

# Outcome and Treatment of *Bartonella* Endocarditis

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**Background:** Endocarditis caused by *Bartonella* species is a potentially lethal infection characterized by a subacute evolution and severe valvular lesions.

**Objectives:** To evaluate the outcome of patients with *Bartonella* endocarditis and to define the best antibiotic regimen using the following measures: recovery, relapse, or death.

**Methods:** We performed a retrospective study on 101 patients who were diagnosed in our laboratory as having *Bartonella* endocarditis between January 1, 1995, and April 30, 2001. *Bartonella* infection was diagnosed using immunofluorescence with a 1:800 cutoff, polymerase chain reaction amplification of DNA, and/or culture findings of

*Bartonella* species from whole blood, serum, and/or valvular biopsy specimens. A standardized questionnaire was completed by investigators for each patient.

**Results:** Twelve of the 101 patients died and 2 relapsed. Patients receiving an aminoglycoside were more likely to fully recover ( $P=.02$ ), and those treated with aminoglycosides for at least 14 days were more likely to survive than those with shorter therapy duration ( $P=.02$ ).

**Conclusion:** Effective antibiotic therapy for *Bartonella* endocarditis should include an aminoglycoside prescribed for a minimum of 2 weeks.

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**B**ARTONELLA SPECIES are small, gram-negative bacilli that have recently been shown to cause endocarditis.<sup>1</sup> Currently, *Bartonella quintana*, the agent of trench fever, and *Bartonella henselae*, the agent of cat-scratch disease, are the major causes of *Bartonella* endocarditis.<sup>2-5</sup> Single cases of endocarditis caused by *Bartonella elizabethae* and *Bartonella vinsonii* subspecies *berkhoffii* have also been reported.<sup>6,7</sup>

The treatment of *Bartonella* endocarditis is not clearly established. Many of the described patients have been cured by empiric therapies for blood culture-negative endocarditis, which include  $\beta$ -lactam and aminoglycoside antibiotics, and often the surgical resection of the infected valve. At the Unité des Rickettsies, we have received samples from patients with blood culture-negative endocarditis. A total of 101 of these patients, all of whom were classified as having definite endocarditis according to the Duke criteria for the diagnosis of infective endocarditis,<sup>8</sup> were shown to have *Bartonella* endocarditis by serologic analysis and/or culture findings and genomic amplification

by polymerase chain reaction (PCR). The purpose of this article is to examine the treatment and outcome of the 101 patients with *Bartonella* endocarditis and to define the most effective antibiotic regimen for this disease.

## METHODS

Patients were considered to have definite endocarditis according to the Duke criteria.<sup>8</sup> *Bartonella* infection was diagnosed by culture findings or positive results on *Bartonella* DNA amplification from valvular tissue or blood or when patients exhibited IgG titers of 1:800 or more as determined by microimmunofluorescence.<sup>9</sup> The study sites included Unité des Rickettsies, Faculté de Médecine; Laboratoire de Microbiologie, Hôpital Edouard Herriot; Department of Infection, St Thomas' Hospital; Department of Medicine and Microbiology, Dalhousie University, Halifax, Nova Scotia; Public Health Laboratory Service, William Harvey Hospital, Willesborough; Microbiology Department, St Bartholomew's Hospital; and Laboratoire de Microbiologie, Hôpital Bichat.

Between January 1, 1995, and April 30, 2001, the Unité des Rickettsies received serum specimens from 52 500 patients for the detection of antibodies to *Rickettsia* species, *Coxiella burnetii*, and *Bartonella* species. Of these,

593 patients had endocarditis, including 228 patients with blood culture–negative endocarditis. The 365 patients with positive blood culture findings were hospitalized in Marseille and were systematically tested serologically, whereas specimens from the 228 patients with blood culture–negative endocarditis were sent from the various study sites, mostly for the detection of antibodies to *C burnetii* and *Bartonella* species. Blood samples and material from excised heart valves, when available, were submitted for PCR amplification and culture. In 61 patients, *Bartonella* endocarditis was diagnosed by culture or PCR findings and in 40 patients on the basis of positive *Bartonella* serologic test results, which were recently demonstrated to have a positive predictive value of 0.955 for the detection of *Bartonella* infection among patients with endocarditis.<sup>9</sup> In the latter group of patients, no other origin of endocarditis could be found despite extensive investigation.

A standardized questionnaire was completed for each patient. Questions included those used in the diagnostic score of the Duke Endocarditis Service,<sup>8,10</sup> previous antibiotic therapy, the outcome within 1 year following the diagnosis of culture-negative endocarditis (a relapse of *Bartonella* endocarditis was defined as a new episode of definite endocarditis based on the Duke criteria<sup>8</sup> after at least 3 months following therapy without any clinical or echocardiographic signs of endocarditis and the isolation or PCR amplification of a *Bartonella* from the patient's specimens), presence of vegetations or other cardiologic findings consistent with the infective endocarditis, and presence of environmental exposure factors, such as homelessness (people who did not have customary and regular access to a conventional dwelling or residence for the past year), chronic alcoholism (>100 g/d of alcohol for more than 1 year), and immunodeficiency, which are epidemiologic features associated with other *Bartonella*-induced diseases. If such data were not available in the medical records, the patients were contacted by telephone. Data were analyzed at the Unité des Rickettsies.

#### MICROBIOLOGICAL AND MOLECULAR METHODS

*Bartonella quintana* strain Oklahoma; *B quintana* strain Marseille, isolated from a French patient from this series<sup>3</sup>; *B henselae* strain Houston-1 (ATCC 49882T); *B henselae* strain Marseille<sup>2</sup>; and *B elizabethae* (ATCC 49927T) were used as antigens. The bacteria, between the fourth and seventh passages in a human endothelial cell line (ECV 304), were harvested, pelleted, and used as crude antigen in a microimmunofluorescence assay performed as described previously.<sup>1</sup> In our laboratory, we use a 1:800 cutoff for the diagnosis of *Bartonella* endocarditis.<sup>1</sup>

Specimens of blood and excised valve were inoculated onto both 5% blood agar (bioMérieux SA, Marcy-l'Étoile, France) and into tissue cultures of ECV 304 cells. Inoculated media were incubated at 37°C in a 5% carbon dioxide atmosphere for 10 days. Isolates obtained were identified using species-specific mouse polyvalent antisera or PCR.<sup>11</sup> Molecular amplification and identification of isolates were performed as follows: the DNA used as a template in PCR amplifications was prepared from agar-grown single colonies of the isolate or from isolates obtained in endothelial cells. They were digested with proteinase K and sodium dodecyl sulfate and their DNA extracted using phenolchloroform and ethanol precipitation. Crude DNA extracts were also prepared from the valve biopsy specimens and whole blood samples using the QIAamp tissue kit (QIAGEN, Hilden, Germany) as described by the manufacturer. The presence of the genes encoding the citrate synthase and the 16S to 23S ribosomal RNA intergenic spacer region was determined by PCR using previously described protocols.<sup>12,13</sup> In addition, we extracted the DNA from 200 µL of patients' serum, when available, using the QIAamp blood kit (QIAGEN). *Bartonella*

species were detected from serum using a nested PCR assay that incorporated primers derived from the riboflavin synthase-encoding gene (Zaher Zeaiter, P.-E.F., Gilbert Greub, MD, D.R., unpublished data, 2002). In all PCR reactions, serum specimens or valve biopsy specimens from patients without *Bartonella* infection were processed as described herein and used as negative controls for every 7 samples. The identification of the amplified DNA was determined by base-sequence determination as previously described.<sup>1</sup>

#### STATISTICAL ANALYSIS

The Fisher exact test was used to compare proportions, and the *t* test (2-tailed) for matched samples was used to compare means using Epi Info version 6.04a statistical software.<sup>14</sup>

### RESULTS

From January 1, 1995, to April 30, 2001, 101 patients were diagnosed as having *Bartonella* endocarditis. Sixty-one of these had direct evidence of the infecting species by culture or PCR findings: 49 were infected with *B quintana* and 12 with *B henselae*. In the remaining 40 patients, elevated IgG titers to *Bartonella* species were the only proof of infection. We observed no demographic, epidemiologic, or clinical difference between patients with a direct evidence of *Bartonella* infection and those with only a positive serologic test result (**Table 1**). Therefore, we analyzed the 101 patients together.

The mean ± SD age of the 101 patients with *Bartonella* endocarditis was 50 ± 15 years (range, 16–81 years). Eighty-six patients (85%) were male. Epidemiologic information was partially missing for some of the patients; 38 (38%) of 101 were homeless, 47 (48%) of 97 were alcoholic, 17 (18%) of 93 had contact with body lice, 31 (33%) of 94 reported cat bites or scratches, and 14 (15%) of 92 reported contact with cat fleas. Clinical information was available for all patients; endocarditis occurred on native valves in 100 patients and on a bioprosthesis in 1 patient; 58 (57%) had previously known valvular heart disease, 84 (83%) presented with fever (temperature, >38°C) on admission, and 44 (43%) had embolic phenomena. Five patients initially presented with acute renal insufficiency and had mesangioproliferative glomerulonephritis apparent on renal biopsy specimens. On echocardiography, 95 patients (94%) had findings consistent with endocarditis, vegetations were present in 91, a valvular abscess was present in 1, and a valvular leak was evident in 2. In the remaining 6 patients, who were febrile, the cardiac auscultation revealed a new aortic murmur in 2 patients and a new mitral murmur in 3; the remaining patient was hospitalized for cardiac insufficiency. The echocardiogram revealed a valvular regurgitation in all 6. Direct evidence of *Bartonella* infection was present in these 6 patients. Eighty-seven patients recovered, 12 died, and 2 relapsed. A 32-year-old man with PCR-proven *B quintana* endocarditis relapsed despite surgery 1 year after completion of a 6-week course of doxycycline monohydrate and rifampin. The diagnosis was based on isolation of *B quintana* from the blood during the relapse. He was then treated with doxycycline for 6 weeks and gentamicin sulfate for the first 2 weeks, with recovery. A 77-year-old

**Table 1. Comparison of the Epidemiologic and Clinical Characteristics of Patients With Direct Evidence of *Bartonella* Endocarditis and Those With Positive Serologic Test Results Only\***

Characteristic	Patients With Direct Evidence of <i>Bartonella</i> Infection (n = 61)	Patients With Positive <i>Bartonella</i> Serologic Test Results (n = 40)	P Value	OR (95% CI)
Patients	61/101 (60)	40/101 (40)		
Age, mean ± SD, y	47.8 ± 14.0	53.3 ± 14.8	.06	
Male-female ratio	51:10 (84)	35:5 (87)	.59	0.7 (0.2-2.6)
Homelessness	27/61 (44)	11/40 (27)	.09	2.1 (0.8-5.4)
Chronic alcoholism	29/59 (49)	18/38 (47)	.90	1.0 (0.4-2.4)
Contact with body lice	11/58 (19)	6/35 (17)	.80	1.1 (0.3-3.9)
Contact with cats	19/58 (33)	12/36 (33)	.90	0.9 (0.4-2.6)
Contact with cat fleas	7/57 (12)	7/35 (20)	.30	0.6 (0.1-2.0)
Previously known valvular defect	33/61 (54)	25/40 (62)	.40	0.7 (0.3-1.7)
Body temperature >38°C	51/61 (84)	33/40 (82)	.90	1.1 (0.3-3.5)
Embolism or immunologic manifestations	26/61 (43)	18/40 (45)	.80	0.9 (0.4-2.2)
Valve involved				
Aortic	36/61 (59)	22/40 (55)	.70	1.2 (0.5-2.8)
Mitral	9/61 (15)	12/40 (30)	.06	0.4 (0.1-1.2)
Aortic and mitral	6/61 (10)	4/40 (10)	>.99	1.0 (0.2-4.5)
Aortic, mitral, and tricuspid	3/61 (5)	0/40 (0)	.20	Infinite
Aortic and tricuspid	3/61 (5)	0/40 (0)	.20	Infinite
Tricuspid	1/61 (2)	2/40 (5)	.30	0.3 (0.01-4.7)
Aortic, mitral, and pulmonary	1/61 (2)	0/40 (0)	.70	Infinite
Pulmonary	1/61 (2)	0/40 (0)	.70	Infinite
Tricuspid and pulmonary	1/61 (2)	0/40 (0)	.70	Infinite
Valvular surgery	34/61 (56)	22/40 (55)	.90	1.0 (0.4-2.5)
Recovery	54/61 (88)	33/40 (82)	.70	1.6 (0.5-5.8)
Relapse	2/61 (3)	0/40 (0)	.40	Infinite
Death	5/61 (8)	7/40 (17)	.10	0.4 (0.1-1.6)

Abbreviations: CI, confidence interval; OR, odds ratio.

\*Data are presented as number/total number (percentage) of patients unless otherwise indicated

woman with culture-proven *B henselae* endocarditis relapsed despite surgery 5 months after completion of a 6-week course of doxycycline only. She underwent a second valvular replacement, and *B henselae* was isolated again from the excised valve; she was then treated with doxycycline for 6 weeks and gentamicin for the first 2 weeks and recovered. Both patients were followed up 1 year after the relapse. The rate of relapse was statistically higher among patients who did not receive aminoglycosides vs those who were treated with any regimen that included an aminoglycoside (2 of 19 vs 0 of 82;  $P=.03$ ). Seventy-six patients underwent valvular surgery because of severe valvular damage at the time of diagnosis. Sixty-three of these 76 surgically treated patients had received aminoglycosides vs 18 of the 25 who did not undergo surgery ( $P=.18$ ).

One hundred of the 101 patients received antibiotics (**Table 2**) for a mean±SD duration of 43±17 days. Eighty-two patients received aminoglycosides, for a mean±SD duration of 15±11 days (range, 2-50 days); 64 of these received a β-lactam (amoxicillin in 38, ceftriaxone sodium in 13, benzylpenicillin sodium in 10, and oxacillin sodium in 3) in association with an aminoglycoside (gentamicin in 53, netilmicin sulfate in 8, amikacin sulfate in 2, and isepamicin in 1), including 18 patients who received 1 additional antibiotic (doxycycline in 8, ofloxacin in 6, ciprofloxacin chlorhydrate in 2, and vancomycin chlorhydrate in 2); 1 patient was treated with amikacin alone; 17 patients received an aminoglycoside in combination with other antibiotics (vancomycin and

gentamicin in 5; doxycycline and gentamicin in 7; vancomycin, netilmicin, and ofloxacin in 1; teicoplanin and netilmicin in 1; rifampin and gentamicin in 1; rifampin and amikacin in 1; and cotrimoxazole [sulfamethoxazole-trimethoprim] and netilmicin in 1). Patients who received aminoglycosides received a complete course of antibiotics for 44±17 days vs 43±19 days for those treated with other antibiotics ( $P=.82$ ).

Aminoglycoside-treated patients were hospitalized for a mean±SD of 17±12 days following the onset of therapy vs 17±10 days for those who were treated with other antibiotics ( $P=.11$ ). Aminoglycoside dosage was monitored in 76 of 82 patients to achieve therapeutic levels. In 11 patients, the development of a renal insufficiency during therapy required the use of lower doses of aminoglycosides in 9 and the interruption in 2. Seventy-four of the 82 patients treated with aminoglycosides recovered vs 13 of 19 of those who received no aminoglycosides ( $P=.02$ ). Among patients treated with aminoglycosides, 65 of the 69 patients who recovered had received aminoglycosides for 14 or more days vs 9 of the 13 patients treated for fewer than 14 days ( $P=.02$ ). The shorter course of aminoglycoside therapy taken by the 4 patients who died was due to the interruption of therapy because of acute renal failure in 1 patient and the duration of prescribed therapy in the remaining 3. The remaining 18 patients did not receive aminoglycosides, but 3 were given amoxicillin and ciprofloxacin, 3 were given doxycycline alone, 3 were given doxycycline and ciprofloxacin, 4 were given rifampin and doxycycline, 1 was

**Table 2. Antibiotic Regimens of Patients With *Bartonella* Endocarditis\***

Variable	$\beta$ -Lactam†	$\beta$ -Lactam With Aminoglycosides	Rifampin‡	Aminoglycosides‡	Doxycycline‡	Doxycycline†	Fluoroquinolones‡
Total patients	6	64	7	82	26	10	18
Recovery	4	56	5	74	19	6	14
Death	2	8	1	8	5	3	4
Relapse	0	0	1	0	2	2	0

\*Data are presented as number of patients.

†With or without other antibiotics, except aminoglycosides.

‡With or without other antibiotics.

given rifampin and pefloxacin dihydrate, 1 was given ceftriaxone and ciprofloxacin, 1 was given amoxicillin and doxycycline, 1 was given ciprofloxacin alone, and 1 was given amoxicillin alone. Among these 18 patients, the administration of aminoglycosides was precluded by renal failure in 4. The remaining patient underwent valvular replacement but was not administered antibiotics, except for a prophylactic antibiotic therapy during surgery.

Twelve patients (12%) died despite antibiotic therapy and valvular surgery, 10 of acute heart failure and 2 of multiple organ failure. The recovery rate was lower in the group of patients receiving doxycycline only or doxycycline associated with other antibiotics except aminoglycosides than in patients who received aminoglycosides (6 of 11 vs 74 of 82;  $P < .001$ ). In addition, in these patients the relapse rate was significantly higher (2 of 11 vs 0 of 82;  $P = .01$ ) but not the mortality rate (3 of 11 vs 8 of 82;  $P = .10$ ). Eighteen patients received a fluoroquinolone antibiotic, which was not more effective than other antibiotic regimens (14 recoveries per 18 patients vs 72 recoveries per 82 patients,  $P = .22$ ), but only 9 patients received fluoroquinolones without aminoglycosides and therefore their own efficacy could not be evaluated. Similarly,  $\beta$ -lactams without aminoglycosides did not exhibit a higher efficacy when compared with other antibiotics (4 recoveries per 6 patients vs 84 recoveries per 94 patients,  $P = .15$ ).

#### COMMENT

In this article, we examine the treatment and outcome of *Bartonella* endocarditis. This disease accounts for 3% of cases of endocarditis, at least in France.<sup>1</sup> From January 1, 1995, to April 30, 2001, we diagnosed 101 cases, the largest reported series of *Bartonella* endocarditis to our knowledge. The higher rate of *Bartonella* endocarditis in our study (101 of 593 patients, 17%) is explained by a recruitment bias, because specimens from blood culture–negative patients were sent from several investigation centers, whereas we received specimens from blood culture–positive patients mainly from hospitals in Marseille, which explains an overrepresentation of blood culture–negative endocarditis and thus *Bartonella* infections. We identified 12 other cases in the literature.<sup>4,6,15-23</sup> None of these patients relapsed or died, 11 received aminoglycosides, and 1 was treated for 11 months with ceftriaxone and erythromycin ethylsuccinate.<sup>22</sup> Because the diagnosis of *Bartonella* endocarditis

may be delayed, since it often affects homeless and alcoholic patients with poor medical care, it might be expected to have a higher mortality rate than that seen in other patients with endocarditis. Moreover, the usual clues for the diagnosis of endocarditis may be missing, since only 59% of our patients had a history of a previous valvular disease and only 83% were febrile. We have previously demonstrated that patients with *Bartonella* endocarditis, such as those included in our series, have a high death rate and undergo valvular surgery more frequently than patients with endocarditis caused by other pathogens.

The optimum antibiotic treatment for *Bartonella* endocarditis is unknown. *Bartonella* species exhibit a paradoxical antibiotic susceptibility pattern. The minimal inhibitory concentrations of most tested antibiotics are usually low, but only aminoglycosides are bactericidal.<sup>24</sup> This is observed in axenic media and cell cultures.<sup>25</sup> Because the purpose of antibiotic treatment during endocarditis is to obtain a bactericidal regimen, it might be expected that a regimen that includes at least 1 aminoglycoside would be effective in treating *Bartonella* endocarditis. In this study, we showed that aminoglycoside-containing regimens are more effective than other regimens. The recovery rate was higher when aminoglycosides were used ( $P = .02$ ). We observed that this difference was not related to a longer course of antibiotics or to a longer stay in the hospital. Moreover, an aminoglycoside therapy longer than 2 weeks was associated with a better prognosis ( $P = .02$ ). We observed that those patients who recovered had received aminoglycoside therapy for at least 14 days, significantly longer than the duration of treatment among those who died. Therefore, the empiric treatment of blood culture–negative endocarditis, which frequently combines a  $\beta$ -lactam and an aminoglycoside, may be effective for *Bartonella* endocarditis. However, no difference in the frequency of surgery was observed in patients treated or not treated with aminoglycosides. This may be explained by the severity of valvular lesions at the time when the diagnosis of endocarditis is made.<sup>26</sup> Other antibiotics, such as fluoroquinolones or  $\beta$ -lactams alone or in combination with any other antibiotic except aminoglycosides, did not exhibit a significantly higher efficacy than other regimens. However, the number of studied patients was small. The least effective regimens were those containing doxycycline and no aminoglycoside (Table 2). Antibiotic therapy for endocarditis probably cannot be deduced from infections at other sites caused by the same microorgan-

ism. Therefore, the clinical experience in treating cat-scratch disease is probably irrelevant for *B henselae* endocarditis, since no antibiotic regimen has been shown to be consistently effective. For patients with bacillary angiomatosis, one of the keys to success is the duration of treatment, which may include macrolides.<sup>27,28</sup> However, to the best of our knowledge, aminoglycosides have never been tested in such an indication. Finally, our data strongly suggest that aminoglycosides are effective therapy for the treatment of *Bartonella* endocarditis, and a minimum 2-week course is the optimal therapy duration.

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