International Journal of Antimicrobial Agents xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Review

Pathogenicity and treatment of Bartonella infections

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ARTICLE INFO

Article history:
Received 20 March 2014
Accepted 30 April 2014

Keywords:
Bartonella spp.
Treatment
Pathogenicity

ABSTRACT

Bartonella spp. are responsible for emerging and re-emerging diseases around the world. The majority of human infections are caused by *Bartonella henselae*, *Bartonella quintana* and *Bartonella bacilliformis*, although other *Bartonella* spp. have also been associated with clinical manifestations in humans. The severity of *Bartonella* infection correlates with the patient's immune status. Clinical manifestations can range from benign and self-limited to severe and life-threatening disease. Clinical conditions associated with *Bartonella* spp. include local lymphadenopathy, bacteraemia, endocarditis, and tissue colonisation resulting in bacillary angiomatosis and peliosis hepatis. Without treatment, *Bartonella* infection can cause high mortality. To date, no single treatment is effective for all *Bartonella*-associated diseases. In the absence of systematic reviews, treatment decisions for *Bartonella* infections are based on case reports that test a limited number of patients. Antibiotics do not significantly affect the cure rate in patients with *Bartonella* lymphadenopathy. Patients with *Bartonella* spp. bacteraemia should be treated with gentamicin and doxycycline, but chloramphenicol has been proposed for the treatment of *B. bacilliformis* bacteraemia. Gentamicin in combination with doxycycline is considered the best treatment regimen for endocarditis, and erythromycin is the first-line antibiotic therapy for the treatment of angioproliferative lesions. Rifampicin or streptomycin can be used to treat verruga peruana. In this review, we present recent data and recommendations related to the treatment of *Bartonella* infections based on the pathogenicity of *Bartonella* spp.

Introduction

Bartonella spp. are intracellular bacteria that cause prolonged intraerythrocytic bacteraemia in their hosts and are typically transmitted by haematophagous insects such as phlebotomine sandflies, human body lice and cat fleas, or via animal scratches and bites [1]. To date, more than 30 *Bartonella* spp. and several *Candidatus* spp. have been isolated from humans as well as from wild and domestic animals around the world (Table 1) [2,3]. The suspected role of ticks in the transmission of *Bartonella* spp. is supported by direct and indirect evidence [4–6]. A wide range of mammals serve as reservoirs for *Bartonella* spp., but humans are the only known reservoir for *Bartonella bacilliformis* and *Bartonella quintana* [1].

Bartonella henselae, *B. quintana* and *B. bacilliformis* are responsible for the majority of infections in humans [1,7]. The ability to cause acute or chronic infections and vascular proliferative or suppurative manifestations is a remarkable feature of *Bartonella* spp. The severity of clinical manifestations correlates with the patient's immune status. As a result, *Bartonella* spp. can persist in the blood of their hosts resulting in intraerythrocytic parasitism [1], and they are responsible for a number of diseases including Carrion's disease, cat-scratch disease (CSD), chronic lymphadenopathy, trench fever, chronic bacteraemia, endocarditis, bacillary angiomatosis, peliosis hepatis and neurological disorders [1]. Without treatment, *Bartonella* infections are associated with high mortality and the potential for relapse due to the existence of an intraerythrocytic phase that may provide a protective niche for the bacteria [7].

Owing to the variety of known clinical manifestations and localisations of *Bartonella* spp., no single treatment exists for all *Bartonella*-associated diseases. As a result, treatment approaches must be adapted to each species and clinical situation (Fig. 1) [1,7]. Moreover, clinical studies that include a standard case definition, culture confirmation, rigidly defined disease outcomes, and patients with similar host defences are limited. Clinical data related to the treatment of *Bartonella* infections are primarily based on case reports that test a limited number of patients. As a consequence, current recommendations for the treatment of *Bartonella* infections are based primarily on the clinical course and the immunological status of the patient and rely less on the infective species. The objective of this review is to present recent

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http://dx.doi.org/10.1016/j.ijantimicag.2014.04.006
0924-8579/

Table 1
Bartonella spp. reported to date: epidemiological and clinical data.

Bartonella spp.	First cultivation		Year of description	Reservoir host/vector	Human disease(s)
	Mammal	Area, country			
B. alsatica	Wild rabbit (*Oryctolagus cuniculus*)	Alsace, France	1999	Rabbit	Endocarditis, lymphadenopathy
B. australis	Gray kangaroo (*Macropus giganteus*)	Queensland, Australia	2007		Not described
B. bacilliformis	Human		1909	Human/sandfly	Oroya fever and verruga peruana
B. birtlesii	Mouse (*Apodemus* spp.)	Bodensee, Germany	2000	Rat	Not described
B. bovis (*B. weissii*)	Cow	Bissy, France	2002	Cow	Not described
B. capreoli	Roe deer (*Capreolus capreolus*)	Chizé, France	2002	Ruminant	Not described
B. chomelii	Domestic cattle (*Bos taurus*)	Loire-Atlantique and Nord, France	2004		Not described
B. clarridgeiae	Cat		1996	Cat/cat flea	Lymphadenitis
B. coopersplainsensis	Mottle-tailed rat (*Rattus leucopus*)	Queensland, Australia	2008		Not described
B. doshiae	Woodland mammal (*Microtus agrestis*)	UK	1995	Rat	Not described
B. elizabethae	Endocarditis patient	USA	1993	Rat	Endocarditis, neuroretinitis
B. grahamii	Woodland mammal (*Clethrionomys glareolus*)	UK	1995	Rat, insectivore	Neuroretinitis
B. henselae	Cat		1990	Cat/cat flea	Lymphadenitis, endocarditis, bacillary angiomatosis, bacillary peliosis, Parinaud's oculoglandular, neuroretinitis, osteomyelitis, arthropathy, bacteraemia with fever
B. koehlerae	Domestic cat	California, USA	1999	Cat	Endocarditis, lymphadenitis
B. peromysci	Mouse (*Peromyscus* spp.)		1995	Mice	Not described
B. phoceensis	Wild rat (*Rattus norvegicus*)	Marseille, France	2004		Not described
B. queenslandensis	Grassland melomys (*Melomys* spp.)	Queensland, Australia	2008		Not described
B. quintana	Human		1920	Human/body louse	Trench fever, endocarditis, bacillary angiomatosis, lymphadenitis
B. rattimassiliensis	Rat (*R. norvegicus*)	Marseille, France	2004		Not described
B. rattiaustraliensis	Tunney's rat (*Rattus tunneyi*)	Queensland, Australia	2008		Not described
B. rochalimae	Human	USA	2007		Bacteraemia, fever, splenomegaly
B. schoenbuchensis	Wild roe deer (*C. capreolus*)	Germany	2001	Ruminant/deer ked	Not described
B. talpae	Mole		1995	Mole	Not described
B. tamiae	Human	Khon Kaen, Thailand	2008		Febrile illness
B. taylorii	Woodland mouse (*Apodemus* spp.)	UK	1995	Rat	Not described
B. tribocorum	Wild rat (*R. norvegicus*)	France	1998		Not described
B. vinsonii subsp. *arupensis*	Cattle rancher	USA	1999	Dog, rodent/ticks	Bacteraemia, fever, endocarditis
B. vinsonii subsp. *berkhoffii*	Dog	USA	1995	Dog/ticks	Endocarditis
B. vinsonii subsp. *vinsonii*	Vole (*Microtus pennsylvanicus*)		1946	Vole/vole ear mite	Endocarditis, bacteraemia
B. washoensis	Human	USA	2000	Fleas	Myocarditis, meningitis
B. weissii	Domestic cat	USA	2000	Deer, elk, beef, cattle	Not described
Candidatus spp.					
B. mayotimonensis	Human	France	2010		Endocarditis
B. melophagi	Sheep	USA	2004	Sheep ked (*Melophagus ovinus*)	Bacteraemia
B. ancashi	Human	Peru	2013		Verruga peruana
B. merieuxii	Canids	Iraq	2012		Not described
B. antechini	Fleas and ticks	Australia	2011		Not described
B. thailandensis	Rodents	Thailand	2009		Not described

data and recommendations related to the treatment of *Bartonella* infections based on the pathogenicity of *Bartonella* spp.

Pathogenicity of *Bartonella* spp.

In humans, the infection cycle of *Bartonella* spp. is initiated by colonisation of the primary niche [8,9]. In this stage, the infection is usually controlled by the immune system and the clinical manifestations are characterised by local lymphadenopathy (i.e. associated with *B. henselae*, *B. quintana* and *Bartonella alsatica*) [1,10,11]. However, under certain poorly defined circumstances, the commensal relationship between reservoir-adapted *Bartonella* spp. and the host is imperfect, resulting in a stealth pathogen strategy [12]. As a result, *Bartonella* spp. are rapidly cleared from the blood after

Please cite this article in press as: Angelakis E, Raoult D. Pathogenicity and treatment of Bartonella infections. Int J Antimicrob Agents (2014), http://dx.doi.org/10.1016/j.ijantimicag.2014.04.006