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MINIREVIEW

Recommendations for Treatment of Human Infections Caused by *Bartonella* Species

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Members of the genus *Bartonella* are facultative intracellular bacteria belonging to the alpha 2 subgroup of the class *Proteobacteria* and are phylogenetically closely related to *Brucella* species (15, 73). Until 1993, only three diseases were known to be caused by *Bartonella* species: Carrion's disease (*Bartonella bacilliformis*), trench fever (*Bartonella quintana*), and cat scratch disease (CSD; *Bartonella henselae*). The genus now comprises *B. bacilliformis*, species of the former genera *Rochalimea* and *Grahamella* (14, 18), and additional, recently described species (Table 1). In mammals, each *Bartonella* species is highly adapted to its reservoir host; the bacteria can persist in the bloodstream of the host as the result of intraerythrocytic parasitism (49). Intraerythrocytic localization of *B. henselae* has been demonstrated in cat erythrocytes (88), and *B. bacilliformis* bacilli have been observed within erythrocytes during the acute phase of Carrion's disease (Oroya fever) (88). Bartonellae also have a tropism for endothelial cells, and intracellular *B. henselae* can be identified in endothelial cells infected in vitro (28), although intraendothelial cell bacilli have not been identified in vivo.

Bartonella species cause long-recognized diseases, such as Carrion's disease, trench fever, and CSD, and more recently recognized diseases, such as bacillary angiomatosis (BA), peliosis hepatis (PH), chronic bacteremia, endocarditis, chronic lymphadenopathy, and neurological disorders (Table 2) (73). A remarkable feature of the genus *Bartonella* is the ability of a single species to cause either acute or chronic infection and either vascular proliferative or suppurative manifestations.

The pathological response to infection with *Bartonella* spp. varies substantially with the status of the host immune system. Indeed, infection with the same *Bartonella* species (e.g., *B. henselae*) can result in a focal suppurative reaction (CSD in immunocompetent patients), a multifocal angioproliferative response (BA in immunocompromised patients), endovascular multiplication of the bacteria (endocarditis), or an exaggerated inflammatory response without evidence of bacteria in patient tissues (meningoencephalitis) (86).

Some of the diseases due to *Bartonella* species can resolve spontaneously without treatment, but in other cases, the disease is fatal without antibiotic treatment and/or surgery. The clinical situations are so different that a single treatment for all *Bartonella*-related diseases has not been identified, and the approach to treatment must be adapted to each species and clinical situation (49). Moreover, the database of clinical studies with a standard case definition, culture confirmation, rigidly defined disease outcomes, and patients with similar host defenses is very limited. Thus, case reports with a very limited number of subjects often serve to dictate therapy. The objective of this minireview is to summarize the antibiotic treatment recommendations for the different infections caused by *Bar-*

TABLE 1. Epidemiological and clinical data for species of the genus *Bartonella*

Bartonella species	Reservoir host	Disease in humans[a]	First cultivation (yr)	Reference(s)
B. bacilliformis	Human	Carrion's disease	1919	68
B. talpae	Mole	Unknown		14
B. peromysci		Unknown	1942	14
B. vinsonii subsp. *vinsonii*	Rodents	Unknown	1946	7
B. quintana	Human	TF, BA, BAC, END	1961	61
B. henselae	Cats	CSD, BA, BAC, END	1990	96
B. elizabethae	Rats	END (one case)	1993	27
B. grahamii		RET (one case)	1995	14
B. taylorii		Unknown	1995	14
B. doshiae		Unknown	1995	14
B. clarridgeiae	Cats	Unknown	1995	59
B. vinsonii subsp. *berkhoffii*	Dogs	END (one case)	1995	17
B. tribocorum	Rats	Unknown	1998	43
B. koehlerae	Cats	Unknown	1999	33
B. alsatica	Rabbit	Unknown	1999	42
B. vinsonii subsp. *arupensis*	Rodents	BAC (one case)	1999	107
B. bovis (*weissii*)	Cows	Unknown	2002 (1999)	12, 22
B. washoensis	Rodents	MYOC (one case)	2000	16
B. birtlesii	Rats	Unknown	2000	13
B. schoenbuchensis	Ruminant	Unknown	2001	29
B. capreoli	Ruminant	Unknown	2002	12

[a] Abbreviations: BAC, bacteremia; END, endocarditis; MYOC, myocarditis; RET, retinitis; TF, trench fever.

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TABLE 2. Human diseases caused by *Bartonella* spp.

Bartonella species	Human disease(s)
B. bacilliformis	Carrion's disease (acute Oroya fever and chronic verruga peruana)
B. henselae	CSD, BA, PH, endocarditis, bacteremia, neuroretinitis, encephalopathy
B. quintana	BA, endocarditis, trench fever, chronic bacteremia, pericarditis
B. vinsonii subsp. *berkhoffii*	Endocarditis
B. vinsonii subsp. *arupensis*	Bacteremia
B. elizabethae	Endocarditis
B. grahamii	Retinitis
B. washoensis	Myocarditis

tonella species. We have compiled the in vitro antibiotic susceptibility data and our knowledge of the in vivo efficacies of antibiotics for each clinical manifestation, and finally, we have summarized and ranked our treatment recommendations according to the Infectious Diseases Society of America (IDSA) practice guidelines (see Table 5) (51).

ANTIBIOTIC SUSCEPTIBILITIES OF *BARTONELLA* SPECIES

Culture of *Bartonella* spp. Because *Bartonella* spp. are facultative intracellular organisms, isolation can be performed in either cell cultures or axenic media with blood-enriched agar plates (63) (Fig. 1 and 2). However, *Bartonella* bacteria are very fastidious, and primary isolation is difficult, with detection of colonies only after 1 to 4 weeks of incubation on blood agar plates (63). The growth of subcultured isolates on blood agar plates is more rapid, usually yielding colonies after 3 to 5 days. Cell coculture systems have been reported to be more sensitive and allow more rapid growth of bartonellae than blood agar plates (63). Since 1992, several studies have reported on the isolation of *B. henselae* from the blood and lymph nodes of patients with CSD, with confirmation by serology, PCR, or culture (9, 71). However, isolation of *B. henselae* from the lymph nodes of CSD patients is very rare compared to the more frequent detection of *B. henselae* DNA in these patients by PCR assays (63, 109). At present, there is no optimal procedure for the isolation of *Bartonella* species; rather, several techniques and agars (e.g., cocultivation with eukaryotic cells, in addition to plating onto rabbit blood and chocolate agars) should be combined in order to isolate strains.

In vitro susceptibilities of *Bartonella* species to antibiotics. The results of susceptibility testing with *Bartonella* spp. are summarized in Table 3. Evaluation of susceptibilities to antibiotics has been performed either in the presence of eukaryotic cells or without cells, i.e., in axenic media. Use of these different methods of culture for the determination of the bacteriostatic activities of antibiotics yielded similar results. Determination of antibiotic susceptibility in axenic media has been carried out either with solid media enriched with 5 to 10% sheep or horse blood or with liquid media (74, 97). It should be noted that the conditions required to grow *Bartonella* during susceptibility testing do not meet the standardized criteria established by NCCLS. Bacteria of the genus *Bartonella* are susceptible to many antibiotics when they are grown axenically, including penicillin and cephalosporin compounds, aminoglycosides, chloramphenicol, tetracyclines, macrolide compounds, rifampin, fluoroquinolones, and co-trimoxazole (74, 79). However, the in vitro and the in vivo antibiotic susceptibilities of *Bartonella* do not correlate well for a number of antibiotics; for instance, penicillin has no in vivo efficacy, despite the very low MICs observed in vitro.

In vitro antibiotic susceptibilities of *Bartonella* species cocul-

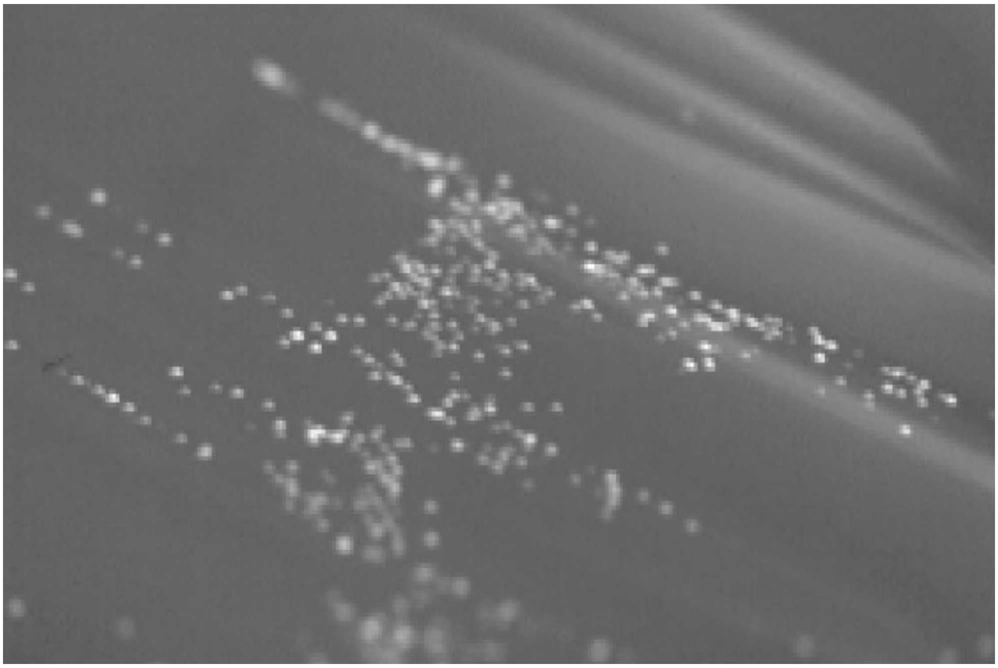

FIG. 1. Colonies of *B. quintana* on a blood agar plate.

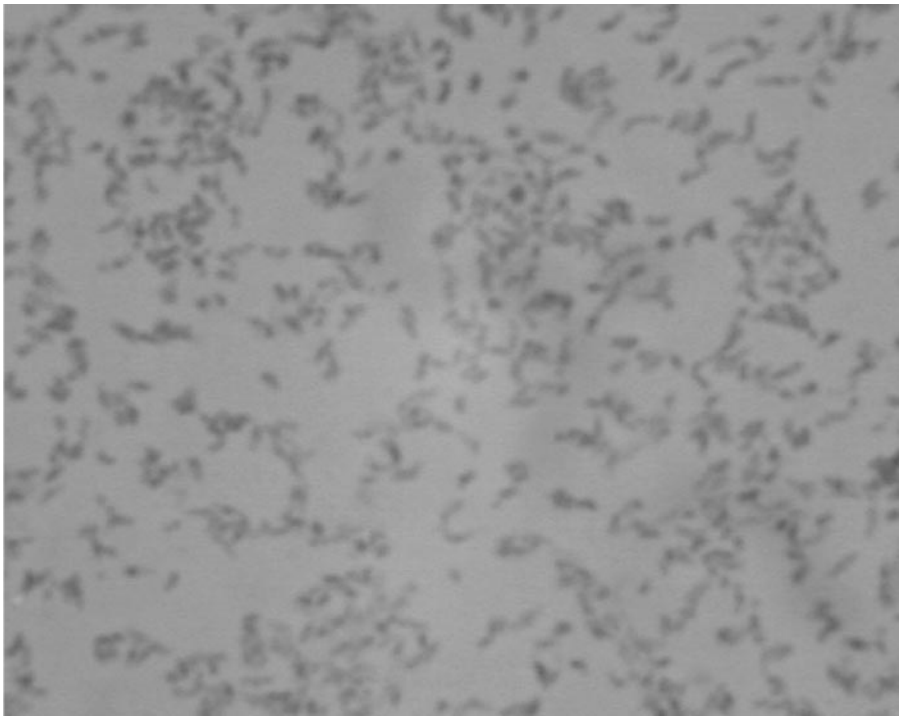

FIG. 2. *B. quintana* as viewed after Gimenez staining. Magnification, ×1,000.

tivated with eukaryotic cells have also been examined. As with agar-based susceptibilities, these studies demonstrated that *Bartonella* spp. are susceptible to many antibiotics in vitro (46). However, all of these antibiotics (48) had only bacteriostatic activity (47, 48). It was recently demonstrated in vitro that aminoglycosides alone are bactericidal against *Bartonella* species grown either in liquid medium (91) or in endothelial cells (78). With a recently established erythrocyte coculture model, it was found that most of the antibiotics tested (i.e., doxycycline, fluoroquinolone compounds, and beta-lactams) were not bactericidal against *Bartonella* (90). Gentamicin was bactericidal at 4 μg/ml, as was rifampin. At this concentration, gentamicin was shown to enter erythrocytes slowly and to reach a peak level of 0.26 μg/ml after 24 h. However, when the ability of gentamicin to kill extraerythrocytic *B. quintana* at the concentration of 0.26 μg/ml achieved in the erythrocyte was tested, it was found that gentamicin was not bactericidal, even after 96 h of incubation (90). We hypothesize that erythrocytes may be a reservoir for *B. quintana* and that the bactericidal activity of gentamicin that was observed occurs mainly when the bacteria emerge from the erythrocytes and are found extracellularly.

EVALUATION OF ANTIBIOTIC THERAPY IN FELINE ANIMAL MODELS

Feline animal models have been used to evaluate the efficacies of antimicrobial therapies for *B. henselae* infections. Regnery et al. (85) and Greene et al. (40) evaluated the efficacies of antibiotics during acute infection in cats inoculated with laboratory-cultivated *B. henselae*, whereas Kordick et al. (60) studied naturally infected cats with chronic infections. Regnery et al. (85) cultured the blood of the cats at intervals after experimental inoculation and determined that only tetracycline or erythromycin treatment significantly decreased the number of bacteria in the bloodstream. However, there were no significant differences among the four antibiotics with regard to the ultimate resolution of bacteremia (85).

In the study by Kordick et al. (60), various antibiotics, including doxycycline and amoxicillin, appeared to be effective in reducing the bacterial count in blood (40). However, subsequent bacteremia was observed after therapy was discontinued, suggesting that antibiotics did not eradicate the infection. Kordick et al. (60) reported that bacteremia in naturally, chronically infected cats was successfully cleared from only 9 of 14 cats treated with enrofloxacin and 2 of 8 cats treated with doxycycline. These reports are difficult to compare because the strain used as the inoculum for the experimental infection was grown on agar, and the virulence of these bacteria was probably different from that of *B. henselae* in the naturally infected cats. In addition, one trial treated acutely infected cats, while the other treated naturally, chronically infected cats. Acute experimental infections may be more susceptible to antibiotics than chronic infections in naturally infected cats; this may be similar to the situation in humans infected with *B. quintana* (35).

CLINICAL MANIFESTATIONS AND TREATMENT OF *BARTONELLA* INFECTIONS

MICs correlate poorly with the in vivo efficacies of antibiotics in patients with *Bartonella*-related infections (74). The lack of a bactericidal effect of antibiotics against *Bartonella* spp. and the different niches that *Bartonella* occupies in the human host,

TABLE 3. MICs for *Bartonella* sp. strains determined by the agar dilution technique with Columbia agar supplemented with 5% horse blood[a]

Drug group and drug	MIC (μg/ml)				
	B. henselae	*B. quintana*	*B. bacilliformis*	*B. vinsonii*	*B. elizabethae*
Aminoglycosides					
Amikacin	2–4	4–8	2–8	4	1
Gentamicin	0.12–0.25	0.12–2	1–2	0.5	0.12
Streptomycin	ND	ND	4	ND	ND
Tobramycin	0.5–1	0.5–4	2–4	2	0.25
Cephalosporins					
Cefotaxime	0.12–0.25	0.12–0.25	0.03–0.12	0.12	0.06
Cefotetan	0.25–0.5	0.12–0.5	2	1	1
Ceftazidime	0.25–0.5	0.25–0.5	0.12–0.25	0.25	0.5
Ceftriaxone	0.12–0.25	0.06–0.25	0.003–0.006	0.06	0.12
Cephalothin	8–16	8–16	4–8	16	8
Macrolides					
Azithromycin	0.006–0.015	0.006–0.03	0.015	0.015	0.006
Clarithromycin	0.006–0.03	0.006–0.03	0.015–0.03	0.03	0.015
Erythromycin	0.06–0.25	0.06–0.12	0.06	0.25	0.12
Roxithromycin	0.015–0.03	0.015–0.06	0.03	0.12	0.06
Telithromycin	0.003	0.006	0.015	ND	ND
Penicillins					
Amoxicillin	0.6–0.12	0.03–0.06	0.03–0.06	0.06	0.03
Oxacillin	1–2	1–4	0.25–0.5	1	4
Penicillin G	0.03–0.06	0.03	0.015–0.03	0.03	0.015
Ticarcillin	0.25	0.06–0.25	0.06–0.12	0.25	0.12
Quinolones					
Ciprofloxacin	0.25–1	0.5–2	0.25–0.5	1	0.5
Pefloxacin	4–8	2–8	1–2	4	2
Sparfloxacin	0.06	0.06–0.12	0.25	0.06	0.06
Tetracyclines					
Doxycycline	0.12	0.06–0.25	0.03–0.06	0.25	0.06
Miscellaneous					
Clindamycin	2–4	4–16	32–64	8	8
Colistin	4–16	4–16	16	8	4
Fosfomycin	16–32	32–64	8–16	16	16
Imipenem	0.5	0.25–1	0.5–1	2	0.25
Rifampin	0.03–0.06	0.06–0.25	0.003	0.12	0.03
TMP-SMX	1/5	0.25/1.25–1/5	0.4/2–0.8/4	1/5	0.5/2.5
Vancomycin	2–8	8–16	4–8	8	8

[a] Data are from previous reports (74, 75, 79, 89 90). Note that the in vitro MICs correlate poorly with the in vivo efficacies of antibiotics in patients with *Bartonella*-related infections (74), and thus, these MICs should not be used for the selection of antibiotics for patient treatment. MICs are the concentrations at which there is complete inhibition of growth. Abbreviations: ND, not determined; TMP-SMX trimethoprim-sulfamethoxazole.

e.g., sequestration in erythrocytes, may explain such discrepancies between in vitro and clinical data. For serious *Bartonella* infections, it is critical to use two antibiotics, each of which has good in vivo efficacy against *Bartonella*. This is particularly important if gentamicin is one of the drugs in the regimen, because the gentamicin protection assay with red blood cells infected in vivo, as well as the in vitro erythrocyte cell culture model, document that bartonellae residing within erythrocytes are protected from gentamicin (90, 93). Thus, with our current knowledge, addition of another antibiotic with good in vivo activity against *Bartonella* is crucial, because the two antibiotics may eradicate the bacteria in different niches in the host.

We present the relevant clinical studies for each clinical situation (Table 4) and recommendations for the treatment of human *Bartonella* infections (see Table 6), with recommendations ranked according to IDSA practice guidelines (Table 5) (51).

INFECTIONS DUE TO *B. HENSELAE*

Identification of *B. henselae* as the etiologic agent of CSD occurred only after decades of searching for the cause. In 1988, English and collaborators (34) isolated and cultured a bacterium that was named *Afipia felis* in 1992. This agent was initially considered the etiologic agent of CSD; however, the results of further studies failed to support this conclusion. However, serological evidence linking CSD with a different bacterium, *B. henselae*, was reported in 1992 (73); and in 1993, Dolan and colleagues (30) isolated *Rochalimaea henselae* (now named *B. henselae*) from the lymph nodes of patients with CSD. Nearly simultaneously, this species was also identified as a cause of bacteremia, BA, and PH in immunocompromised patients (57) and bacteremia and endocarditis in both immunocompromised and immunocompetent patients (5).

Cats are the main reservoir of *B. henselae*, and the bacterium

TABLE 4. Relevant clinical data on efficacy of antibiotic treatment of *Bartonella*-related infections[a]

Disease	Drug	Duration	No. of patients			Reference
			Total	Cured	Relapse	
Chronic bacteremia	No treatment		9	2	7	36
	Gentamicin + doxycycline	14 + 28 days	7	7	0	36
	Amoxicillin	5 days	1	0	1	65
	Ceftriaxone	10 days	2	2	0	65
BA-PH	Erythromycin	2–12 wk	8	5	3	38
		2–4 mo	4	3	1	55
		NI	1	1	0	102
		4–6 wk	1	1	0	105
		28–56 days	10	8	2	75
	Clarithromycin	8 wk	1	1	0	38
	Tetracycline	8 wk	1	1	0	38
		7–56 days	3	2	1	75
	Penicillin G	NI	2	0	2	54
	TMP-SMX	14 days	3	0	3	75
Endocarditis	Aminoglycoside > 15 days with or without another antibiotic	2–6 wk	82	74	8	83
	Other regimens	6 wk	19	13	4	83
Carrion's disease						
Oroya fever	Chloramphenicol with or without another antibiotic	10–14 days	65	62	3	66
	No treatment		16	2	14	39
	Chloramphenicol	7–14 days	10	10	0	39
Verruga peruana	Rifampin	10 days	46	37	9	66
	Streptomycin	10 days	9	5	4	66

[a] Abbreviations: NI, duration of treatment not indicated; TMP-SMX, trimethoprim-sulfamethoxazole.

is transmitted to cats by the cat flea (*Ctenocephalides felis*) (23). Most patients with CSD give a history of contact with a cat and receiving a scratch and/or bite (71). CSD is manifested by gradual regional lymph node enlargement, usually accompanied by a distal scratch and/or red-brown skin papule. The enlarged lymph node is often painful and tender. The infection is usually self-limited, with the frequent development of extensive regional lymph node enlargement that typically lasts 2 to 3 months and occasionally longer. The lymph node may suppurate if it is not drained; if drainage is necessary, needle aspiration is preferred. Most patients with typical CSD remain afebrile and are not systemically ill throughout the course of the disease (9, 21, 71). Lymphadenopathy occurs most often in nodes that drain the area where cat scratches usually occur, mainly the axilla, the neck, and the groin (21, 71).

Systemic or severe disease can complicate CSD in 5 to 14% of cases (21, 71). Atypical presentations include prolonged fever (>2 weeks), malaise, fatigue, myalgia and arthralgia, weight loss, splenomegaly, and Parinaud's oculoglandular syndrome (9). Encephalopathy and neuroretinitis are less common complications of CSD (9).

CSD typically does not respond to antibiotic therapy. The clinical manifestations of the disease may be due to an immunological reaction in the lymph nodes, and there are probably

TABLE 5. System for ranking recommendations in clinical guidelines recommended by IDSA[a]

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from one or more properly randomized, controlled trials
II	Evidence from one or more well-designed clinical trials, without randomization; from cohort or case-controlled analytic studies (preferably from more than one center); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

[a] Reprinted from reference 51 with permission.

few or no viable *Bartonella* bacilli by the time that a biopsy is performed. Indeed, although PCR assays with samples from lymph nodes are often positive at the time of acute disease, isolation of the bacteria from lymph nodes has been reported only rarely (30, 64, 109). Numerous reports have evaluated the effectiveness of many antimicrobial agents for the treatment of typical, uncomplicated CSD (9). Most investigators have observed no benefit with antibiotic treatment, whereas anecdotal reports have indicated that ciprofloxacin, rifampin, and co-trimoxazole may be effective. In a 1960 study reporting on the treatment of 83 cases of CSD, Spaulding and Hennessy (101) noted that they were impressed with the failure of any antibiotics to shorten the course of the illness. Margileth (70) retrospectively reviewed the effects of various antibiotics for the treatment of 268 patients with typical CSD. The mean duration of illness was 14.5 weeks for 66 patients without treatment and 14.5 weeks for 113 patients treated with antibiotics thought to be ineffective. In contrast, the mean duration of illness was 2.8 weeks for 89 patients treated with rifampin, ciprofloxacin, gentamicin, or co-trimoxazole.

The only prospective treatment trial, a double-blind, placebo-controlled study of azithromycin treatment of immunocompetent patients with uncomplicated CSD, was reported by Bass et al. (8). An 80% decrease in the initial lymph node volume was documented in 7 of 14 azithromycin-treated patients but in only 1 of 15 placebo-treated controls during the first 30 days of observation ($P = 0.026$) (8). There was no difference in any clinical outcome measurement except for the rate and degree of decrease of total lymph node volume as determined by sonographic documentation. At 30 days, patients treated with azithromycin had a significantly greater reduction in the total lymph node volume, as demonstrated by sonography, in comparison to the total lymph node volume of the placebo group (8). The investigators did not demonstrate any efficacy of azithromycin for the treatment of disseminated CSD, either for prevention of the evolution of localized CSD to disseminated disease or for prevention of complications such as encephalitis or endocarditis. Thus, a recommendation to treat immunocompetent CSD patients with azithromycin remains very premature at present.

For the reasons outlined above, it is not clear that antibiotic therapy is useful for the treatment of CSD in immunocompetent patients; and because antibiotic therapy adds the risk of adverse drug reactions and the generation of resistant flora, the current recommendation for the mild to moderately ill immunocompetent patient with CSD is no antibiotic treatment (Table 6, recommendation CIII). After evaluation of an adequate fine-needle aspirate has ruled out fungal or mycobacterial infection and malignancy, patients and parents should be reassured that the adenopathy is benign and that it will probably subside spontaneously within 2 to 4 months (72). Management consists of treatment with analgesics for pain and prudent follow-up. Treatment with an azithromycin regimen (500 mg orally [p.o.] on day 1 and 250 mg p.o. on days 2 to 5 as single daily doses) could be an alternative for patients with large, bulky lymphadenopathy (Table 6, recommendation BI) (8). The combination of doxycycline (100 mg p.o. or intravenously [i.v.] twice daily) with rifampin (300 mg p.o. twice daily) could also be an alternative. When CSD lymph nodes suppurate, needle aspiration is probably the best treatment, and the patient usually notes decreased pain within 24 to 48 h. If fluid reaccumulates, needle reaspiration may be needed (72).

Complicated CSD. Various antibiotic regimens have been used to treat patients with complicated CSD (retinitis, encephalopathy, and visceral forms) (56, 108). The combination of doxycycline (100 mg p.o. or i.v. twice daily) with rifampin (300 mg p.o. twice daily) has been successful in treating patients with retinitis (Table 6, recommendation AII) (56, 84, 108). If treatment is chosen for patients with central nervous system (CNS) disease, the combination of doxycycline and rifampin is preferred. The optimum duration of antibiotic therapy for immunocompetent patients with complicated CSD has not been determined. Of note, there is a marked difference between the dramatic clinical response to antibiotics observed in immunocompromised patients with CSD and the minimal response observed in immunocompetent patients.

INFECTIONS DUE TO *B. QUINTANA*

B. quintana is transmitted by the human body louse, and humans are the only known reservoir (76). An acute form (trench fever) and a chronic form (chronic bacteremia) of the disease have been reported in immunocompetent individuals (76).

Trench fever, also known as 5-day fever or quintan fever, is a manifestation of initial infection with *B. quintana* and is characterized by infection of human red blood cells. Detailed descriptions of the disease were first reported in infected troops during World War I (76). Clinical manifestations of trench fever range from asymptomatic infection to severe illness. The classical presentation reported among troops was that of a febrile illness of acute onset, often accompanied by severe headache, dizziness, and pain in the shins. A minority of patients with trench fever developed chronic infection, with or without attacks of fever and aching (20); some of these soldiers developed persistent bacteremia (76). More recently, *B. quintana* has been demonstrated to cause chronic bacteremia in homeless people (19, 35, 100). In a study performed in emergency rooms of university hospitals in Marseilles, France, 14% of homeless were found to be chronically bacteremic, some for several months, without any signs or symptoms of disease (19, 61).

Most cases of trench fever, the acute form of *B. quintana* bacteremia, were reported prior to the antibiotic era. There were no fatal cases of trench fever, and the clinical manifestations lasted for 4 to 6 weeks before full recovery. Aspirin was the most effective drug for the pain; and during World War II, soldiers with trench fever were "maintained in hospital no longer than necessary, then sent to convalescent depot where fresh air, good food and progressive exercise quickly restored them to full capacity so that they were able to return to duty" (44). During World War I, soldiers with trench fever cleared the infection in the absence of antibiotic treatment. However, successful treatment of some trench fever patients with tetracycline or chloramphenicol was reported after World War II, although these data remain anecdotal (10). Thus, it seems reasonable to prescribe doxycycline for such patients. In addition, we recommend that patients with the acute form of *B. quintana* bacteremia be treated with gentamicin (3 mg/kg of body weight i.v. once daily for 14 days), in combination with

TABLE 6. Guidelines and recommendations for the treatment of infections caused by *Bartonella* species[a]

Disease	Regimen for[a]: Adults	Regimen for[a]: Children	Strength of recommendation	Reference(s)
Typical CSD	No recommendation	No recommendation		56
	For patients with extensive lymphadenopathy, consider azithromycin at 500 mg p.o. on the first day and 250 mg p.o. on days 2 to 5 as a single daily dose	For patients with extensive lymphadenopathy, consider azithromycin at 10 mg/kg p.o. on day 1 and 5 mg/kg p.o. on days 2 to 5 as a single daily dose	BI	8, 84
Retinitis	Doxycycline at 100 mg p.o. BID for 4–6 wk and rifampin at 300 mg p.o. BID for 4–6 wk	Unknown	AII	56, 84
Trench fever or chronic bacteremia with *B. quintana*	Doxycycline at 200 mg p.o. QD for 4 wk and gentamicin 3 mg/kg i.v. QD for 2 wk	Unknown	AI	36
BA[b]	Erythromycin at 500 mg p.o. QID for 3 mo	Erythromycin ethylsuccinate p.o. at a total of 40 mg/kg/day in four divided doses (maximum total daily dose, 2 g/day) for 3 months	AII	58
	Or doxycycline at 100 mg p.o. BID for 3 mo		AII	58
PH[b]	Erythromycin at 500 mg p.o. QID for 4 mo	Erythromycin ethylsuccinate p.o. at 40 mg/kg total/day in four divided doses (maximum total daily dose, 2 g/day) for 4 mo	AII	58
	Or doxycycline at 100 mg p.o. BID for 4 mo		AII	58
Endocarditis	Suspected *Bartonella*, culture negative:			
	Gentamicin at 3 mg/kg/day i.v. for 14 days	Unknown	AII	83
	and ceftriaxone at 2 g i.v. or i.m. QD for 6 wk		BII	83
	with or without doxycycline at 100 mg p.o. or i.v. BID for 6 wk		BII	83
Endocarditis	Documented *Bartonella*, culture positive:			
	Doxycycline at 100 mg p.o. BID for 6 wk and		BII	83
	gentamicin at 3 mg/kg/day i.v. for 14 days[c]		BII	83
Carrion's disease				
Oroya fever	Chloramphenicol at 500 mg p.o. or i.v. QID for 14 days and another antibiotic (a beta-lactam is preferred)	Chloramphenicol at 50–75 mg/kg/day p.o. or i.v. divided into four doses for 14 days and another antibiotic (a beta-lactam is preferred)	AII	67
	Or ciprofloxacin at 500 mg p.o. BID for 10 days	Or ciprofloxacin in children 7–12 years 250 mg p.o. BID for 10d	BIII	—[d]
Verruga peruana	Rifampin at 10 mg/kg/day p.o. for 14 days	Rifampin at 10 mg/kg/day p.o. for 14 days (maximum total daily dose of 600 mg/day)	AII	67
	Or streptomycin at 15–20 mg/kg/day i.m. for 10 days		AII	67

[a] Abbreviations: BID, twice a day; QD, once a day; QID, four times a day.
[b] Longer treatment for HIV-infected and other immunocompromised patients (AII) (56).
[c] If gentamicin cannot be given, replace it with rifampin at 300 mg p.o. twice daily.
[d] Maguina, unpublished.

doxycycline (200 mg p.o. daily) for 28 days (Table 6, recommendation AI). Treatment of paucisymptomatic, persistent *B. quintana* bacteremia may be of importance for the prevention of endocarditis in these patients (35). A retrospective review of the treatment histories for patients with chronic bacteremia found that only those who were treated with doxycycline for 4 weeks and gentamicin for 14 days were cured, whereas those treated with beta-lactams or doxycycline alone were not (35). These results have been confirmed recently in a randomized, placebo-controlled clinical trial (36). In that study, homeless people with blood cultures positive for *B. quintana* were randomized to receive either no treatment (untreated controls) or a combination of gentamicin (3 mg/kg of body weight/day i.v. for 14 days) and doxycycline (200 mg/day p.o. for 28 days). Patients were evaluated by blood cultures, performed between day 28 (the end of treatment) and day 90 postinclusion. In the per-protocol analysis, eradication was obtained for seven of seven treated patients and two of nine untreated controls ($P =$

0.003). Consequently, patients with chronic *B. quintana* bacteremia or trench fever should be treated with gentamicin (3 mg/kg i.v. once daily) for the first 14 days, in addition to doxycycline (200 mg daily) for 28 days (Table 6, recommendation AI) (36). Doxycycline could be given either as a single daily dose of 200 mg every 24 h or as a twice-daily dose of 100 mg every 12 h. Patients with chronic bacteremia should be carefully evaluated for endocarditis, because the presence of this complication will necessitate a longer duration of therapy and closer monitoring. The gentamicin levels in patients with renal insufficiency, obesity, or increased fluid volume should be monitored closely; and a reduced total daily dose of gentamicin should be administered as a twice-daily dosing schedule to avoid the nephrotoxicity of the drug.

INFECTIONS DUE TO *B. HENSELAE* OR *B. QUINTANA*

Both *B. henselae* and *B. quintana* can cause endocarditis and can cause BA in immunocompromised hosts, such as human immunodeficiency virus (HIV)-infected patients (5, 57). Bacillary PH occurs in immunocompromised patients and is caused by *B. henselae*, but not *B. quintana* (Table 2) (57).

BA and PH. Severe, progressive, disseminated disease may occur in immunocompromised patients, especially those with HIV infection. Without appropriate therapy, infection spreads systemically and can involve virtually any organ, and the outcome is sometimes fatal (9).

BA is a vascular proliferative disease most often involving the skin, but it may involve other organs. The disease was first described in HIV-infected patients (102) and organ transplant recipients (50), but it can also rarely affect immunocompetent patients (105). The clinical differential diagnosis includes pyogenic granuloma, hemangioma, subcutaneous tumors, and Kaposi's sarcoma (76). The skin lesions are very similar to those reported for verruga peruana, the chronic form of Carrion's disease. BA lesions can also involve the bone marrow, liver, spleen, or lymph nodes (24, 54, 69, 77).

PH is defined as a vascular proliferation of sinusoidal hepatic capillaries resulting in blood-filled spaces in the liver. This disease was first described in patients with tuberculosis and advanced cancers and in association with the use of drugs such as anabolic steroids (53). *B. henselae* is now recognized as an infectious cause of PH in HIV-infected patients (73, 80). PH has also been reported in organ transplant recipients (1). PH can occur simultaneously with peliosis of the spleen, as well as BA of the skin, in HIV-infected patients (58, 64).

Antibiotic treatment of BA and PH has never been studied systematically. Two criteria must be met to achieve successful eradication of *Bartonella* infections in the immunocompromised patient: first, the specific strain of *B. henselae* and *B. quintana* infecting the patient must have excellent in vivo susceptibility to the prescribed antibiotic, and second, the treatment must be of sufficient duration to prevent relapse. The first patient with BA to be described was treated empirically with erythromycin, and the lesions resolved completely (102). Subsequently, erythromycin has become the drug of first choice and has successfully been used to treat many patients with BA (Table 4) (58, 105). Treatment of BA and PH with oral doxycycline (100 mg twice daily) has also been consistently successful (58). Lesions resolved in several patients treated with ceftriaxone or fluoroquinolone compounds (65, 96), but the progression of BA lesions in patients has been observed during treatment with ciprofloxacin (104). Additionally, a *Bartonella* species has been isolated from the blood or BA lesions of patients being treated with narrow-spectrum cephalosporins (55), nafcillin, gentamicin, and trimethoprim-sulfamethoxazole (but never from patients being treated with a macrolide, rifamycin, or a tetracycline) (57). We therefore do not recommend fluoroquinolones, trimethoprim-sulfamethoxazole, or narrow-spectrum cephalosporins for the treatment of BA or PH (58). Treatment failures have been reported with many different antibiotics, and these are usually attributable to a lack of susceptibility of *Bartonella* in vivo and/or an insufficient duration of therapy (58, 75).

The drug of choice for the treatment of BA is erythromycin given p.o. (500 mg p.o. four times daily) for 3 months (Table 6, recommendation AII), but i.v. administration should be used in patients with severe disease (58). Patients intolerant of erythromycin can be treated with doxycycline (100 mg p.o. or i.v. twice daily) (Table 6, recommendation AII) (52, 58, 81). The response to treatment appears to be equivalent whether erythromycin or doxycycline is prescribed (56). Combination therapy, with the addition of rifampin (300 mg p.o. twice daily) to either erythromycin or doxycycline, is recommended for immunocompromised patients with acute, life-threatening *Bartonella* infection. The intravenous route is especially important in cases of gastrointestinal intolerance or poor absorption. The combination of doxycycline and rifampin is preferred for the treatment of patients with CNS *Bartonella* infection because of the superior CNS penetration of doxycycline compared with those of the other first-line antibiotics.

The response to treatment can be dramatic in immunocompromised patients. In one patient who received a single 250-mg oral dose of erythromycin, blood cultures became sterile and a palpable subcutaneous lesion disappeared within hours (but recurred months later). More chronic lesions resolve more slowly, but after approximately 4 to 7 days of therapy, cutaneous BA lesions usually improve and resolve completely after 1 month of treatment (11). Bacillary PH responds more slowly than cutaneous BA, but hepatic lesions should improve after several months of treatment.

Relapses of PH and BA lesions in bone and skin have been reported frequently (38, 55, 62, 103). Relapses occur when antibiotics are given for a shorter duration (<3 months), especially in severely immunocompromised HIV-infected patients (58, 96). For this reason and from our extensive experience treating patients with BA and PH, we recommend that treatment be given for at least 3 months for BA and 4 months for PH (Table 6, recommendation AII) (25, 56). All immunocompromised patients with a *Bartonella* infection should receive antibiotic therapy (erythromycin 500 mg p.o. four times daily or doxycycline 100 mg p.o. twice daily); patients who have relapses after the recommended treatment should then receive secondary prophylactic antibiotic treatment with erythromycin (500 mg p.o. four times daily) or doxycycline (100 mg p.o. twice daily) as long as they are immunocompromised (56). Of note, AIDS patients receiving prophylaxis with a macrolide or rifamycin antibiotic for *Mycobacterium avium* complex infection appear to be protected from developing infections with *Bartonella* species (57). Some immunocompromised patients develop a potentially life-threatening Jarisch-Herxheimer-like reaction within hours after institution of antibiotic therapy (55). Physicians should advise patients of this possible treatment complication, and patients with severe respiratory and/or cardiovascular compromise should be monitored carefully following institution of antimicrobial therapy (56).

Endocarditis. Evidence of *Bartonella* infection was found in 3% of all patients diagnosed with endocarditis tested at reference centers in three different countries (73). *B. quintana* (32, 37, 82, 83, 98, 99), *B. henselae* (31, 37, 41, 82, 83), and other species, such as *Bartonella elizabethae* (27) and *Bartonella vinsonii* subsp. *berkhoffii* (92), have been isolated from individual patients with bacterial endocarditis. Of the *Bartonella* species, *B. quintana* is the one that most commonly causes endocarditis, followed by *B. henselae*. The first case of *Bartonella* endocarditis was reported in an HIV-infected homosexual man in 1993 (98). *B. quintana* endocarditis has subsequently been reported in three non-HIV-infected, homeless men in France (32). All three patients required valve replacements because of extensive valvular damage, and pathological investigation confirmed the diagnosis of endocarditis.

B. quintana endocarditis is most often observed in homeless people with chronic alcoholism and exposure to body lice and in patients without previously known valvulopathy. *B. henselae* endocarditis most often occurs in patients with known valvulopathy who have contact with cats or cat fleas (37).

Bartonella endocarditis is usually indolent and culture negative, and thus, diagnosis is often delayed, resulting in a mortality rate higher than that for some other forms of endocarditis. It was previously demonstrated (37) that patients with *Bartonella* endocarditis have a higher death rate and undergo valvular surgery more frequently than patients with endocarditis caused by other pathogens. Selection of an adequate treatment regimen is critical, even when *Bartonella* infection is suspected but not yet documented. Among 101 patients with *Bartonella* endocarditis recently described in a retrospective study (83), 82 received aminoglycosides for a mean of 15 ± 11 days with either a beta-lactam (64 cases) or other antibiotics (vancomycin, doxycycline, rifampin, or co-trimoxazole). Seventy-four of the 82 patients who received an aminoglycoside recovered, whereas 13 of 19 of those who received no aminoglycoside recovered ($P = 0.02$) (84). Among the patients treated with aminoglycosides, 65 of the 69 who recovered had received aminoglycosides for 14 or more days, whereas 9 of the 13 patients who recovered had been treated for less than 14 days ($P = 0.02$). Patients receiving an aminoglycoside were more likely to recover fully and, if they were treated for at least 14 days, were more likely to survive, confirming the important role of this antibiotic in the treatment of *Bartonella* endocarditis (83). These data strongly support the use of aminoglycoside therapy for at least 14 days for patients with suspected *Bartonella* sp. endocarditis (Table 6, recommendation AII). Aminoglycoside therapy should be accompanied by treatment with a beta-lactam compound, preferably ceftriaxone (which is especially important for patients for whom blood cultures are negative, to adequately treat other potential bacteria that cause culture-negative endocarditis, e.g., β-lactamase-producing *Haemophilus* spp.). Thus, we recommend that patients with suspected (but culture-negative) *Bartonella* endocarditis receive treatment with gentamicin for the first 2 weeks and ceftriaxone (Table 6, recommendation BII) with or without doxycycline (Table 6, recommendation BII) for 6 weeks (83).

Because chronic *B. quintana* bacteremia has been shown to be optimally treated with doxycycline plus gentamicin (36), in the absence of any prospective study for the treatment of documented *Bartonella* endocarditis, it is logical that the same regimen should be used for endocarditis when a *Bartonella* sp. has been identified as the causative agent. It is important that no difference in the frequency of surgery was observed in patients whether or not they were treated with aminoglycosides. This may be explained by the severity of valvular lesions at the time when the diagnosis of endocarditis is made (37, 83). Patients should be monitored closely, and the dose of gentamicin should be chosen and adjusted according to the renal function of the patient, with a twice-daily dosing schedule for patients with renal insufficiency or those at risk for the development of aminoglycoside-induced renal failure. If renal dysfunction precludes the use of gentamicin for documented *Bartonella* endocarditis, rifampin could be considered as the second drug to be added to doxycycline.

INFECTION DUE TO *B. BACILLIFORMIS*

Oroya fever (acute Carrion's disease). *B. bacilliformis* is a sandfly-transmitted *Bartonella* species (3) that is responsible for life-threatening septicemia with acute hemolysis known as Oroya fever (2). This infection occurs most commonly in the Andes of Peru, especially in immunologically naive people, such as tourists and transient workers (39, 68, 94, 95). Oroya fever results from the massive invasion of human red blood cells by *B. bacilliformis* and causes death in 40 to 85% of infected humans who do not receive treatment (45). In 35% of cases, Oroya fever is complicated by superinfections, primarily non-serovar Typhi *Salmonella enterica* and *S. enterica* serovar Typhimurium infections and sepsis caused by *Enterobacter*, *Staphylococcus aureus*, *Pseudomona aeruginosa*, and other organisms.

Before the antibiotic era, the only available treatment for the acute anemia of Oroya fever was blood transfusion, but the effectiveness of this treatment was poor and the mortality rate was high (about 80% of cases) (94). Penicillin G, chloramphenicol, tetracycline, and erythromycin have been used for the treatment of Oroya fever. Treatment with these drugs produces rapid defervescence, with disappearance of the organisms from the blood, usually within 24 h (10). However, because many patients suffer from secondary infections, especially salmonellosis and infections caused by other enteropathogenic bacteria, chloramphenicol has become the recommended antibiotic therapy (26, 106). In Peru, 14 of 16 (88%) patients with Oroya fever who were not treated died, but none of any of 10 patients who were treated with chloramphenicol died (Table 4) (39). In a large series of acute cases of Oroya fever reported recently, all 23 patients who received chloramphenicol with another antibiotic were cured, whereas 6 of 42 patients treated with chloramphenicol alone failed therapy and needed penicillin (3 patients) and 3 developed chronic verruga peruana lesions within the first 3 months of recovery after the acute phase (Table 4) (66). Therapeutic failures and persistent bacteremia have been reported when chloramphenicol was used, and successful treatment with this drug does not appear to eliminate the patient's risk for development of the eruptive phase of *B. bacilliformis* infection. Because chloramphenicol is effective in most but not all patients with Oroya fever, simultaneous treatment with another antibiotic (especially a beta-lactam compound) is recommended (Table 6, recommendation AII) (66). Trimethoprim-sulfamethoxazole, macrolides (roxithromycin), and fluoroquinolones (norfloxacin and ciprofloxacin) have also been used successfully in some patients (68). Fluoroquinolone compounds have been used successfully in the last 5 years in adults and children over age 6 years and represent an alternative to chloramphenicol for the treatment of Oroya fever (Table 6, recommendation BIII) (C. Maguina, unpublished data). Note that fluoroquinolones should be used with caution in children.

Verruga peruana. Among the native population of the Andes of Peru, Carrion's disease also presents as a chronic illness called "verruga peruana." The infection is characterized by benign cutaneous vascular lesions which typically consist of round papules that are frequently pruritic and bleeding, and the infection is accompanied by osteoarticular pain (6, 66, 68). Only 5% of patients with verruga peruana recall having had an acute febrile illness in the previous 3 months (66). *B. bacilliformis* can be isolated from blood cultures and can be observed in blood films in 13% of patients with verruga peruana, indicating that these patients are sometimes bacteremic (66).

Verruga peruana is caused by the same bacterium that causes Oroya fever, but chloramphenicol is ineffective treatment for this eruptive stage of infection with *B. bacilliformis* (68). The treatment used for verruga peruana has traditionally been streptomycin (15 to 20 mg/kg of body weight intramuscularly [i.m.] once daily) for 10 days (Table 6, recommendation AII), but the use of the i.m. route remains problematic, especially in children (66). Since 1975, rifampin has become the drug of choice for treatment of the eruptive phase of Carrion's disease (Table 6, recommendation AII) (66). In a recent study, 55 of 77 patients with the eruptive phase of Carrion's disease received antimicrobial therapy; 46 of the 55 patients received oral rifampin (10 mg/kg/day for 10 to 14 days) and 9 received i.m. streptomycin (15 mg/kg/day for 10 days). Thirty-seven (80%) of the 46 patients treated with rifampin had a good response, whereas 5 (56%) of the 9 patients treated with streptomycin had a good response (Table 4). The efficacy of rifampin has been found to be comparable to that of streptomycin, with the disappearance of cutaneous lesions within a month of therapy. However, failures of rifampin treatment have also been reported (68). Rapid resistance to rifampin can develop when rifampin is used alone, and thus, rifampin alone is not recommended for the treatment of any *Bartonella* infection except verruga peruana. More recently, ciprofloxacin at 500 mg p.o. twice daily for 7 to 10 days has been used with success for the treatment of adults with multiple eruptive-phase lesions, as has azithromycin (67).

Data for treatment during pregnancy are scarce. There are conflicting reports on the safety of chloramphenicol during pregnancy (4). Gray baby syndrome is seen in premature babies given chloramphenicol. Eight pregnant women with *B. bacilliformis* infection were evaluated in a study by Maguina and Gotuzzo (66); five of the women presented in the acute phase and three presented in the eruptive phase. Two of the five women in the acute phase died. Among the three surviving pregnant patients who were treated with chloramphenicol, one had an abortion with typhoid fever, the second had fetal demise, and the third delivered the baby without complications. Among the three pregnant women who had verruga peruana and who were treated with rifampin, the babies were born with no complications or lesions (66).

PERSPECTIVES

Well-designed clinical trials with numerous subjects, a standard case definition, and molecular biology assay and/or culture confirmation are needed in order to better define the optimum treatment for *Bartonella* infections. Multicenter clinical trials will be necessary in order to accrue a sufficient number of patients with *Bartonella* infections, such endocarditis, BA, and CSD.

CONCLUSION

Bacteria of the genus *Bartonella* are responsible for emerging and reemerging diseases worldwide and can present as illnesses ranging from benign and self-limited diseases to severe and life-threatening diseases. *Bartonella* infections present a unique treatment challenge because they are persistent and often relapse and they involve an intraerythrocytic phase that apparently provides a protective niche for the bartonellae. The extreme diversity of disease manifestations is dependent on the infecting species of *Bartonella* and on the immune status of the patient. Because there are only two reports of randomized clinical trials for the treatment of *Bartonella* infections, an unequivocal treatment for all *Bartonella* infections does not exist, and thus, antibiotic treatment recommendations differ for each clinical situation. Treatment of *Bartonella* infections should be adapted to each clinical situation, to the infecting *Bartonella* species, and to whether the disease is in the acute or the chronic form. It is important that when the more severe *Bartonella* infections are recognized, diagnosed, and treated in a timely manner, the outcome is usually favorable.

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