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section 8 Infectious diseases 1262 that patients with valvulopathy who have acute Q fever should re- ceive 12 months of doxycycline and hydroxychloroquine to pre- vent chronic Q fever. The duration of treatment for chronic Q fever is determined by monitoring the serum antibody titres to C. burnetii, although some authorities recommend lifelong therapy for chronic Q fever. In general, antibiotics can be discontinued when the IgA anti- body titre to phase I antigen is less than 1:200. The treatment of choice for chronic Q fever is doxycycline 100 mg twice daily and hydroxychloroquine 200 mg three times daily to maintain a plasma level of between 0.8 and 1.2 µg/ml. This regimen is given for 18 months. Photosensitivity to doxycycline is a potential ad- verse reaction and patients should be warned to take preventive measures. In addition, an ophthalmologist must examine the optic fundus every 6 months for chloroquine accumulation. We have used rifampicin 300 mg twice a day and ciprofloxacin 750 mg twice a day to treat patients with chronic Q fever. Rifampicin and doxy- cycline or tetracycline and trimethoprim/sulfamethoxazole have also been used to treat chronic Q fever. Antibody titres should be measured every 3 months for the first 2 years. A progressive de- cline in antibody titre reflects the successful treatment of chronic fever. Cardiac valve replacement may be necessary as part of the management of chronic Q fever. Many patients with granulomatous hepatitis due to Q fever have a prolonged febrile illness that does not respond to antibiotics. For these individuals treatment with prednisone 0.5 mg/kg has resulted in defervescence within 2 to 15 days. Once defervescence has oc- curred the dose of steroids is tapered over the next month. Q fever occurring during pregnancy should be treated with co- trimoxazole for the duration of the pregnancy. In one retrospective study this approach reduced obstetrical complications from 81 to 44%. There were no intrauterine fetal deaths in the co-trimoxazole- treated group. Those with a chronic Q fever serological profile should be treated with doxycycline and hydroxychloroquine for 1 year fol- lowing delivery. Prevention A formalin-inactivated C. burnetii whole-cell vaccine is protective against infection and has a low rate of side effects; 1% of vaccinees developed an abscess at the inoculation site and another 1% had a lump at this site 2 months after vaccination. The vaccine should be offered to those whose occupation places them at high risk for C. burnetii infection. Good animal husbandry practices are important in preventing widespread contamination

of the environment by C. burnetii. Prevention of zoonotic spread is best accomplished by isolating aborting animals for up to 14 days, raising feeding troughs to prevent contamination of feed by excreta, destroying aborted materials by burning and burying fetal membranes and stillborn animals, and wearing masks and gloves when handling aborted materials. Only seronegative pregnant animals should be brought into the facilities where research is to be done. In addition, only seronegative animals should be used in petting zoos. Blood donation should be suspended in outbreak areas for up to 4 weeks following cessation of the outbreak. FURTHER READING Angelakis E, et al. (2014). Emergence of Q fever arthritis in France.
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history, onset, response and reflection. Epidemiol Infect, 139, 1–12. Schneeberger PM, et al. (2014). Q fever in the Netherlands 2007–2010. What we have learned from the largest outbreak ever. Med Mal Infect, 44, 339–53. 8.6.43 Bartonellas excluding B. bacilliformis Bruno B. Chomel, Henri-Jean Boulouis,
Matthew J. Stuckey, and Jean-Marc Rolain ESSENTIALS Bartonellae are Gram-negative bacilli or coccobacilli belonging to the α-2 subgroup of Proteobacteria. A given Bartonella species usu- ally persists within a given mammalian host, with transmission be- tween hosts by haematophagous arthropods. A single species, such as B. henselae or B. quintana, can cause acute or chronic infection, with vascular, proliferative, or suppurative features depending on the host's immune response. Many new Bartonella species isolated from various mammals have been identified as zoonotic. Cat-scratch disease—caused by B. henselae and commonly asso- ciated with a cat scratch, presents with a discrete papule or vesicle typically developing at the site within a week, followed by regional lymphadenopathy, sometimes with fever and constitutional symp- toms. Disseminated infection can cause neuro-retinitis and (rarely) encephalopathy. Trench fever/Urban trench fever—caused by B. quintana; trans- mitted by the body louse and typically presents as an acute febrile illness with recurring (quintan) fever, often accompanied by severe headache and shin pain. Bacillary angiomatosis—caused by B. henselae or B. quintana, par- ticularly in immunocompromised patients (mainly those with HIV infection), and presents with the gradual appearance of numerous vascular tumours of the skin and subcutaneous tissues. Bacillary peliosis—reported mainly in immunocompromised pa- tients infected with B. henselae, it causes vascular proliferation in solid internal organs with reticuloendothelial elements. In peliosis

 hepatis there are multiple randomly-distributed blood-filled cavities throughout the liver. Bacteraemia and endocarditis—frequently 'culture-negative' and most commonly caused by B. quintana or B. henselae, but also by many other Bartonella species. Diagnosis of Bartonella infections is difficult because of the fas- tidious nature of these bacteria and their nonspecific clinical mani- festations. Diagnostic techniques include culture from blood and other tissues, detection of the organisms in lymph nodes or other organs by immunofluorescence, polymerase chain reaction amplifi- cation of Bartonella genes, and serology. Bartonella bacteria are susceptible to a wide range of anti- biotics in vitro, but there is poor correlation with in vivo efficacy. General recommendations are as follows: (1) cat-scratch disease—

symptomatic treatment only, with azithromycin in severe or com- plicated cases; (2) trench fever/urban trench fever—combination of doxycycline with gentamicin; (3) bacillary angiomatosis or peliosis— erythromycin; (4) endocarditis—gentamicin with ceftriaxone, with or without doxycycline. Bartonella quintana infections can be prevented by delousing, changing, and/or washing clothes. Pet cats and pet cat environment (bedding, and so on) should be treated regularly with flea control products to prevent B. henselae infection. Immunocompromised pa- tients should avoid cat scratches and exposure to cat fleas. Introduction Until the early 1990s, the genus Bartonella was composed of two spe- cies, B. bacilliformis, the agent of Carrión's disease (Chapter 8.6.44) and B. quintana, the agent of trench fever. In 1993, Brenner et al. proposed to unify Rochalimaea spp. within the Bartonella genus in the family of Bartonellaceae based on comparison of the 16SrDNA gene sequences. Similarly, Birtles et al. proposed the unification of the genus Grahamella within the genus Bartonella. Since then, many new species or subspecies of Bartonella have been isolated or detected from a wide range of terrestrial and flying mammals. More than 30 species have been described and many Candidatus Bartonella spp. still await to be either described (i.e. B. washoen sis) or isolated (i.e. B. merieuxii). Among these, at least 16 species or subspecies are zoonotic (capable of infecting both animals and people). Bartonella quintana infection in humans was first described during the First World War when more than a million soldiers were infected and got trench fever, mainly among the Russian, German, and British troops. Cat-scratch disease (CSD) was initially identified in 1931 in France by Debré et al. and clinically described in 1950. However, its agent, B. henselae, was not isolated until 1992 and its role in bacillary angiomatosis was demonstrated using molecular methods. In the 1980s, Afipia felis had been proposed as the aetio- logical agent of CSD, but it was later proven that this bacterium was an environmental contaminant. Aetiology and genetics The bacteria of the genus Bartonella are short, pleomorphic, fas- tidious aerobes that are oxidase and catalase negative. They are closely related phylogenetically to the genera Brucella, Agrobacterium and Rhizobium (Fig. 8.6.43.1). The 1.6 Mb genome of B. quintana was found to be a derivative of the 1.9 Mb genome of B. henselae. Prophages and horizontally acquired genomic islands have been identified in B. henselae, but are absent from B. quintana. Type IV secretion system located on plasmids in Bartonella might act as a powerful system to transfer genes laterally between bacteria living in a sympatric lifestyle in amoeba. As Bartonella have no major distinguishing phenotypic characteristics, identi- fication and phylogenetic classification are mainly based on gen- etic techniques. Many DNA regions and encoding gene sequences have been used, including the 16S rDNA gene, 16S-23S rRNA intergenic spacer region (ITS), citrate synthase gene (gltA), heat shock protein gene (groEL), RNA polymerase β-subunit gene (rpoB), genes encoding the PAP31 and 35-kDa proteins and cell division protein gene (ftsZ). A phylogenetic neighbour-joining tree resulting from comparison of sequences of the concatenated genes of Bartonella species is shown in Fig. 8.6.43.2. As suggested by La Scola et al., a new Bartonella isolate can be considered a new species if a 327-bp gltA fragment shares less than 96% sequence similarity with the existing species and if an 825-bp rpoB frag- ment shares less than 94% sequence similarity with the validated species. Epidemiology Worldwide, the most common Bartonella infection is CSD, caused by B. henselae. Human cases have been reported from several continents, including Europe, North and South America, North and South Africa, Asia, and Australia, and from most countries where presence of this infection was investigated. Domestic cats are the natural reservoir of B. henselae (but also B. clarridgeiae and B. koehlerae) and infection is highly prevalent in cats in- fested by fleas living in warm and humid climates. Transmission from cat to human mainly occurs by direct inoculation via a cat scratch. The role of cat bite as a source of infection is still questioned and transmission to

humans by cat flea or tick bite seems to be quite uncommon (less than 2% of cases). Flea faeces are likely the infective material that is inoculated through a cat scratch. Other Bartonella species have also been detected in cat fleas (B. clarridgeiae, B. koehlerae, and B. quintana), in rabbit fleas (B. alsatica) (Table 8.6.43.1), in various rodent fleas, sev- eral hard tick species, and recently in chiggers. B. tamiae was de- tected in chigger mites (genera Leptotrombidium, Schoengastia, and Blankarrtia) collected on wild rodents in Thailand and bed- bugs in Rwanda were polymerase chain reaction (PCR)-positive for B. quintana. Finally, biting flies seem to play an important role in the transmission of Bartonella species among ruminants (B. schoenbuschensis, B. chomelii, B. bovis, B. capreoli, candidatus B. melophagi) and bat flies are increasingly associated with bat- borne Bartonella species. B. quintana infections are transmitted by the body louse, Pediculus humanus. Outbreaks of trench fever are linked mainly with poor socioeconomic conditions and wars, which predispose to body louse infestation. B. quintana infections decreased after the World War I and re-emerged during the Second World War. More

section 8 Infectious diseases 1264 recently, there have been sporadic outbreaks of urban trench fever in Europe and the United States of America in homeless popula- tions and alcoholics. B. quintana has also been detected in head lice, especially in Africa. The epidemiology of the many other Bartonella species is still not well understood. They usually cause asymptomatic bacteraemia in reservoir hosts: B. henselae and B. clarridgeiae in cats, B. bovis in cattle, B. alsatica in rabbits, and B. tribocorum in rats. However, endocarditis cases have also been reported in dogs, cats, and cattle (Fig 8.6.43.3). Clinical features and pathology A remarkable feature of Bartonella is the ability of a single species to cause either acute or chronic infection with either vascular prolifera- tive or suppurative features. The pathological response to infection with Bartonella varies substantially with the host’s immune status. There have been few clinical studies employing a standard case def- inition, culture confirmation, and rigidly defined disease outcomes in patients with similar immunocompetence. 1.6 Mb Bq Bh Bm Bs MI Sm At Bj Rhp Cc Rp Rc Wp 1.9 3.3 3.3 7.6 6.7 5.6 9.1 5.5 4.0 1.1 Arthropod/ mammal associated Aquatic Plant associated Mammal/arthropod associated Arthropod/ associated 1.3 1.3 Size in Mb <0.2 0.5 1 2 3 4 5 6 7 8 9 Fig. 8.6.43.1 Variation in genome sizes and lifestyles in the α-proteobacteria. The phylogenetic relationships are shown for the 13 α-proteobacterial species for which complete genome sequence data are currently available. Genome structures, genome sizes, and host organisms are depicted graphically. Colours along branches indicate net loss (blue) and gain (red) of genes. Roots indicate nitrogen-fixing species that belong to the rhizobacteria. The size of the filled circles corresponds to the relative sizes of the individual replicons, with red indicating the main chromosomes in each species. Agrobacterium tumefaciens has a linear chromosome, represented by a short line. At, Agrobacterium tumefaciens; Bh, Bartonella henselae; Bj, Bradyrhizobium japonicum; Bm, Brucella melitensis; Bq, Bartonella quintana; Bs, Brucella suis; Cc, Caulobacter crescentus; Ml, Mesorhizobium loti; Sm, Sinorhizobium meliloti; Rc, Rickettsia conorii; Rhp, Rhodopseudomonas palustris; Rp, Rickettsia prowazekii; Wp, Wolbachia pipientis. Reprinted by permission from Macmillan Publishers Ltd: Batut J. et al. (2004). The evolution of chronic infection strategies in the α-proteobacteria. Nature Reviews Microbiology 2: 933–945, copyright © 2004.

1265 8.6.43 Bartonellas excluding B. bacilliformis B vinsonii berkhoffii B vinsonii vinsonii B vinsonii arupensis B alsatica B taylorii B rattimassiliensis B graharnii B elizabethae B tribocorum B quintana B phoceensis B henselae B koehlerae B doshiae B bovis B schoenbuchensis B birtlesii B bacilliformis B clarridgeiae dog318006 B rochalimae dog131 fox008 63 100 84 53 52 92 100 100

88 97 100 100 99 99 71 100 100 99 51 Fig. 8.6.43.2 Neighbour-joining tree of Bartonella species based on the combined gltA, rpoB, ftsZ, and
ITS sequence alignments. Reprinted from Henn JB et al. (2009). Infective endocarditis in a dog and the phylogenetic relationship of the associated “Bartonella rochalimae” strain with isolates from dogs, grey foxes, and a human. J Clin Microbiol 47: 787–90. Table 8.6.43.1 Species of Bartonella reported to date with epidemiological and clinical data Bartonella spp. Reservoir host Vector detection in arthropods Disease in humans First cultivation B. bacilliformis Human Sand fly (Lutzomyia spp.) CSD, END 1919 B. talpae Moles Unknown Unknown 1911 B. peromysci Unknown Unknown Unknown 1942 B. vinsonii subsp. vinsonii Canadian voles (Microtus sp.) Unknown, Ear mites? Unknown 1946 B. quintana Human, cats Human body louse (Pediculus humanus corporis) and fleas TF, BA, BAC, END 1961 B. henselae Cats, (dogs?) Cat Flea (Ctenocephalides felis) CSD, BA, BAC, LMF, END, PH, RET 1990 B. elizabethae Rodents Fleas END (1 case) 1993 B. grahamii Voles, rodents Fleas? RET (1 case) 1995 B. taylorii Rats Fleas? Unknown 1995 B. doshiae Voles Fleas? Unknown 1995 B. clarridgeiae Cats, (dogs?) Cat flea Ctenocephalides felis Unknown 1995 B. vinsonii subsp. berkhoffii Dogs, coyotes, grey foxes Fleas, ticks? END 1995 B. vinsonii subsp. arupensis Rodents, cattle Deer ticks? Fleas? BAC (1 case) 1999 B. tribocorum Rats Unknown Unknown 1998 B. koehlerae Cats Fleas END (1 case) 1999 (continued)

1266 section 8 Infectious diseases Trench fever Trench fever is also known as quintan fever or 5-day fever (because of its tendency to relapse on the fifth day), and Wolhynia fever (be- cause the disease was first observed by German medical officers on the East German front in Wolhynia). After the bite of the body louse the incubation period ranges generally from 15 to 25 days. However, in volunteers inoculated with a large volume of crushed infected lice, incubation was less than nine days. The illness varies widely from asymptomatic to severe. The classic clinical presenta- tion among troops was an acute febrile illness, often accompanied by severe headache and shin pain. The interval between attacks of pyrexia ranges from 4 to 8 days, but is usually 5 days. Trench fever often results in prolonged disability, but mortality is rare. The first 4 to 6 weeks of the illness are the most severe and, in a few cases, Bartonella spp. Reservoir host Vector detection in arthropods Disease in humans First cultivation B. alsatica Rabbit (Oryctolagus cuniculus) Fleas, ticks? END (2 cases), LMF (1 case) 1999 B. bovis (weissii) Cow (Bos taurus), cats? Biting flies Unknown 1999 B. washoensis Rodents, dogs Fleas MYOC (1 case) 2000 B. birtlesii Rats Unknown Unknown 2000 B. schoenbuchensis Roe deer (Capreolus capreolus) Deer keds (Lipoptena cervi, L. mazamae) BAC 2001 B. capreoli roe deer Deer keds (Lipoptena cervi) Unknown 2002 B. chomelii Cows (Bos taurus) Biting flies Unknown 2004 B. rattimassiliensis Rats Unknown Unknown 2004 B. phoceensis Rats Unknown Unknown 2004 B. australis Grey kangaroos (Macropus giganteus) Unknown Unknown 2007 B. tamiae Rodents? Unknown fatigue, myalgia, headache, rash 2008 B. rattaustraliani Rattus tunneyi Unknown Unknown 2009 Bartonella queenslandensis Melomys rat Unknown Unknown 2009 B. coopersplainsensis Rattus leucopus Unknown Unknown 2009 B. japonica Apodemus argenteus Unknown Unknown 2010 B. silvatica Apodemus speciosus Unknown Unknown 2010 B. jaculi greater Egyptian jerboa (Jaculus orientalis) Unknown Unknown 2013 B. calloscuiri plantain squirrel (Callosciurus notatus) Unknown Unknown 2013 B. pachyuromidis fat-tailed gerbil (Pachyuromys duprasi) Unknown Unknown 2013 B. acomydis golden spiny mouse (Acomys russatus) Unknown Unknown 2013 B. senegalensis Unknown Ornithodoros sonrai Unknown 2013 B. florenciae Shrew (Crocidura russula) Unknown Unknown 2013 B. mayotimonensis Daubenton’s bat (Myotis daubentonii) Bat flies END (2009) (1 case) 2014 B. naantaliensis Daubenton’s bat (Myotis daubentonii) Bat flies Unknown 2014 B. dromedarii camels (Camelus dromedarius) Hyalomma

ticks? Unknown 2014 B. ancashensis Humans Sandflies? Verruga peruana 2015 B. apis Honey bees (Apis mellifera) symbiont Unknown 2016 B. koehlerae subsp. boulouisii Puma (felis concolor) Fleas? Unknown 2016 B. koehlerae subsp. bothieri Bobcat (Lynx rufus) Fleas? Unknown 2016 Candidatus B. melophagi Sheep (Ovis aries) Sheep ked (Melophagus ovinus) Pericarditis Fatigue, muscle pain (2009) 2007 Candidatus B. thailandensis Red spiny rat Maxomys surifer Unknown Unknown 2009 Candidatus B. antechini Mardos/Yellow-footed antechinus (Antechinus flavipes) Fleas (Acanthopsylla jordani) and ticks (Ixodes antechini) Unknown 2011 Candidatus B. merieuxii Canids (dogs, Jackals) Fleas? Unknown 2012 Candidatus B. hemsundetiensis Daubenton's bat (Myotis daubentonii) Bat flies Unknown 2015 BA, bacillary angiomatosis; BAC, bacteraemia; CSD, cat-scratch disease; END, endocarditis; LMF, lymphadenopathy; MYOC, myocarditis; PH: peliosis hepatis; RET, retinitis; TF, trench fever. Table 8.6.43.1 Continued

1267 8.6.43 Bartonellas excluding B. bacilliformis chronic fever, anaemia, loss of weight, and neuropsychiatric symp- toms develop over time. Cat-scratch disease (CSD) CSD is a common infection that is seasonal throughout the world. Cats are the main reservoir of B. henselae, and the bacterium is trans- mitted between cats by the cat flea Ctenocephalides felis. Depending on the clinical manifestations, CSD has been characterized in two forms: (1) classic typical clinical CSD with lymphadenopathy and a history of a cat scratch and/or bite, and (2) atypical CSD. Classic CSD usually occurs in children and young adults but can also affect elderly people. Most patients with typical CSD remain afebrile. The main clinical manifestations in an immunocompetent host appear approximately two weeks after inoculation, although B. henselae DNA can be isolated from the peripheral blood of patients as long as four months after infection. One-third of the patients present with a history of fever lasting from 0 to 70 days (mean 14.8 days) with a maximum temperature between 37.9°C and 42.0°C. The localiza- tion of lymphadenopathy is mainly axillary, cervical, or submaxil- lary, that is, the lymph nodes that usually drain the area where the cat scratch occurs (Fig. 8.6.43.4). Lymphadenopathy can sometimes last for months, and in a few cases can be prolonged for as long as 12 to 24 months. General symptoms including malaise, headache, convulsion, sore throat, otalgia, vomiting, diarrhoea, anorexia, and tiredness can persist for long durations. B. henselae has also been identified in skin biopsy specimens of patients with CSD at the pri- mary site of inoculation. Atypical CSD occurs in a minority of cases, most of whom have se- vere systemic symptoms indicating disseminated infection. Patients with atypical CSD can have prolonged fever (>2 weeks), myalgia, arthralgia/arthropathy, malaise, fatigue, weight loss, splenomegaly, neuroretinitis, encephalopathy, and Parinaud's oculoglandular syndrome. This syndrome appears to be the most common ocular complication of CSD, affecting approximately 5% of symptomatic patients. Bacteria from an infected cat are inoculated indirectly into the eye rather than by direct contact through a scratch. Two- thirds of patients with neuroretinitis have evidence of past infection with B. henselae. Other Bartonella species causing retinitis include B. quintana, B. grahamii, B. clarridgeiae, and B. elizabethae. Retinitis is typically stellar; other ocular lesions include optic disc oedema and macular star formation, loss of vision with central scotoma, and glaucoma (Fig. 8.6.43.5). The onset of neurological complications varies from a few days to 2 months after the onset of lymphadenopathy and tends to occur more often in older school-age children. Symptoms include head- ache, malaise, lethargy lasting for one to several weeks, impaired consciousness, and acute hemiplegia. Bacillary angiomatosis Bacillary angiomatosis, also called epithelioid angiomatosis, is a vascular proliferative disease most often involving the skin, which mainly occurs in immunocompromised patients, especially HIV- infected individuals in an advanced stage of AIDS (<40 CD4 cells/ ml). Without appropriate therapy, infection spreads

systemic- ally, can involve virtually any organ, and is usually fatal. Rarely, it can also affect immunocompetent patients. Both B. henselae and B. quintana are considered aetiological agents. In the case of B. quintana infection, lesions are subcutaneous and/or osteolytic, Fig. 8.6.43.3 Vegetative endocarditis on the aortic valve of a dog. Courtesy of B. Chomel. Fig. 8.6.43.4 Axillary lymphadenitis in cat-scratch disease. Fig. 8.6.43.5 Stellar retinitis due to B. henselae. Courtesy of Dr M. J. Dolan.

section 8 Infectious diseases 1268 whereas peliosis hepatis is characteristic of B. henselae infection. Bacillary angiomatosis is manifested by the gradual appearance of numerous brown to violaceous or colourless vascular tumours of the skin and subcutaneous tissues, numbering a few to several hun- dred and varying in size from a few millimetres to several centi- metres. Three morphologically distinct cutaneous lesions have been described: (1) pyogenic granuloma-like lesions—the most common type, (2) subcutaneous nodules, and (3) hyperpigmented indurated plaques. The clinical differential diagnosis includes pyogenic granuloma, haemangioma, subcutaneous tumours, and Kaposi's sarcoma. The skin lesions are very similar to those re- ported for verruga peruana, the chronic form of Carrión's disease. Bacillary angiomatosis lesions can also involve the bone marrow, liver, spleen, or lymph nodes. Bacillary peliosis Bacillary peliosis is a condition affecting solid internal organs with reticuloendothelial elements, especially the liver, in which bacillary peliosis causes vascular proliferation of sinusoidal hepatic capil- laries resulting in blood-filled spaces (peliosis hepatis). The spleen, abdominal lymph nodes, and bone marrow can also be affected. The disease was first described in patients with tuberculosis and ad- vanced cancers and was associated with the use of anabolic steroids. It has also been reported in organ transplant recipients and HIV- infected patients with B. henselae. Bacteraemia and endocarditis Infection due to B. quintana should be suspected in homeless, indi- gent, or chronic alcoholic patients with culture-negative endocar- ditis, especially those with a long-standing valve lesion. B. quintana bacteraemia has also been reported in patients without endocar- ditis. Evidence of Bartonella endocarditis was found in 0.5–12% of all patients diagnosed with endocarditis tested at reference centres in different countries in the Old World, decreasing from north to south. Among human cases of Bartonella endocarditis in Europe, 75% were associated with B. quintana and 25% with B. henselae. In North Africa, most cases were caused by B. quintana, which is also responsible for asymptomatic, prolonged, and intermittent bacter- aemia in homeless people in cities both in Europe and in the United States of America. Endocarditis caused by B. henselae should be suspected in patients with previous valve disease and culture-negative endocarditis, espe- cially those who have contacts with cats. Endocarditis and/or bacteraemia caused by other Bartonella species is uncommon. B. elizabethae, B. vinsonii subsp. berkhoffii, B. vinsonii subsp. arupensis, B. koehlerae and B. alsatica, B. mayotim onensis have been isolated or detected from heart valves of patients with culture-negative endocarditis. One case of myocarditis has been attributed to B. washoensis. Prolonged fever Prolonged fever (>15 days) might occur in patients with atypical CSD. Prolonged fever without lymphadenopathy or fever of un- known origin has been described in several paediatric cases of CSD. Diagnosis Diagnosis is difficult because of the fastidious nature of Bartonella and the nonspecific clinical manifestations. Diagnostic techniques include culture and detection of organisms in lymph nodes by im- munofluorescence, molecular techniques including PCR, and ser- ology. Table 8.6.43.2 presents the most common clinical features caused by Bartonella and the best techniques for their identification, and Fig. 8.6.43.6 presents the current diagnostic strategy. Specimen collection Various specimens, especially serum, blood, biopsy specimens, and arthropods, are useful. They should be sampled as soon as possible after the onset

of disease. For serological diagnosis, serum samples should be collected early and during convalescence two to three weeks later. Serum samples can be stored easily at −20°C or below for long periods without degradation of antibodies. Blood should be sampled before antimicrobial therapy either in citrate-containing vials for culture in cell monolayers or in ethylenediaminetetraacetic acid (EDTA) for culture on blood agar or for PCR techniques. EDTA should be avoided for cell culture since it leads to detachment of cell monolayers. Biopsies of lymph nodes, cardiac valves, vascular aneur- ysms, or grafts should be taken in two parts, one in absolute alcohol for histopathology and immunodetection and another frozen and Table 8.6.43.2 Clinical manifestations and diagnostic methods for Bartonella infections in humans Disease in humans Commonly isolated Rarely isolated Specimen Methods Cat-scratch disease B. henselae Lymph nodes PCR, serology Endocarditis B. henselae, B. quintana B. elizabethae, B. koehlerae, B. vinsonii subsp. berkhoffii, B. vinsonii subsp. arupensis, B. alsatica, candidatus B. mayotimonensis Blood, serum, valves PCR, serology Retinitis B. henselae B. grahamii Serum, aqueous humour PCR, serology Bacillary angiomatosis B. henselae, B. quintana Blood, serum, cutaneous biopsy PCR Bacteraemia B. quintana B. henselae, B. vinsonii subsp. arupensis, B. rochalimae, B. doshiae, B. schoenbuschensis, B. tribocorum, B. tamiae, B. vinsonii subsp. vinsonii Blood, serum PCR, serology Peliosis hepatis B. henselae Blood, serum, hepatic biopsy PCR, serology Osteomyelitis B. henselae B vinsonii subsp. berkhoffii (in a cat) Blood, serum, bone biopsy PCR, serology Trench fever B. quintana Blood, serum PCR

1269 stored at −70° C in a sterile vial for culture and PCR analysis. These methods can be also used to detect Bartonella in various arthro- pods including ticks, lice, and fleas (xenodiagnosis). The arthropod should be disinfected with iodinated alcohol and then crushed in medium before being inoculated into a shell vial for culture or pro- cessing using molecular methods. Arthropods can be easily stored dry in a box and sent by mail to a reference centre for analysis. Direct diagnosis Culture The most widely used methods for isolation are direct plating of sample material onto solid media, blood culture in broth, and cocultivation in cell cultures. Bartonella can be grown on blood agar at 35°C to 37°C in a 5% CO2 atmosphere, except for B. bacilliformis which should be grown at 28–30°C. Primary isolates in humans are typically obtained after 12 to 14 days, although an incubation period of up to 45 days can be necessary (Fig. 8.6.43.7). In animals, growth might occur in three to seven days (especially for cat and rodent isolates). Subculture in blood broth in shell vials is the most efficient culture method in human patients with endocarditis. Specimens are placed on human embryonic lung cells in shell vials and incubated at 37°C in an atmosphere of 5% CO2. Culture might be successful using blood samples, skin, lymph nodes, or other organ biopsy sam- ples. Lysis centrifugation and freezing have been shown to enhance the recovery of Bartonella from blood. However, despite improved culture methods, blood cultures might be negative if the patient has recently received antibiotics or if the organism is fastidious and/or re- quires special culture techniques. A Bartonella-Alphaproteobacteria growth medium has been developed and provides an improved method to isolate these fastidious microorganisms, especially from human and dog samples. MALDI-TOF mass spectrometry is an ac- curate and reproducible tool for the rapid and inexpensive identifi- cation of Bartonella species. Immunodetection Detection of Bartonella using specific antibodies has been achieved in various situations. Demonstration of microorganisms in valve tis- sues by Warthin–Starry staining (Fig. 8.6.43.8) is a classic criterion Serum Blood Arthropods Biopsies Samples Direct diagnosis Immunodetection PCR Culture IHC IF CA IF Elisa WB analysis PCR Serology Indirect diagnosis Fig. 8.6.43.6 Strategy for the diagnosis of Bartonella spp. infections Fig. 8.6.43.7 Colony morphology of B. henselae on Columbia 5% sheep

blood agar. Fig. 8.6.43.8 Warthin–Starry staining of a cardiac valve of a patient with B. quintana endocarditis. Arrow shows the clumps of bacilli. Magnification ×400. 8.6.43 Bartonellas excluding B. bacilliformis

section 8 Infectious diseases 1270 for the histological diagnosis of infective endocarditis. Direct immunological detection in lymph nodes has been reported in patients with CSD, for patients with peliosis hepatis, in red blood cells of bac- teraemic homeless people, in cardiac valves, and in skin biopsies. Immunohistochemistry is a convenient tool for detecting B. quintana in tissues, but specific antibodies are often not available. Molecular biology PCR is a convenient method for detecting Bartonella either in fresh (best) or in formalin-fixed and paraffin-embedded tissues (not as good and reliable). The most common target genes used for the de- tection and identification of Bartonella are the citrate synthase gene (gltA), the 16S RNA gene, the 16S–23S rRNA ITS, the 60-kDa heat shock protein (groEL), the RNA polymerase β-subunit gene (rpoB) and the pap31 gene. Although these methods are highly specific, their sensitivity varies according to sample type. Thus, the current strategy for the diagnosis of Bartonella infections is to use two dif- ferent target genes (e.g. ITS and gltA gene), complemented with a third gene (groEL or rpoB) if initial results are discordant. Samples should be considered positive only if at least two genes are positive and if sequences obtained give similar identification. Improvement of molecular methods might increase the test sensitivity, especially when using real-time PCR. The diagnosis of Bartonella endocarditis by real-time nested PCR assays performed on a LightCycler appar- atus (LCN-PCR) using serum was proposed, which can shorten the delay in diagnosis. For the typing and characterization of B. hense lae isolates, multilocus sequence typing is another method that groups bacteria based on comparison of nucleic acid sequences of 450–500 bp derived from the internal fragments of a number (typ- ically seven) of housekeeping genes. A molecular typing method based on the sequences of noncoding zones rather than sequences of housekeeping genes called multispacer typing has also been developed. Indirect diagnosis: Serology Serology is the only useful noninvasive method for the diagnosis of Bartonella infections, especially for CSD, bacteraemia, and endocar- ditis. The sensitivity of serological tests varies between laboratories, from nearly 100% to less than 30% depending on the method used for preparation of antigens. Sources of antigens for serology can be either whole-cell lysates or outer membrane protein preparations and, more recently, recombinant proteins. The most widely used serological test for diagnosis is the indirect fluorescence assay (IFA) to detect antibodies against B. henselae whole cells. An IgG anti- B. henselae antibody titre ≥1:64 is considered positive for infection when patients are tested at least two to three weeks after a suspected infection. Bartonella-associated endocarditis in humans and animals is usually associated with much higher IFA antibody titres (>1:800). False-negative results are due to either antigenic heterogeneity among B. henselae species or to other diseases such as mycobacterial infections, lymphoma, or Kaposi’s sarcoma. Cross-reactions have been infrequently reported either with other Bartonella species, or between Bartonella species and Coxiella burnetii or Chlamydia. Lepidi et al. have developed autoimmunohistochemistry, which is a peroxidase-based method with the patient’s own serum as the source of antibodies directed against the aetiological microorganism, for the diagnosis of infective endocarditis. The rate of detection of bacteria by autoimmunohistochemistry was significantly higher than that by culture but was similar to that by PCR. A more sophisticated serological method, western blot analysis after cross-adsorption, has been shown to be a powerful tool for the identification of Bartonella to the species level in cases of endocarditis (Fig. 8.6.43.9). Treatment In vitro susceptibility to antibiotics This can be performed in either eukaryotic cells or axenic media. Bartonella species are susceptible to a wide

range of antibiotics when they are grown axenically, including penicillin and cephalo- sporin compounds, aminoglycosides, chloramphenicol, tetracyc- lines, macrolide compounds, rifampicin, fluoroquinolones, and co-trimoxazole. However, these results correlate poorly with in vivo efficacy, because most antibiotics are not bactericidal, except for aminoglycosides. This has also been reported in cell-culture models for B. henselae in murine macrophage-like cells and for B. quin tana in red blood cells. In vivo data have demonstrated the benefit of a combination of doxycycline with gentamicin in the treatment of infections, including endocarditis and bacteraemia in home- less individuals. Mutations in the 23S RNA gene and insertion of Fig. 8.6.43.9 Western blot of a patient with B. quintana endocarditis before (a) and after cross-adsorption with B. quintana (b) or B. henselae (c). Line 1: B. quintana; line 2: B. henselae; line 3: B. elizabethae; line 4: B. vinsonii subsp. berkhoffii; line 5: B. alsatica.

1271 nine aminoacids in the L4 ribosomal protein for B. henselae and B. quintana, respectively, can be selected in vitro by erythromycin. Mutations such as the A2059G transition have been detected dir- ectly in the lymph node of a patient with CSD, suggesting that natur- ally erythromycin-resistant strains may infect humans. Trench fever Most cases of trench fever were reported before the antibiotic era. However, successful treatment with tetracycline or chloram- phenicol was reported during the Second World War. In cases of urban trench fever, patients with chronic B. quintana bacteraemia should be treated with gentamicin (3 mg/kg intravenously once a day) for 14 days and with doxycycline (200 mg/day orally once a day) for 28 days. Patients with chronic bacteraemia should be carefully evaluated for endocarditis, which requires prolonged therapy under close monitoring. CSD Cases of CSD typically do not respond well to antibiotic therapy. Management consists of analgesics for pain, follow-up, and drainage when necessary. Patients who do not improve clinically benefit from excision of affected lymph nodes and investigation for coinfection such as Mycobacterium tuberculosis and/or lymphoma. The only double-blind placebo-controlled study for the treatment of CSD with azithromycin in immunocompetent patients showed only a faster reduction of their lymph node volume as compared to pla- cebo. Thus, the current recommendation for the treatment in mild to moderately ill immunocompetent patients with CSD is no anti- biotic treatment. Treatment with azithromycin could help patients with bulky lymphadenopathy or those with complicated CSD with retinitis and central nervous system disease. Endocarditis Effective antibiotic therapy for suspected Bartonella endocarditis should include an aminoglycoside (gentamicin) for at least 14 days together with ceftriaxone with or without doxycycline for 6 weeks to achieve a bactericidal effect. Valve replacement is necessary in most patients due to the extensive damage. Bacillary angiomatosis and peliosis hepatis Erythromycin is the antibiotic of choice for bacillary angiomatosis and peliosis hepatis. Treatment should be continued for at least three months for bacillary angiomatosis and four months for peliosis hepatis. Longer treatment should be given in HIV-infected and im- munocompromised patients. An in vitro model of B. quintana cul- tured in endothelial cells has shown that erythromycin acts mainly antiangiogenically rather than as an antibiotic, explaining the often dramatic response to this antibiotic in bacillary angiomatosis. Bacillary peliosis hepatis responds to antibiotics more slowly than cutaneous bacillary angiomatosis, but hepatic lesions usually im- prove after several months of treatment. Relapses of peliosis hepatis and bacillary angiomatosis lesions in bone and skin have fre- quently been reported, mainly in severely immunocompromised HIV-infected patients. Finally, patients who have relapses after the recommended treatment should receive secondary prophylactic antibiotic treatment with erythromycin or doxycycline as long as they are immunocompromised. Prevention B. quintana infections can be prevented by delousing, changing, and/or washing clothes. Pet cats and pet cat environment (bedding, and so on) should be treated

regularly with flea control products to prevent B. henselae infection. Immunocompromised patients should avoid cat scratches and exposure to cat fleas. Only seronega- tive cats should be kept by immunocompromised people and regu- larly treated with flea preventatives. For other zoonotic Bartonella species, a better understanding of their epidemiology is needed to be able to apply effective prevention strategies. For instance, the modes of contamination of humans by B. alsatica, B. tamiae or B. vinsonii subsp. berkhoffii have not been elucidated. Conclusions Bacteria of the genus Bartonella are responsible for an increasing number of emerging or re-emerging infections worldwide and can present a wide clinical spectrum, from benign and self-limited in- fections to severe and life-threatening diseases. Consequently, diag- nosis and treatment of these infections should be adapted to each clinical situation, to the species involved, and to whether the disease is in an acute or chronic stage. FURTHER READING Alsmark CM, et al. (2004). The louse-borne human pathogen Bartonella quintana is a genomic derivative of the zoonotic agent Bartonella henselae. Proc Natl Acad Sci U S A, 101, 9716–21. Angelakis E, et al. (2010). Bartonella henselae in skin biopsy specimens of patients with cat-scratch disease. Emerg Infect Dis, 16, 1963–5. Batut J, Andersson SG, O’Callaghan D (2004). The evolution of chronic infection strategies in the alpha-proteobacteria. Nat Rev Microbiol, 2, 933–45. Birtles RJ, et al. (1995). Proposals to unify the genera Grahamella and Bartonella, with descriptions of Bartonella talpae comb. nov., Bartonella peromysci comb. nov., and three new species, Bartonella grahamii sp. nov., Bartonella taylorii sp. nov., and Bartonella doshiae sp. nov. Int J Syst Bact, 45, 1–8. Biswas S, Raoult D, Rolain JM (2006). Molecular characterization of resistance to macrolides in Bartonella henselae. Antimicrob Agents Chemother, 50, 3192–3. Boulouis HJ, et al. (2005). Factors associated with the rapid emergence of zoonotic Bartonella infections. Vet Res, 36, 383–410. Breitschwerdt EB, et al. (2010). Bartonellosis: an emerging infectious disease of zoonotic importance to animals and human beings. J Vet Emerg Crit Care (San Antonio), 20, 8–30. Brenner DJ, et al. (1993). Proposals to unify the genera Bartonella and Rochalimaea, with descriptions of Bartonella quintana comb. nov., Bartonella vinsonii comb. nov., Bartonella henselae comb. nov., and Bartonella elizabethae comb. nov., and to remove the family Bartonellaceae from the order Rickettsiales. Int J Syst Bact, 43, 777–86. Chomel BB, et al. (1996). Experimental transmission of Bartonella henselae by the cat flea. J Clin Microbiol, 34, 1952–6. Chomel BB, et al. (2009). Ecological fitness and strategies of adaptation of Bartonella species to their hosts and vectors. Vet Res, 40, 29. 8.6.43 Bartonellas excluding B. bacilliformis

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