

***Bartonella* as a Cause of Blood Culture-Negative Endocarditis. Description of 5 Cases**

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There is evidence that *Bartonella* is an etiologic factor in human endocarditis. The objective of this article was to describe cases of endocarditis due to *Bartonella* observed at a tertiary-care hospital during 1995-2006. Overall, 140 cases of infective endocarditis were seen, of which 10 were blood culture-negative endocarditis, with 5 being due to *Bartonella*. In 4 cases, there had been contact with cats. Only 2 patients had pre-existing cardiac valvular disease. Three had extracardiac disease manifestations. In 3 cases, polymerase chain reaction (PCR) tests on cardiac valvular tissue gave positive results. Two patients had positive serology test results for *Chlamydomphila* and another two, positive results for *Coxiella burnetii*. All 5 patients needed surgery, and the outcome was favorable in all 5. The presence of *Bartonella* must be considered in patients with blood culture-negative endocarditis. Although serological testing is essential for the diagnosis, cross-reactions between *Bartonella* and *C. burnetii* or *Chlamydomphila* are frequent, and PCR tests on cardiac valvular tissue, therefore, play an important diagnostic role.

Key words: *Bartonella*. Endocarditis. Blood culture-negative endocarditis.

***Bartonella* como causa de endocarditis con hemocultivos negativos. Descripción de 5 casos**

Bartonella está implicada como agente etiológico de la endocarditis en humanos. El objetivo del artículo es describir los casos de endocarditis por *Bartonella* diagnosticados en un hospital de tercer nivel durante el período 1995-2006. Hubo 140 casos de endocarditis infecciosa, de los cuales 10 cursaron con hemocultivos negativos (5 por *Bartonella*). Se había producido contacto con gatos en 4 casos; sólo 2 pacientes presentaban valvulopatía previa; 3 tuvieron clínica extracardiaca; en 3 se realizó PCR de tejido valvular, con resultado positivo; 2 pacientes tenían además serología positiva para *Chlamydomphila* y otros dos, para *Coxiella burnetii*. Los 5 precisaron tratamiento quirúrgico. La evolución fue favorable en todos. Se debe sospechar infección por *Bartonella* ante un paciente con endocarditis y hemocultivos negativos. La serología es fundamental para el diagnóstico, pero es habitual encontrar reacciones cruzadas entre *Bartonella* y *C. burnetii* o *Chlamydomphila*, por lo que la PCR del tejido es importante para el diagnóstico.

Palabras clave: *Bartonella*. Endocarditis. Endocarditis con cultivos negativos.

INTRODUCTION

Bartonella is a Gram-negative bacterial genus that is difficult to culture. These bacteria produce a wide range of infectious diseases,¹ including blood

culture-negative endocarditis. Due to improvements in culturing and molecular biology techniques, 5 species have been recognized as causing infective endocarditis in humans (*B. quintana*, *B. henselae*, *B. elizabethae*, *B. vinsonii*, and *B. koehlerae*), although most cases are produced by the first 2. According to recent reports, *Bartonella* accounts for 1% to 17% of all cases of endocarditis.² A Spanish review by Oteo et al³ described 6 cases published in the past 10 years. The purpose of the present article is to analyze cases of endocarditis caused by *Bartonella* diagnosed at a tertiary hospital and to determine the importance of this pathogen as a cause of endocarditis in our setting.

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METHODS

This is a descriptive study based on a retrospective review of the medical records of patients diagnosed with *Bartonella* endocarditis between January 1995 and December 2006. The minimum basic data set (MBDS) was used to identify all patients who had been coded at discharge according to the International Classification of Diseases, Ninth Revision, as infective endocarditis or Q fever endocarditis, because no specific code exists for *Bartonella* endocarditis. The diagnosis of endocarditis was considered to be definitive or probable if the patient fulfilled the modified Duke criteria,⁴ and the infection was considered to be caused by *Bartonella* when the *Bartonella* immunoglobulin (Ig) G antibody titer was higher than 1/800 by indirect immunofluorescence (Focus Diagnostic) or *Bartonella* DNA screening by polymerase chain reaction (PCR) (amplification of the 16S ribosomal RNA [rRNA] gene and intergenic spacer region, performed at Centro Nacional de Majadahonda, Madrid, Spain).

The following variables were analyzed: age, sex, risk factors, epidemiologic history, clinical picture, valvular and extravalvular involvement, microbiologic data, treatment, and clinical progress.

RESULTS

During the period of 1995 to 2006, there were 140 cases of infective endocarditis, 10 of which yielded negative blood cultures (7% of all cases of endocarditis). Of these 10 cases, 2 had been caused by *Coxiella burnetii*, 4 by *Bartonella* species, and 1 by both *Bartonella* and *C burnetii*; 1 case was considered Loeffler endocarditis, another was tuberculous endocarditis, and in 2, an etiological diagnosis was not established.

The main characteristics of the cases of *Bartonella* endocarditis are summarized in Table.

All 5 cases of *Bartonella* endocarditis occurred in men between 30 and 72 years of age; 4 had a history of contact with cats and 1 was infected with HIV. Only 2 patients had previous valve disease. The aortic valve was affected in all cases. The mean time to diagnosis was 143 days (range, 7-540). The predominant symptoms were fever and constitutional syndrome. Three patients presented with acute heart failure secondary to valve regurgitation and 1 with cerebral infarction. Three patients had embolic infarctions of splenic, mesenteric, and cerebral regions, and 1 patient with a prosthetic aortic valve presented aortitis of the aortic root and postinfectious glomerulonephritis with secondary renal failure. Serologic testing was positive for *Bartonella* in all 5 patients, with antibody titers above 1/800. PCR

study of valve tissue was performed in 3 patients with positive results, although the species (*B henselae*) was determined in only 1 patient. Pericardial fluid culture yielded *Bartonella* in 1 patient. In addition, serology was positive for *Chlamydothila* in 2 patients and for *C burnetii* in 2 others (coinfection was confirmed by PCR of valve tissue in only 1). All required valve replacement, but the clinical progress was favorable, and only 1 had residual chronic renal failure. *Bartonella* antibody titers were subsequently negative or reduced in all patients except 2, who continued with antibiotic therapy at the time of writing.

DISCUSSION

The incidence of blood culture-negative endocarditis varies from 3% to 31% of all cases of endocarditis, according to the series.⁵ Although the main reason is prior administration of antibiotics, endocarditis caused by zoonosis and bacteria transmitted by arthropods (mainly *C burnetii* and *Bartonella*) is prevalent in the Mediterranean countries,⁶ a fact that should be taken into account.

In the present study, culture-negative endocarditis accounted for 7% of all cases of endocarditis, and the *Bartonella* genus was implicated in 3.6% of endocarditis cases and 50% of culture-negative endocarditis. These findings are consistent with the results of other authors, such as Raoult et al⁷ who reported 22 cases of blood culture-negative endocarditis, 9 of them caused by *Bartonella* (3% of all the infective endocarditis cases) and the French National Reference Center for Rickettsial Diseases study,⁸ which reported 348 cases of culture-negative endocarditis between 1993 and 2001, with 48% of cases caused by *C burnetii* and 28% by *Bartonella* species.

Bartonella endocarditis may be difficult to diagnose because it presents a subacute clinical course with nonspecific symptoms, such as fever (not always present and often intermittent), weight loss, and asthenia. Embolic phenomena are not unusual and immune-complex glomerulonephritis has been described as a complication of *Bartonella* endocarditis that can lead to chronic renal failure.^{9,10}

Serology techniques are used for the diagnosis. An IgG antibody titre $\geq 1/800$ has a positive predictive value of 95% for the detection of *Bartonella* infection among patients with culture-negative endocarditis. Cross-reactions with *Chlamydothila* and *C burnetii* species that can lead to diagnostic error have been reported.¹¹ PCR study of valve tissue is useful for the diagnosis; however, despite a high specificity (around 100%), its sensitivity to identify the pathogen in culture-negative endocarditis varies between 40% and 60%,¹² probably due to prior use of antibiotics.

TABLE. Characteristics of Patients with *Bartonella* Endocarditis

	Age, y/Sex	Risk Factor	Days to Diagnosis	Affected Valve	Extracardiac Involvement	<i>Bartonella</i> Serology	Microbiology	Antibiotic Therapy/Duration	Follow-Up Serology	Progress
Patient 1	30, male	Contact with cats, HIV	20 days	Aortic	Splenic infarct, subannular abscess	IgM (+), IgG 1/2048	<i>Bartonella</i> PCR (+), pericardial fluid culture (+), <i>Chlamydophila psittaci</i> serology (+)	Initial: ampicillin, ciprofloxacin, gentamicin. Maintenance: doxycycline, ciprofloxacin. 7 months	6 months. <i>Bartonella</i> : IgG 1/512	Favorable
Patient 2	54, male	None	60 days	Aortic	Cerebral aneurysm	IgM (-), IgG 1/2048	<i>Chlamydophila pneumoniae</i> serology (+)	Initial: cloxacillin, gentamicin. Maintenance: cloxacillin, azithromycin. 6 months	6 months. <i>Bartonella</i> : IgM (-), IgG 1/400. <i>Chlamydophila pneumoniae</i> : IgM (-), IgG 1/256	Favorable
Patient 3	56, male	Contact with cats, alcoholism	7 days	Aortic	Mesenteric artery aneurysm	IgG 1/1024	<i>Bartonella</i> PCR (-)	Initial: vancomycin, ceftazidime, tobramycin. Maintenance: doxycycline, ciprofloxacin. 12 months	12 months. <i>Bartonella</i> : IgM (-), IgG (-)	Favorable
Patient 4	72, male	Contact with cats, aortic regurgitation	90 days	Aortic	No	IgM (+), IgG 1/4096	<i>Bartonella henselae</i> PCR (+), <i>Coxiella</i> PCR (+), <i>C burnetii</i> serology: Phase I, IgM (-), IgG 1/16384; Phase II, IgM (-), IgG 1/16384	Doxycycline, ciprofloxacin. Still under treatment	<i>Bartonella</i> : IgM (-), IgG 1/4096. <i>C burnetii</i> : Phase I, IgM (-), IgG 1/16384; Phase II, IgM (-), IgG 1/8192	Favorable
Patient 5	52, male	Cat scratch, aortic prosthesis	540 days	Aortic root abscess	No	IgM (+), IgG 1/8192	<i>Bartonella</i> PCR (+), <i>C burnetii</i> serology: Phase I, IgG 1/9192; Phase II, IgG 1/512	Initial: ampicillin, gentamicin, doxycycline. Maintenance: doxycycline, ciprofloxacin. Still under treatment	<i>Bartonella</i> : IgM (-), IgG 1/256. <i>C burnetii</i> : Phase I, IgM (-), IgG 1/128; Phase II, IgM (-), IgG 1/128	Favorable

The technique can also help to identify the causative agent in patients who additionally have elevated titers of *Chlamydophila* or *C burnetii* and to rule out mixed disease. Moreover, PCR can often establish the species of *Bartonella*. Therefore, in patients who require valve replacement, valve tissue should be sent to the reference laboratory for analysis. A real-time PCR technique has been developed for the specific diagnosis of *Bartonella*, but it has a low sensitivity

(58%). It may, however, be useful when *Bartonella* endocarditis is suspected and only serum samples are available. Nonetheless, the role of the technique in the diagnosis of nonsurgical endocarditis requires further study.¹³

There are no randomized studies on the treatment of *Bartonella* endocarditis, and the recommendations are based on series of case studies. Doxycycline is probably the best option for long-term therapy.

Treatment should be maintained between 3 and 6 months,¹⁴ although most patients require valve replacement.

In summary, *Bartonella* should be considered an important etiologic agent of culture-negative endocarditis in our setting. It is probably underdiagnosed and, because the clinical picture is nonspecific, the risk factors for this zoonosis should be investigated and serology tests should be performed in all blood culture-negative endocarditis. Cross-reactions with *C burnetii* and *Chlamydochila* are common, hence, PCR study of valve tissue may be useful to confirm the diagnosis if surgery has been performed.

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