular finding. Neuroretinitis secondary to CSD presents with unilateral or bilateral involvement and is characterized by blurred vision from 20/25 to light perception, optic disk edema, serous detachment, and macular star. Patients may present with central scotoma and papillary defects. Studies have suggested that neuroretinitis secondary to CSD is a benign disease and visual acuity returns to normal within approximately four weeks without treatment. Although many patients show good recovery without treatment, some authors have suggested oral treatment in cases of severe ocular symptoms and systemic complications. Solley et al. (1999) reported 24 patients with the diagnosis of CSD and ocular disease in the posterior segment of the eye. In this study, the most common finding was

small whitish lesions in the retina or choroid measuring from 50 to 3000 μm . Ormerod et al. (1998) reported two cases of CSD presenting with several small whitish lesions, choroidal infiltrates, and vascular occlusions.

Several small case series have been published regarding *Bartonella* infection and its ocular manifestations. Neuroretinitis has been considered in most of these series as the major ocular manifestation of CSD (Reed et al. 1998, Suhler et al. 2000, Kodama et al. 2003). Other studies showed granuloma of the optic disk associated with abnormal vascular network as the hallmark of intraocular CSD. Wade et al. (2000) published a case series of seven patients presenting with disc edema and peripapillary serous retinal detachment. Isolated cases of CSD and unusual ocular changes have been described. Soheilian et al. (1996) described a case of intermediate uveitis in a young man with CSD. The patient presented with retinal vasculitis and vitritis. Pollock & Kristinson (1998) reported a case of helioid unifocal choroiditis secondary to CSD. This syndrome was first described by Hong et al. (1997) in patients presenting with solitary yellowish lesions without any infectious or inflammatory associated conditions. Other rare associations include inflammatory masses and lesions mimicking the Vogt-Koyanagi-Harada syndrome.

In Brazil, few publications are available, but recently, more attention is being given to this zoonosis, mainly in HIV-positive patients in whom ocular manifestations are different from IHI. Single case reports have been described in the Brazilian ophthalmological literature regarding intraocular changes secondary to CSD. Amaro (1996) reported a case of CSD and retinal infiltrates. The same author (Amaro 1998) described a case of neuroretinitis and CSD. Curi et al. (2006) showed the presence of angiomatic lesions in retinal vessels in HIV-positive patients. The lesions showed good response to oral therapy. Another publication by the same author (Curi et al. 2003) described a case of helioid unifocal choroiditis in an HIV-positive patient with CSD. Additionally, a Brazilian case of Parinaud's, involving a 9-year-old child, was published in the 1990s (Yamashita et al. 1996). More recently, a case of granulomatous conjunctivitis in a 23-year-old female, without lymph node involvement, was reported (Oliveira et al. 2004).

Neurological complications - Several neurological manifestations of *Bartonella* infections have been described (Lyon 1971, Carithers & Margileth 1991). They are, in order of frequency: seizures with encephalopathy, status epilepticus and coma, neuroretinitis, aseptic meningitis, transverse myelitis, radiculitis, cerebral arteritis, acute hemiplegia, and dementia (Stevens 1952, Selby & Walker 1979, Miller & Bell 1980, Carithers 1985, Lewis & Tucker 1986, Baker et al. 1995, Hadley et al. 1995, Hamilton et al. 1995, Noah et al. 1995, Schwartzman et al. 1995, Wong et al. 1995, Riviello & Ruoff 1998, Walter & Eppes 1998, Hmaimess et al. 2004, Rocha et al. 2004, Stockmeyer et al. 2007, Baylor et al. 2007). Overall neurological complications account for 1-2% of cases of CSD (Carithers 1985, Carithers & Margileth 1991, Noah et al. 1995).

Bartonella encephalopathy was first reported in 1952 (Stevens 1952), and others described it years later. Seizures are a common associated manifestation occurring in nearly half of the cases in some series, and some patients develop status epilepticus lasting several hours or even days. Combative behaviour follows seizures or status epilepticus, but full recovery is generally achieved (Carithers 1985, Carithers & Margileth 1991). Encephalopathy occurs more often in older children and adults (Carithers 1985, Carithers & Margileth 1991, Hadley et al. 1995, Rocha et al. 2004) and usually follows lymphadenopathy by 2-6 weeks.

Clusters of cases have also been described by Noah et al. (1995). After finding five cases of encephalopathy in children in a limited geographic area, the authors studied cats in the area where affected children were diagnosed. Cats had a seropositivity of 62% and bacteremia was detected in 22%. Cases with unusual associations, such as pleural effusions, have also been described (Whitman & Krafte-Jacobs 1995).

A case of acute hemiplegia in an 11-year-old Brazilian patient has been published recently (Rocha et al. 2004). This patient had a slight pleocytosis on cerebrospinal fluid (CSF) analysis and a magnetic resonance scan with a non-enhancing subcortical fronto-parietal lesion. He was discharged from the hospital still exhibiting neurological motor signs, and no details on permanent sequels were provided by the authors. It is hypothesized that the mechanism of neurological damage was vasculitis.

Aseptic meningitis is rarely described in *Bartonella* infections; only four cases (one in a HIV-seropositive patient) have been reported to date, one of which was in Brazil (Wong et al. 1995, Lucey et al. 1992, Pinto Jr et al. 2008). The Brazilian case was of a 40-year-old male who presented with visual blurring in addition to lymphadenopathy and persistent headache. Optic neuropathy with optic disk swelling and the presence of a partial macular star was noted on funduscopy. These findings characterize neuroretinitis. CSF analysis showed slight pleocytosis and tomographic brain scans were normal. Wong et al. (1995) described an incidence of 5/19 IHI and 1/4 HIV-positive individuals with *Bartonella* (CSD, lymphadenopathy, fever of unknown etiology, etc) infection presenting with stellate retinitis in a series collected between 1991 and 1993, showing its relatively high incidence.

Cognitive decline has been associated with cat ownership in HIV-positive patients (Schwartzman et al. 1995). A report of two patients with psychiatric symptoms (depression and psychosis) associated with BA and HIV showed resolution of manifestations with antibiotic treatment (Baker et al. 1995). Possibly due to earlier diagnosis of HIV seropositivity, neurological manifestations such as dementia, associated or not with *Bartonella*, and other psychiatric features, have been uncommon in recent years.

Fever of unknown etiology (FUO) - Prolonged fever (of more than 4 weeks duration), not associated with regional or systemic lymphadenopathy, may be a manifestation of *Bartonella* infection. It usually does not exceed 39°C (Carithers 1985). Jacobs and Schutze (1998) report-

ed 7/146 children with FUO who had *Bartonella* infection: all had temperatures above 38°C for more than four weeks, and these fevers were associated with malaise, listlessness, headache, and anorexia in some of these children. Six of the seven had had contact with cats. In two, hepatosplenic abscesses were found. A recent series (Murakami et al. 2002) reported 2.8% FUO in 130 patients, nearly a third of which lacked lymphadenopathy. Recurrent infection may occur (Margileth et al. 1987). In HIV-positive patients, *Bartonella* may also be the cause of FUO (Koehler et al. 2003).

Hepatosplenic abscesses - Hepatosplenomegaly, often associated with fever, has been reported in several papers (Greenbaum et al. 1986, Golden 1993, Waldwogel et al. 1994, Arisoy et al. 1999, Ventura et al. 1999, Rolain et al. 2003). Despite feeling feverish, most patients are not unwell and most give a history of cat exposure. Ultrasound scans are mandatory in the evaluation of FUO, and may reveal nodules, 2-3 cm in diameter, which resolve with calcification (Golden 1993). There may be associated intraabdominal lymphadenopathy. A case of right axillary lymphadenopathy and systemic CSD in a 12-year-old boy with liver transplantation has been reported, showing that immunosuppression may play a role in dissemination (Apalsch et al. 1993). However, bacillary angiomatosis and bacillary splenitis have been reported in adult IHI (Tappero et al. 1993). Splenomegaly, lasting several weeks, was reported in 4/18 cases of severe CSD, and abscesses were identified in one of these (Margileth 1992). Granulomatous hepatitis caused by *Bartonella* has probably been under diagnosed (Golden 1993).

Cardiovascular complications - Myocarditis, pericarditis, and endocarditis have been described in animals infected with *Bartonella* (Breitschwerdt et al. 1995, 1999). In human beings, however, endocarditis is the main associated feature. Clinical features of *Bartonella* infective endocarditis (IE) are persistent fever, with left sided valve involvement being the most common (the aortic valve in 66%, the mitral in 18% and both in 13%). Embolic phenomena are common, especially petechiae, splinters and purpura, as the course tends to be subacute. For the same reason, splenomegaly and digital clubbing may be seen, as may glomerulonephritis, clinically manifested as haematuria. Vegetations are detected in most (over 90%) of the cases by transthoracic echocardiograms. Patients tend to be younger than those in usual series of endocarditis (Fournier et al. 2001, Raoult et al. 2003) with a mean age of 45 versus 55 years.

Bartonella endocarditis has been recognized since the first reports from the 1990s (Hadfield et al. 1993, Daly et al. 1993, Spach et al. 1993, 1995a, Drancourt et al. 1995, Holmes et al. 1995, Mainardi et al. 1996, Breathnach et al. 1997, Bruneel et al. 1998) and its importance in blood-culture negative infective endocarditis (BCNE) has been reinforced in recent series (Hoen et al. 1995, Raoult et al. 1996, Fournier et al. 2001, Lamas & Eykyn 2003, Houpiikian & Raoult 2005). So far, *B. quintana* has been the most frequently identified species, with *B. henselae*, *B. vinsonii* subsp. *berkhoffi* (Roux et al. 2000), *B. elizabethae* (Daly et al. 1993), and *B. koehlerae* (Avidor et al. 2004) being infrequently reported (one case each).

A recent and large series of BCNE cases revealed that 99/348 (28%) of cases were caused by *Bartonella* spp. Of these, 53 of 99 (75%) were *B. quintana*, 17 (24%) were *B. henselae*, and 1 was *B. vinsonii* subsp. *berkhoffi* (Houpiikian & Raoult 2005). Although most studies on BCNE are European or American, two studies (Benslimani et al. 2005, Znazen et al. 2005), showed that *Bartonella* is a worldwide problem and may actually be more prevalent in developing countries. In a study from Algeria (Benslimani et al. 2005), of 62 cases of BCNE, *B. quintana* was identified by serum immunofluorescence or polymerase chain reaction in 14. This represented 50% of the cases that had a defined etiology, since in 34 of 62 cases of BCNE, no microorganism was detected. This population had a high prevalence of rheumatic heart disease as a predisposing condition to IE. A study from Tunisia (Znazen et al. 2005) proposed to analyze seroreactivity to *Bartonella* in 40 samples that had tested positive for *Chlamydia* sp. High levels of antibody (titer above 1:800 by indirect immunofluorescent assay - IFA) were found in samples from 13 individuals, 11 of whom had definite endocarditis by the Duke criteria. Molecular biological studies showed that ten were *B. quintana* and one was *B. henselae*. Most patients were of rural origin and had poor living conditions, and nearly 2/3 had predisposing valvulopathy. Despite the well-described relationship between acquiring *B. henselae* disease and cat exposure, and the relationship between poor personal hygiene and homelessness and *B. quintana* disease, the mode of transmission of *B. quintana* is not completely clarified. With the more widespread description of *B. quintana* in nature, more associations will likely be reported in the near future.

The first Brazilian case of *Bartonella* endocarditis, alive and well, has been recently published (Lamas et al. 2007). It shows features of *Bartonella* IE that are similar to what is already described in the literature. The patient had predisposing valvular disease (the 46 year-old patient had rheumatic heart disease), absence of fever, exposure to a young cat at home in the months preceding progressive heart failure, the need for valvular surgery (as is often the case with aortic valve involvement), and a good response to an antibiotic regime containing penicillin, gentamycin and doxycycline (Raoult et al. 1996, 2003, Fournier et al. 2001). The diagnosis was made retrospectively based on very high IgG titers (1:4096) to *B. henselae* in serum collected prior to antibiotic therapy, and lower levels (1:512) 14 months after completion of specific treatment. Two possible cases of IE have also been reported by Siciliano et al. (2006) in Brazil. One patient had native aortic valve IE and the other a prosthetic aortic valve IE, and both had domestic cats. Diagnosis was based on only one serological sample analysis. No details on associated conditions were mentioned and the patients died rapidly (7 and 10 days post admission). The diagnosis was made post mortem.

Skin manifestations - Two main syndromes in *Bartonella* disease involve the skin: bacillary angiomatosis in immunocompromised (but also in IHI) adults, and Carrion's disease in its chronic form (verruca peruana).

Skin lesions in HIV-positive patients are proliferative vascular lesions. They may resemble Kaposi's sarcoma, angiomatous nodules, red papules, pedunculated lesions, or deep subcutaneous masses (Regnery et al. 1995, Mohle-Boetani et al. 1996). These patients usually present low CD4 counts (average 30 cells/mm³), fever and weight loss, representing advanced disease. Tappero et al. (1993) published a case control study on bacillary angiomatosis and found, among the 48 case patients, only five HIV negative IHI. Variables associated with disease acquisition, by multivariate analysis, both involved traumatic contact with cats (bite or scratch). No association was found to exposure to insect bites or to terrains.

In Brazil, a case report on a 49 year-old female patient has been published (Velho et al. 2006). She had associated AIDS and scabies, and on physical examination, numerous papules and subcutaneous nodules were present, as well as hepatosplenomegaly. A more recent publication by the same authors (Velho et al. 2007) describes a case of cryptogenic hepatitis, anaemia, and panseritis in an HIV patient with bacillary angiomatosis. *B. henselae* was isolated by MBM and the patient responded to clarithromycin. A case series of 13 patients, collected between 1990 and 1997 (before highly active antiretroviral therapy availability in Brazil) was published (Gazineo et al. 2001). All patients were male, the mean age was 39 years, and the mean CD4 count was 90. Calculated incidence rate of BA was low but comparable to the world literature. Angioproliferative lesions of the liver (peliosis hepatitis) and spleen may be associated with the cutaneous lesions.

A recent report on Peruvian warts (Maguiña et al. 2001) included 77 patients. Their lesions were classified into three types: miliary, nodular, and mular. The miliary form consists of several 1-4 mm papules, which are round, erythematous, and often pruritic. They accounted for most cases (69%) and involved the lower limbs. Nodular or subdermic lesions are usually present as few cutaneous nodules with no inflammatory reaction. Mular lesions are erythematous, greater than 5 mm in diameter and bleed easily. Secondary infection occurred in 12% of cases and bleeding complicated 66%. The most frequently associated features, besides the skin manifestations, were fever (44%), malaise (53%), arthralgia (47%), pallor (47%), lymphadenopathy (29%) and headaches (25%).

Carrion's disease

Carrion's disease has its name because of Daniel Carrion, a Peruvian medical student who inoculated himself in 1885 with material extracted from a wart. Within weeks, he developed the acute phase of the disease, with fever, haemolysis, and severe immunosuppression (Oroya fever), which eventually killed him (Ricketts 1949). He established, therefore, that the same agent (*B. bacilliformis*) was the cause of the acute and chronic forms of the bartonellosis. *B. bacilliformis* was described in 1905 within erythrocytes. Differently from other species in the genus, it is transmitted by a sandfly, *Lutzomyia verrucarum*. Bartonellosis is still endemic in some areas in Peru, Ecuador and Colombia (Kosek et al. 2000, Maguiña et al. 2001). Outbreaks have been de-

scribed in non-endemic areas in Peru (Kosek et al. 2000, Sanchez et al. 2006). The outbreak study by Kosek et al. (2000) showed a 77.5% seroprevalence for *B. bacilliformis* in 554 individuals tested, and most of the seroreactive patients were asymptomatic. Symptoms in the past year, correlated with serostatus, were fever, bone and joint pain, headache, and verruga peruana. Amano et al. (1997) found a 21% seroreactivity rate for *B. bacilliformis* in contacts of index cases in Ecuador.

Description of the acute phase (Maguiña et al. 2001) in 68 patients showed severe anaemia in most, with resultant congestive heart failure and pericardial effusion (possibly secondary to systemic inflammation, septic myocardial dysfunction, and anaemia). Fourteen of the 68 patients had associated neurological symptoms, and CSF analysis showed mononuclear pleocytosis in 3/4 of them. Due to the immunosuppression caused by *B. bacilliformis*, 1/3 of the patients had secondary infections (positive blood cultures to *Salmonella typhi* and non-typhi and reactivation of toxoplasmosis being the most frequent). Lethality was 9%.

Bartonellosis caused by *B. bacilliformis* therefore has a wide clinical spectrum and may go undiagnosed or misdiagnosed in a large number of cases. No cases or seroprevalence studies have been reported from Brazil so far, although the areas endemic in Peru are within the Amazon forest.

Diagnosis and treatment of *Bartonella* infections

Diagnosis of *Bartonella* infections can be confirmed by detection of antibodies in patient's serum, by histopathological examination of lymph nodes or tissue biopsy of skin, liver, or other affected organs, and by molecular detection of *Bartonella* DNA from patients' tissue fragments, CSF or blood (Regnery et al. 1992a, Anderson et al. 1994, Raoult et al. 1994, Dalton et al. 1995, Jalava et al. 1995, Maurin et al. 1997, 2002, Sander et al. 1998, La Scola & Raoult 1999, Avidor et al. 2001).

Sensitivity of IFA in the diagnosis of CSD varies between 84% and 95% using 1:64 titer in commercially available kits. Only 3% of healthy adults had higher titers to *B. henselae* (Regnery et al. 1992b, Dalton et al. 1995, Sander et al. 1998, La Scola & Raoult 1999, Maurin et al. 2002). *Bartonella* serology is limited by cross-reactions between the different species, and also between genera such as *Coxiella* and *Chlamydia* (La Scola & Raoult 1996, Maurin et al. 1997, 2002). Despite these limitations, IFA is the gold standard for the diagnosis of infection, present or previous. Sero-epidemiological studies' primary aim is not to make a diagnosis of active infection, but to show the potential exposure of human or animal populations to an infectious agent. Despite potential limitations in surveys, such as false positive and false negative results, several sero-epidemiological studies have shown their value in alerting scientists as to the dispersion of pathogens, as outlined in this review.

Several antimicrobials have been used widely in the treatment of bartonellosis. The majority of clinical data on therapy has been obtained from small case reports or retrospective reviews (Schutze 2000, Baddour et al. 2005), although there are several in-vitro studies on an-

tibiotic susceptibility (Maurin & Raoult 1993, Rolain et al. 2000). There is only one double-blind placebo-controlled study using azithromycin in CSD, involving a small number of patients (Bass et al. 1998), in which 5-day therapy showed a benefit in lymph node regression in 30 days, as compared with placebo. The treatment response of IHI has been poor and most authors have recommended managing mild to moderate bartonellosis without antimicrobial therapy. Erythromycin, clarithromycin, azithromycin, doxycycline, either co-administered or not with rifampin, are antimicrobials clearly indicated mainly in immunocompromised patients with bacillary angiomatosis and CSD (Bass et al. 1998, Rolain et al. 2004), and the duration of therapy is 4-6 weeks. Steroid treatment may be used in some cases (Lerdluedeporn et al. 2003).

A retrospective evaluation of patients treated for *Bartonella* endocarditis concluded that effective antibiotic treatment should include a minimum of two weeks of an aminoglycoside (Raoult et al. 2003). The American Heart Association consensus on treating infective endocarditis, is ceftriaxone plus gentamicin, with or without doxycycline, when *Bartonella* is suspected, and doxycycline plus gentamicin when *Bartonella* endocarditis is confirmed (Baddour et al. 2005).

The preferred treatment for the acute phase of Carrion's disease has been chloramphenicol since the 1950s, but ciprofloxacin has been increasingly and successfully used (Maguiña et al. 2001). The treatment of choice for the eruptive phase of Carrion's disease is rifampin, although traditionally, the recommended treatment was intramuscular streptomycin. More recently, ciprofloxacin has been used with some success, and in vitro susceptibility has shown sensitivity of *B. bacilliformis* to most beta-lactam antibiotics, chloramphenicol, macrolides, tetracyclines, cotrimoxazol, aminoglycosides, and fluoroquinolones.

CONCLUSION

Bartonellae are widespread in nature. They have several host reservoirs, which are often bacteremic and may serve as a source of infection via arthropod vectors (for example, cat fleas, *Ctenocephalides felis*) or directly through licks, bites, or scratches. Human infection, except for *B. bacilliformis*, which is distinct in its epidemiology, often occurs irrespective of insect vectors. Such is the case in CSD, FUO, endocarditis, and bacillary angiomatosis, where contact with cats, often non-traumatic, is often reported by patients.

Recognition of neurological and ophthalmologic features of *Bartonella* infections, which are the most frequent and important complications of CSD, will lead to correct diagnosis and treatment. Also, the recognition of *Bartonella* spp. as one of the most important microorganisms implicated in blood culture negative endocarditis unassociated with previous antibiotic use will lead to earlier diagnosis and appropriate treatment. The knowledge of the important role of cats as a reservoir in human disease is cause for doctors and nurses to advise their patients of the potential danger of exposure for those with immunosuppressive conditions and those with valvulopathy and/or prosthetic heart valves.

The interest in the study of *Bartonella* has expanded in recent years in the world and can bring more information in several domains. Further investigations are needed to establish the real situation of *Bartonella* infections in Brazil, where the diversity of animal species, vertebrates and insect vectors, can be associated with different *Bartonella* spp., some of which may cause human illnesses with a high public health impact.

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