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# A Prospective Study of Canine Infective Endocarditis in Northern California (1999–2001): Emergence of *Bartonella* as a Prevalent Etiologic Agent

Kristin A. MacDonald, Bruno B. Chomel, Mark D. Kittleson, Rick W. Kasten, William P. Thomas, and Patricia Pesavento

A prospective study was performed (June 1999 to May 2001) to determine the incidence of infective endocarditis (IE) due to *Bartonella* in dogs in northern California and to compare these patients with other dogs with IE. IE was diagnosed antemortem based on clinical signs and echocardiography in 18 dogs. The etiologic agent was *Bartonella* sp. in 5 dogs (28%) and was diagnosed by high seroreactivity to *Bartonella* (titer >1:512; range, 1 : 1,024–1 : 4,096); and confirmed postmortem by positive polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) from the infected valve and partial DNA sequencing of the citrate synthase gene (*glt A*). Conventional bacteria were causative agents in 7 dogs (39%). An etiologic agent was not identified in 6 dogs (33%). *Bartonella vinsonii berkhoffii* (n = 3), *B clarridgeiae* (n = 1), and a *B clarridgeiae*-like organism (n = 1) were identified. Blood culture was positive only for the IE case due to *B clarridgeiae.* All dogs with IE due to *Bartonella* were also seroreactive to *Anaplasma phagocytophilum.* All dogs with IE due to *Bartonella* had lesions only on the aortic valve. Of the cases of IE not due to *Bartonella,* 31% involved the aortic valve, 61% the mitral valve, and 8% both valves. Dogs with mitral valve IE lived longer than all dogs with aortic valve IE ($P = .004$) and dogs with IE of the aortic valve due to *Bartonella* ($P = .002$). In conclusion, *Bartonella* is a common cause of IE in dogs of northern California. A high *Bartonella* serologic titer (>1 : 512) is useful antemortem to diagnose aortic valve IE due to *Bartonella.*

**Key words:** Bacteria; Dog; Serology.

Infective endocarditis (IE) is an uncommon, often deadly, and sometimes difficult-to-diagnose disease in veterinary medicine. Patients most often succumb to congestive heart failure (CHF), sudden death because of cardiac arrhythmias, and thromboembolic disease of the kidneys, spleen, heart, and brain.[1,2] Immune-mediated diseases such as glomerulonephritis and polyarthritis are common secondary problems caused by IE. The diagnosis is dependent on clinical suspicion based on presentation of 1 or more clinical signs commonly associated with IE (eg, shifting leg lameness, newly diagnosed heart murmur, fever, thromboembolic disease) and is most frequently confirmed by the identification of classic echocardiographic features or by pathologic diagnosis.[3] Blood culture is especially helpful for identifying the offending organism and determining the spectrum of antibiotic sensitivity. However, blood cultures frequently are negative (20–70%) in dogs with IE.[1,2] In small-animal medicine, the aortic and mitral valves are almost exclusively affected.[1,2] *Staphylococcus* sp., *Streptococcus* sp., *Escherichia coli,* and *Corynebacterium* are the most common bacterial isolates from dogs with IE.[1,2]

Although negative blood cultures in human patients with known IE are uncommon (5–24%), increased attention has been paid to patients with culture-negative IE over the past decade, and greater efforts currently are made to identify fastidious bacteria such as *Bartonella* and *Coxiella*.[4] *Bartonella* sp. are gram-negative, aerobic, fastidious intracellular bacteria that cause various inflammatory diseases in veterinary medicine, including granulomatous lymphadenitis, granulomatous rhinitis, and peliosis hepatis in dogs.[5–10] Recently, *B henselae, B clarridgeiae,* and *B elizabethae* have been identified by polymerase chain reaction (PCR) from the blood of dogs with several different systemic illnesses.[9–11] In dogs, *Bartonella vinsonii* subsp. *berkhoffii* and *B clarridgeiae* species have been documented as causative agents of IE, whereas *B quintana, B henselae, B elizabethae, B vinsonii* subsp. *berkhoffii,* and *B washoensis* have been associated with IE or myocarditis in humans.[5,12–15]

The hypothesis of the current study was that *Bartonella* is a common cause of IE in dogs living in northern California, especially in those cases in which traditional blood culture is negative. The study was prospectively designed to define the incidence of IE due to *Bartonella* in dogs presented to the University of California (UC), Davis Veterinary Medical Teaching Hospital (VMTH) over a 2-year period (June 1999 to May 2001). A secondary objective was to compare the clinical features and outcome of dogs with IE due to *Bartonella* to those of dogs with IE because of conventional bacterial isolates.

## Materials and Methods

The patient population consisted of dogs presented to the UC Davis VMTH Cardiology Service from June 1999 to May 2001 that were clinically diagnosed with IE. This study included a case of IE because of *B clarridgeiae,* which was previously published as a case report.[11] Signalment, geographic location, history, presenting complaint, history of ectoparasitic infestation (when available), and current medications were recorded. Geographic location was divided into 3 areas: northern California Pacific coast (north of San Francisco), central California

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*Authorship order is sequential and based on importance of material and intellectual contributions.*

*From the Department of Medicine and Epidemiology (MacDonald), Department of Population Health and Reproduction (Chomel), Department of Medicine and Epidemiology (Kittelson), Department of Population Health and Reproduction (Kasten), Department of Medicine and Epidemiology (Thomas), and California Veterinary Diagnostic Laboratory Services (Pesavento), School of Veterinary Medicine, University of California, Davis, CA.*

*Reprint requests: Kristin MacDonald, 2108 Tupper Hall, Department of Medicine and Epidemiology, University of California, Davis, Davis, CA 95616; e-mail: kamacdonald@ucdavis.edu.*

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Pacific coast (south of San Francisco), and northern central valley of California.

Diagnosis of IE was made according to guidelines described by Kittleson and Kienle, which are modified from the Duke criteria.[16] Major criteria included a positive echocardiographic lesion (vegetative lesion, destructive lesion, or thickened aortic valve leaflets), positive blood cultures (at least 3 when common skin bacteria were cultured or at least 2 when other organisms were cultured), and recent development of a diastolic heart murmur or evidence of more than trivial aortic insufficiency on Doppler echocardiographic examination (in the absence of subaortic stenosis or annuloaortic ectasia). Minor criteria included presence of fever, a large dog (>15 kg), and a new or worsening systolic heart murmur. Supporting evidence included thromboembolic disease, immune-mediated disease (eg, glomerulonephritis, polyarthritis), and subaortic stenosis in a dog that was >5 years of age. A definitive or highly probable diagnosis of IE was made if there was histopathologic confirmation of active IE, if clinical criteria consisting of 2 major criteria, or a characteristic echocardiographic lesion and 1 minor criterion were identified.

Clinicopathologic tests performed on each animal diagnosed with IE included a CBC, standard serum biochemistry, and urinalysis (including urine protein-to-creatinine ratio if the urinalysis identified clinically relevant proteinuria). Serum antibody titers for 3 *Bartonella* spp. (*B vinsonii* subsp. *berkhoffii, B clarridgeiae,* and *B henselae*) were measured on each dog with an immunofluorescent (IFA) assay, as previously described.[11] Dogs infected with *Bartonella* often are coinfected with other tick-borne diseases. Consequently, serology also was performed on each dog for presence of antibodies to *Anaplasma phagocytophilum, Ehrlichia canis,* and *Rickettsia rickettsii* with standard IFA tests and *Borrelia burgdorferi* by a kinetic enzyme-linked immunosorbent assay (KeLA) and a Western blot analysis.[17,a,b] A serum antibody titer also was measured for *Coxiella burnetii,* another cause of culture-negative IE in humans, by using a commercial IFA test.[18,c]

Serial aerobic and anaerobic blood cultures for bacteria were obtained from each dog. At least 3 blood culture samples were aseptically obtained from 2 different venous sites 10 minutes apart. A range of 5–10 mL of blood was collected each time and an aliquot was placed into Isolator[d] lysis centrifugation tubes for aerobic bacterial isolation. An aliquot of the blood sample was vortexed immediately and plated onto 50% sheep blood agar. An aliquot also was placed into BBL Septi-Chek Trypticase Soy Broth bottles[e] for anaerobic culture, and after 48 hours, were plated onto *Brucella* plates. Blood (1.5–2 mL) from each dog also was specifically cultured for isolation of *Bartonella* sp. These blood samples were collected in 2-mL plastic tubes containing EDTA[f] and were frozen at −70°C until plated. Blood samples were cultured on heart infusion agar containing 5% fresh rabbit blood and incubated in 5% $CO_2$ at 35°C for up to 4 weeks. Identification of the isolates as *Bartonella* sp. initially was based on morphologic and growth characteristics, as previously described.[19] The isolates then were confirmed by PCR and restriction fragment length polymorphism (RFLP) analysis and partial sequence analysis of the DNA of the citrate synthase (*glt A*) gene.[11] If the dog died and pathologic specimens were available, infected valve tissue was tested for presence of *Bartonella* sp. by PCR/RFLP and the species involved was identified by partial sequencing of the *glt A* gene. Concurrently, 18 pathology-confirmed cases of dogs with IE because of conventional bacteria were tested for *Bartonella* by PCR analysis.

Thoracic radiographs were classified according to presence or absence of cardiomegaly, left atrial enlargement, and pulmonary infiltrates consistent with congestive left heart failure or noncardiogenic pulmonary disease. A 6-lead electrocardiogram (ECG) was obtained if an arrhythmia was present on physical examination. An echocardiogram was performed with a Hewlett Packard Sonos 5500 ultrasound machine.[g] All cardiac valves were carefully examined for the presence of proliferative, oscillating, hyperechoic vegetative lesions, or valvular perforation. Color-flow Doppler was used to identify valvular insufficiency, and continuous-wave Doppler was used to measure the velocity of the valvular insufficiency. Either 2-dimensional or M-mode echocardiography was used to measure left ventricular dimensions at end systole and end diastole, and fractional shortening was calculated from these measurements. Left atrial size was estimated subjectively by comparing the size of the left atrium to the size of the aorta in a right parasternal cross-sectional view and by determining the ratio of the largest left atrial diameter to aortic diameter in this same view.

The 2-tailed Fischer's exact test[h] was used to determine whether differences existed between the patient population infected with *Bartonella* versus those with IE because of another cause with respect to presenting complaint, clinical abnormalities, clinicopathologic tests, serologic tests, immunologic disease, and thromboembolic disease. Significance was defined as $P < .05$.

Mortality data were obtained by examination of the date and cause of death recorded in the hospital record or by calling the owner or referring veterinarian. Deaths were classified as related to IE or unrelated to IE. SPSS[i] software was used to construct Kaplan-Meier curves for survival of dogs with IE due to *Bartonella* versus IE because of all other etiologies. Median survival time and the 95% confidence interval for dogs with IE due to *Bartonella* infection were compared with those with IE not due to *Bartonella* infection with the Tarone-Ware nonparametric statistical test. The same test was used to compare survival time of dogs with IE of the aortic valve to those with mitral valve IE and to compare survival of dogs with IE due to *Bartonella* to those with IE of the aortic valve due to other etiologies.

## Results

Eighteen dogs were clinically diagnosed with IE between June 1, 1999, and May 31, 2001 (Fig 1). Over that same period, 2,029 canine patients were examined by the VMTH Cardiology Service, and the total number of canine patients seen at the VMTH was 23,097. Therefore, the incidence of canine IE was 0.9% of all dogs examined for cardiovascular disease and 0.08% of all dogs examined at the VMTH. Fourteen (78%) of the 18 dogs died, and 7 of these dogs had a postmortem examination and pathologic confirmation of IE (Fig 2).

Of the 18 dogs diagnosed with IE, 5 had a serum antibody titer to at least 1 species of *Bartonella* >1:512 (median 1:1,024; range, 1:1,024–1:4,096) and greater than 1:256 for the other *Bartonella* spp. tested (Table 1). Each of these dogs had an echocardiographic lesion characteristic of IE on only the aortic valve (Fig 1). Each of the 5 dogs with high antibody titers to *Bartonella* sp. died and was subjected to postmortem examination. *Bartonella* species was identified in each of these 5 dogs by PCR-RFLP and partial sequencing of the *glt A* gene. With *Bartonella*-specific blood culture methods, only 1 of these dogs was bacteremic with *Bartonella* (*B clarridgeiae*).

*Bartonella* was the most common bacterial cause of IE in this study (5/18, 28%, Fig 3). *Staphylococcal* sp. was the second most common bacterial agent (3/18, 17%), followed by *Streptococcus canis* (2/18, 11%), *Pseudomonas aeruginosa* (1/18, 6%), and *Escherichia coli* (1/18, 6%). The most common species of *Bartonella* infection in this study was *B vinsonii* subsp. *berkhoffii* (3/5), followed by 1 case due to *B clarridgeiae* and 1 case due to a *B clarridgeiae*-like infection (Table 1). In the 5 cases of IE due to *Bartonella,* no other concurrent bacterial infections were identified based on blood culture and culture of the affected valve at postmortem examination. Despite extensive diagnostic work-up, 33% (6/18) of dogs had no identified eti-

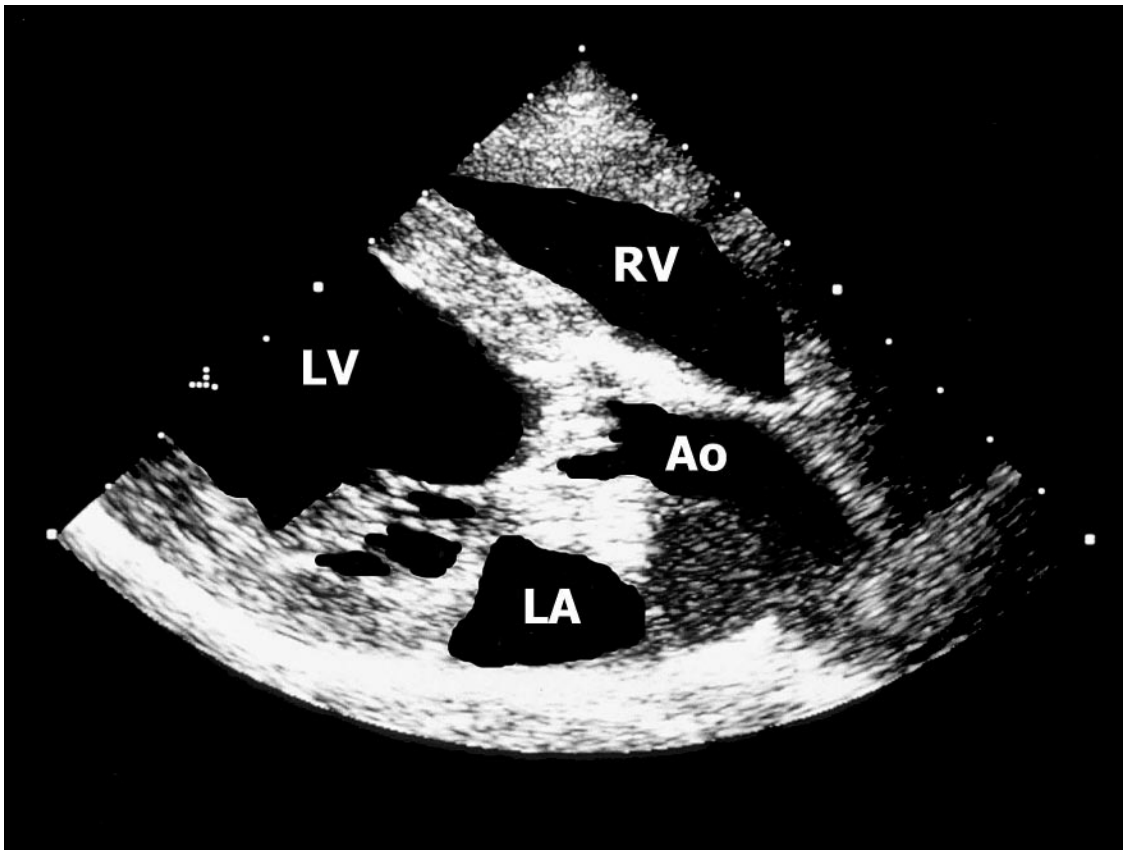


**Fig 1.** Two-dimensional echocardiogram revealing aortic valvular infective endocarditis (picture obtained from previously published case report).[11] This right-sided, parasternal, long-axis view depicts severe hyperechoic, vegetative lesions on the aortic valve cusps. This 3-year-old male neutered Boxer Dog had infective endocarditis due to *Bartonella clarridgeiae.* Left atrium (LA), left ventricle (LV), aorta (AO), right atrium (RA), right ventricle (RV). Image is reproduced with permission from Journal of Clinical Microbiology, 2001;39:3548–3554.

ology of IE (Fig 3). The valves of only 2 dogs with non-*Bartonella* etiology of IE were available for postmortem examination. *Bartonella* was not detected by PCR. Similarly, over the same time period, the infected valves of 18 other dogs with IE due to conventional bacteria and diagnosed only at postmortem examination were tested for *Bartonella* by PCR analysis, and none of them had PCR evidence of *Bartonella.* Unfortunately, serum was not available to test for seroreactivity to *Bartonella* in the 18 dogs with IE diagnosed at postmortem examination.

The aortic valve was infected in 10 (56%) of the 18 dogs with IE, including all 5 cases of IE due to *Bartonella.* Of the other 13 dogs with IE, the aortic valve was infected in 31% (4/13), the mitral valve in 61% (8/13), and both valves in 8% (1/13). The bacterial etiology of IE of the mitral valve was identified in 5 of the 8 dogs: *Staphylococcus* sp. (2/8), *Streptococcus canis,* (2/8) and *Pseudomonas aeruginosa* (1/8). The dog with mitral valve IE due to *S canis* (cultured from blood, a septic splenic infarct at surgery, and a subcutaneous abscess) had a serum antibody titer to *B clarridgeiae* of 1 : 256. Of the 4 non-*Bartonella* cases affecting only the aortic valve, 1 case was due to *Staphylococcus* and no etiology was identified in the other 3 cases. The case of aortic and mitral valve IE was caused by *Escherichia coli.*

All dogs with IE due to *Bartonella* also had a high antibody titer for *Anaplasma phagocytophilum* (median, 1 : 160; range, 1 : 100–1 : 640) (Table 1), whereas only 1 dog with IE not due to *Bartonella* was seroreactive for this organism ($P = .0007$). Three of the 5 dogs with *Bartonella* IE were concurrently seroreactive for other tick-borne diseases (*Rickettsia rickettsii, Ehrlichia canis, Borrelia burgdorferi*). Two *Bartonella*-negative dogs were phase II-positive (1 : 64) and phase I-negative for *Coxiella burnetii.*[4]

Four of the 5 dogs infected with *Bartonella* lived in the northern Pacific Coast region of California, and 1 dog lived in the northern central valley of California. In contrast, the other dogs were divided mainly between the northern Pacific Coast and northern central valley regions (6 dogs in each area). Only 1 dog lived in the southern Pacific Coast region. Information concerning ectoparasitic infestation (eg, fleas, ticks) was available for all 5 dogs with *Bartonella* IE, and only 5 (38%) of 13 dogs with IE because of other causes. Four of 5 dogs with IE due to *Bartonella* and 2 of the 5 patients with IE in the non-*Bartonella* group were known to have been infested with ectoparasites, including ticks and fleas.

No organism was identified by traditional blood culture in 11 (61%) of the 18 specimens. Five of these 11 dogs (45%) had IE due to *Bartonella.* Antibiotic therapy was being administered to 14 (78%) of the 18 dogs at the time of blood collection for culture and to 10 of the 12 dogs

**Fig 2.** Gross pathologic evidence of severe aortic valvular infective endocarditis in the dog depicted in Figure 1. There are severe vegetative lesions on all 3 aortic valve cusps and erosions of the right and noncoronary cusps. There is a mild fibrous subaortic ring, representing subaortic stenosis. Picture is reproduced with permission from Journal of Clinical Microbiology, 2001;39:3548–3554.

(83%) with a negative blood culture. Fluoroquinolones were the most frequently administered antibiotics and were used alone (28%, 4/14) or in combination with other antibiotics (36%, 5/14). Other antibiotics used included cephalosporins (4/14), amoxicillin (4/14), amoxicillin/clavulanic acid (2/14), doxycycline (3/14), and metronidazole (1/14). Two of the 5 dogs with IE due to *Bartonella* were receiving doxycycline and 1 dog was receiving enrofloxacin in the 24 hours before blood collection. The dog that had *B clarridgeiae* cultured from its blood was not receiving antibiotics at the time of blood collection.

No difference in signalment (sex, breed, and age) was observed between dogs with IE due to *Bartonella* versus those with IE due to other organisms. All dogs were medium- to large-sized breeds, with a median weight of 35 kg, and a range of 13–77 kg. Twelve dogs were male (67%) and 6 were female (33%). The following breeds were represented: Labrador Retriever (3), German Shepherd Dog (2), German Shepherd crossbreed (2), Mastiff (2), Golden Retriever (2), Bernese Mountain Dog (1), Australian Shepherd (1), Shetland Sheepdog (1), Boxer dog (1), Great Dane (1), and Airedale Terrier (1). Most of the dogs were middle

**Table 1.** Diagnosis of infective endocarditis due to *Bartonella* and concurrent exposure to tick-borne diseases.

| Patient | PCR Valve | Specific Blood Culture | *Bartonella* Serology | Tick-Borne Disease Serology Panel |
|---|---|---|---|---|
| 1 | *Bartonella clarridgeiae* | Positive *B.c.* | 1:2,048 *B.c.* | 1:100 *Anaplasma phagocytophilum* |
| | | | 1:1,024 *B.h.* | 1:256 *Rickettsia rickettsii* |
| | | | 1:1,024 *B.v.b* | |
| 2 | *Bartonella clarridgeiae*-like | Negative | 1:1,024 *B.c.* | 1:160 *A phagocytophilum* |
| | | | 1:256 *B.h.* | 1:256 *R rickettsii* |
| | | | 1:256 *B.v.b.* | 1:256 *Ehrlichia canis* |
| 3 | *Bartonella vinsonii berkhoffii* | Negative | 1:2,048 *B.v.b* | 1:640 *A phagocytophilum* |
| | | | 1:2,048 *B.h.* | |
| | | | 1:1,024 *B.c.* | |
| 4 | *B vinsonii berkhoffii* | Negative | 1:1,024 *B.v.b* | 1:320 *A phagocytophilum* |
| | | | 1:2,048 *B.h.* | |
| | | | 1:2,048 *B.c.* | |
| 5 | *B vinsonii berkhoffii* | Negative | 1:4,096 *B.v.b* | 1:100 *A phagocytophilum* |
| | | | 1:4,096 *B.h.* | 1:256 *E canis* |
| | | | 1:4,096 *B.c.* | 1:512 *R rickettsii* + *B burgdorferi* |

PCR, polymerase chain reaction; *B.v.b*, *Bartonella vinsonii* subsp. *berkhoffii*; *B.h.*, *Bartonella henselae*; *B.c.*, *Bartonella clarridgeiae*.

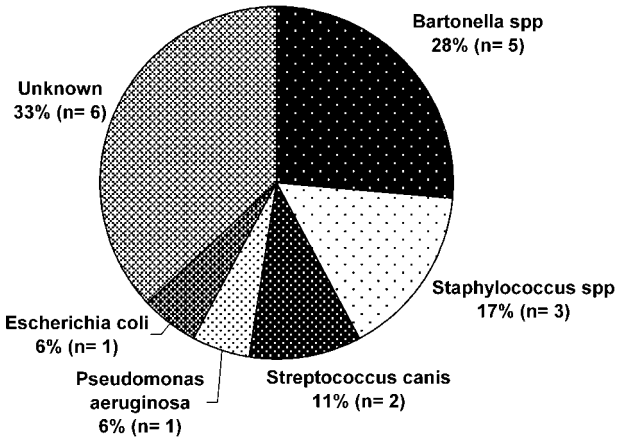


**Fig 3.** Etiology of infective endocarditis in 18 dogs presenting to University of California at Davis Veterinary Medical Teaching Hospital (VMTH) from June 1999 to May 2001.

aged to older, with a median age of 8.5 years (range, 0.5–13 years).

The presenting complaints were not different between dogs with IE due to *Bartonella* versus all other affected dogs (Table 2). The most frequent presenting complaint was lameness (44% of dogs). Lethargy and anorexia were equally frequent presenting complaints (33% each). Respiratory abnormalities (28%) and weakness and collapse (17%) also were common. One dog each was presented for each of the following: epistaxis, vomiting, and obtundation.

Eight (44%) of 18 dogs had a possible predisposing cause for IE. Potential causes included pneumonia and pancreatitis, pneumonia and gastric dilatation with volvulus, rectal carcinoma in situ, staphylococcal cystitis, deep pyoderma, and immunosuppressive therapy for pemphigus foliaceus in 1 dog each and subaortic stenosis treated by balloon dilation in 2 dogs. The only underlying heart disease present in this group was subaortic stenosis in the 2 dogs that developed aortic valvular IE after balloon valvuloplasty (1 dog with *B clarridgeiae* and 1 dog with unknown etiology).

The most common physical examination abnormality was a heart murmur (89%, 17/18) (Table 2). Fever was present in 72% (13/18) of the dogs. An electrocardiogram was obtained in 13 of 18 dogs (72%). Seven (39%) dogs had arrhythmias, which included ventricular premature complexes (3/18, 17%), supraventricular tachycardia (2/18, 11%), third-degree atrioventricular block (2/18, 11%), ventricular tachycardia (1/18, 6%), and atrial fibrillation (1/18, 6%). Two dogs had 2 concurrent arrhythmias (ventricular premature complexes and atrial fibrillation or supraventricular tachycardia). Congestive left heart failure (CHF) was present in 44% (8/18) of dogs, and was diagnosed by thoracic radiographs or postmortem examination. Thoracic radiographs were obtained in 16 dogs and disclosed cardiomegaly and cardiogenic pulmonary edema consistent with CHF in half of these dogs. Surprisingly, left atrial enlargement was seen in only 25% (4/16) of dogs, possibly due to the acute nature of CHF. Noncardiogenic pulmonary infiltrates (eg, pneumonia or pulmonary hemorrhage) were present in 25% (4/16) of these dogs. No marked difference was found in occurrence of CHF between IE of the aortic valve and IE of the mitral valve, IE due to *Bartonella* versus all other dogs, IE due to *Bartonella* versus mitral valve IE (non-*Bartonella*), and aortic valve IE due to *Bartonella* versus other etiology.

The CBC frequently was abnormal (Table 3), but no differences in CBC abnormalities were observed between dogs with IE due to *Bartonella* versus those with IE not due to *Bartonella.* The most common abnormality was leukocytosis (78%, 14/18 dogs), consisting of a mature neutrophilia (78% of dogs) and monocytosis (67% of dogs). Over half of the dogs (56%) had thrombocytopenia (range 25,000–148,000/μL). Mild nonregenerative anemia was present in 44% of dogs (hematocrit range 29–36%). Leukopenia was seen less commonly and included lymphopenia (22%), neutropenia (6%), and monocytopenia (6%).

Serum chemistry abnormalities were not different between dogs with IE due to *Bartonella* versus those with IE due to other organisms (Table 3). The most common serum chemistry abnormality was hypoalbuminemia (67% of

**Table 2.** Clinical characteristics of dogs with infective endocarditis.

| Clinical Abnormality | *Bartonella* | Non-*Bartonella* | Total |
|---|---|---|---|
| Presenting complaint | | | |
| Lameness | 60% (3/5) | 38% (5/13) | 44% (8/18) |
| Anorexia | 0% (0/5) | 46% (6/13) | 33% (6/18) |
| Lethargy | 20% (1/5) | 38% (5/13) | 33% (6/18) |
| Respiratory | 40% (2/5) | 23% (3/13) | 28% (5/18) |
| Weakness/collapse | 20% (1/5) | 15% (2/13) | 17% (3/18) |
| Clinical abnormality | | | |
| Murmur | 80% (4/5) | 100% (13/13) | 89% (17/18) |
| Fever | 40% (2/5) | 85% (11/13) | 72% (13/18) |
| Congestive heart failure | 80% (4/5) | 31% (4/13) | 44% (8/18) |
| Arrhythmia | 60% (3/5) | 31% (4/13) | 39% (7/18) |
| Other clinical sequelae | | | |
| Immune mediated polyarthritis | 100% (2/2) | 67% (4/6) | 75% (6/8) |
| Protein losing nephropathy | 40% (2/5) | 33% (2/6) | 36% (4/11) |
| Systemic thromboembolism | 40% (2/4) | 100% (3/3) | 71% (5/7) |
| Pulmonary hemorrhage | 20% (1/5) | 15% (2/13) | 17% (3/18) |

**Table 3.** Clinicopathologic data of dogs with infective endocarditis.

| Clinicopathologic Test | *Bartonella* | Non-*Bartonella* | Total |
|---|---|---|---|
| Complete blood count | | | |
| Leukocytosis | 60% (3/5) | 85% (11/13) | 78% (14/18) |
| Neutrophilia | 60% (3/5) | 85% (11/13) | 78% (14/18) |
| Monocytosis | 60% (3/5) | 69% (9/13) | 67% (12/18) |
| Thrombocytopenia | 60% (3/5) | 54% (9/13) | 56% (10/18) |
| Anemia (nonregenerative) | 20% (1/5) | 54% (7/13) | 44% (8/18) |
| Serum chemistry | | | |
| Hypoalbuminemia | 80% (4/5) | 62% (8/13) | 67% (12/18) |
| High liver enzyme activity | 60% (3/5) | 54% (7/13) | 56% (10/18) |
| Acidosis | 60% (3/5) | 54% (7/13) | 56% (10/18) |
| Azotemia | 60% (3/5) | 23% (3/13) | 33% (6/18) |
| Hypoglycemia | 20% (1/5) | 15% (2/13) | 17% (3/18) |
| Urinalysis | | | |
| Proteinuria | 50% (2/4) | 43% (3/7) | 45% (5/11) |
| Increased UPC | 75% (3/4) | 25% (1/4) | 50% (4/8) |
| Hemoglobinuria | 50% (2/4) | 29% (2/7) | 36% (4/11) |
| Hematuria | 25% (1/4) | 14% (1/7) | 18% (2/11) |
| Cystitis | 0% (0/4) | 14% (1/7) | 9% (1/11) |

UPC, urine protein creatinine ratio.

dogs), which was mild (2.5–2.8 g/dL) in 5/18 dogs, moderate (2.0–2.5 g/dL) in 6/18 dogs, and severe (<2.0 g/dL) in 1 dog. The serum concentrations of hepatic enzymes (eg, ALT, ALP) were high in 56% of dogs (mild in 9/18, moderate in 1/18). Acidosis was present in 56% of patients and consisted of metabolic acidosis (8/10) and mixed metabolic and respiratory acidosis (2/10). Six of the dogs were azotemic (4/6 mild, 2/6 moderate), with blood urea nitrogen (BUN) concentration ranging from 43 to 77 mg/dL and serum creatinine concentration ranging from 1.8 to 4.0 mg/dL. Azotemia was classified as prerenal (1/6), renal (2/6), or unclassified due to lack of measurement of urine specific gravity (3/6). Hypoglycemia was found in 3/18 dogs. Electrolyte abnormalities were rare.

Abnormalities detected on urinalysis were not markedly different between dogs with IE due to *Bartonella* versus those with IE due to non-*Bartonella* organisms (Table 3). Proteinuria was the most common abnormality and was seen in 5 of the 11 dogs (46%, Table 3) in which it was measured. Out of the 6 dogs with urine cultures performed, 1 dog had a staphylococcal urinary-tract infection as well as staphylococcal bacteremia. Four dogs (36%) had hemoglobinuria and 2 dogs (18%) had hematuria.

Immune-mediated disease was a relatively common finding in dogs with IE (Table 2). There was no marked difference observed in occurrence of immune-mediated diseases between dogs with IE due to *Bartonella* versus those with IE due to other organisms. Protein-losing nephropathy was present in 4 (36%) of 11 dogs and was diagnosed in 3 dogs by urine protein to creatinine ratio and in 1 dog by histopathology at postmortem examination. Cytologic evaluation of joint fluid was performed in 8 dogs that were lame, and immune-mediated polyarthritis was diagnosed in 6 dogs (75%). Immune-mediated thrombocytopenia was diagnosed in 1 dog with thrombocytopenia and antimegakaryocyte antibody.

Necropsies were performed on only 7 dogs (all 5 with IE due to *Bartonella*). Thromboembolic disease was present in 5 of these dogs, consisting of renal infarction (n = 2), splenic infarction (n = 2), and myocardial infarction (n = 2, including 1 dog with concurrent renal, splenic, and myocardial infarctions) (Table 2). No marked difference was observed in the presence of thromboembolic disease between dogs with IE due to *Bartonella* versus those with non-*Bartonella* etiology.

Short-term mortality was defined as time to death or euthanasia within the first 14 days after initial diagnosis of IE. Four (80%) of the 5 dogs with IE due to *Bartonella* died within this period compared with only 4/13 dogs (38%) in the non-*Bartonella* group ($P = .12$). Death shortly after diagnosis usually was cardiac related (3/18 congestive heart failure, 2/18 sudden death). Other causes of death shortly after diagnosis were renal failure, pulmonary hemorrhage, and severe neurologic disease (seizures). Kaplan-Meier curves were constructed comparing dogs with IE due to *Bartonella* to dogs with IE of other etiology (Fig 4). Dogs were censored at the time of last follow-up or at the time of death because of another disease. The median and mean survival times of dogs with IE due to *Bartonella* were 3 days (95% CI = 0–8.4 days) and 45 days (95% CI = 0–126 days), respectively, compared with significantly longer median (330 days, 95% CI = 0–664) and mean (375 days, 95% CI = 193–557 days) survival times in non-*Bartonella* cases ($P = .01$). Dogs with mitral valve IE (none due to *Bartonella*) lived longer (13, 120, >150, 330, 540, 630, >690, and >780 days) than dogs with aortic valve IE due to *Bartonella* (1, 1, 3, 9, and 210 days, $P = .002$) or due to other organisms (1, 14, 210, and 330 days; $P = .004$). No difference in survival was observed between dogs with aortic valve IE due to *Bartonella* versus those with IE not due to *Bartonella* ($P = .18$).

## Discussion

This study confirmed that the fastidious bacterium *Bartonella* is an important cause of IE in dogs living in north-

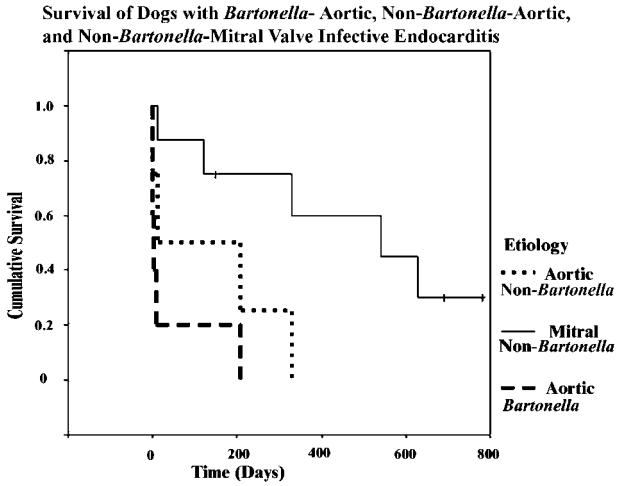


**Fig 4.** Kaplan-Meier survival curves of dogs with infective endocarditis. The 3 groups depicted are dogs with IE of the aortic valve due to *Bartonella* (dashed line), aortic valve IE not due to *Bartonella* (dotted line), and mitral valve IE not due to *Bartonella* (solid line). Dogs with mitral valve IE (non-*Bartonella* etiology) lived longer than dogs with aortic valve IE (*Bartonella* and non-*Bartonella* etiology).

ern California, especially in those living in the northern Pacific Coast region. Identification of the offending organism would have been missed in more than 25% of the cases if diagnostic tests had been limited to standard aerobic and anaerobic blood cultures. By using specialized techniques, we were able to identify *Bartonella* as the causative agent in more than 40% of dogs with IE that had negative conventional blood cultures.

Before clinical awareness of *Bartonella,* the most common bacterial isolates in canine IE were *Staphylococcus, Streptococcus, Escherichia coli, Corynebacterium, and Erysipelothrix.*[1,2] Breitschwerdt and colleagues identified the first dog with IE due to *Bartonella* in 1993 and named the novel subspecies *B vinsonii* subsp. *berkhoffii.*[20] Since that time, 3 additional species, (*B clarridgeiae, B clarridgeiae*-like, and *B washoensis)* have been documented to cause IE in dogs.[11,39] *Bartonella* also is an important but apparently less common cause of culture-negative IE in people.[4] Three percent of all IE cases in human patients were caused by *Bartonella* species in 1 study.[12] The difficulties in diagnosing IE due to *Bartonella* are common to both veterinary and human medicines. The specialized blood culture method for *Bartonella* in the current study was highly insensitive for identifying dogs infected with *Bartonella.* Similarly, only 6% of humans with IE due to *Bartonella henselae* are bacteremic for this organism.[13] With the limitations of the current culture methods, serologic testing for antibodies to *Bartonella* has become the gold standard of clinical diagnosis in affected humans.[21]

This study supports previous studies in veterinary and human medicine that demonstrated that *Bartonella* preferentially infects the aortic valve and rarely infects the mitral valve.[11–13,20,22] *B henselae* also has been implicated as a cause of infective myocarditis, immune-mediated lymphocytic myocarditis, and sudden cardiac death in people.[23,24] Likewise, *B vinsonii* subsp. *berkhoffii* and the closely related *Proteobacterium* species have been shown to cause neutrophilic and granulomatous myocarditis in 2 dogs.[22]

The diagnosis of IE usually is best made by examining the mitral and aortic valves for a characteristic lesion in dogs. Echocardiographic visualization of characteristic valvular lesions in dogs often is easier than in humans due to the favorable thoracic anatomy of the dog.[16] Consequently, whereas physicians often have to rely on transesophageal echocardiography to make the anatomical diagnosis, this is rarely necessary in dogs.[25] The incidence of culture-negative IE in dogs (20–70%), however, is much higher than it is in humans (5–24%).[1,2,4] The large number of blood culture-negative cases hampers the diagnosis of IE and disables the clinician from administering the most appropriate treatment for the specific pathogen. A large number of dogs (62%), including all dogs with IE due to *Bartonella* in this study, had negative blood cultures for conventional organisms. Many of the culture-negative cases were likely due to the high concurrent use of antibiotics, but a marked proportion was due to *Bartonella.* A majority of the cases of IE due to *Bartonella* would have been missed if serology had not been performed. Consequently, it is apparent that all dogs in northern California (and probably many parts of the world) should have *Bartonella* serology performed as part of the diagnostic work-up of IE.

The fastidious nature of the *Bartonella* organism and the presence of antibiotics in the affected patients rendered blood cultures for *Bartonella* ineffective in this study. In humans, other fastidious bacteria that cause culture-negative IE include gram-negative bacilli in the HAECK group (*Haemophilus, Actinobacillus, Eikenella, Cardiobacterium, Kingella*), *Chlamydia psittaci, Mycobacterium, Brucella, Campylobacter,* and *Coxiella.*[4] Millar and colleagues have suggested the addition of molecular techniques including PCR amplification of specific genes of fastidious bacteria or fungi as a new standard criterion for diagnosis of IE due to fastidious bacteria in human medicine.[26] Addition of PCR for molecular diagnosis of bacteria from blood or cardiac valve material increased the number of human patients diagnosed with IE by 25% in 1 study.[26] This technique should be used more widely in veterinary medicine to enhance the accuracy of identifying circulating *Bartonella* organisms in dogs with suspected IE and possibly to enhance the ability to identify appropriate drug therapy.

In the current study, a high serum antibody titer ($>$ 1:1,024) to *Bartonella* sp. was a highly specific antemortem diagnostic tool for diagnosis of IE due to *Bartonella* in dogs with characteristic echocardiographic lesions. All dogs with IE due to *Bartonella* had high antibody titers for all *Bartonella* spp. tested, indicative of cross reactivity to antigens common to most *Bartonella* species. In contrast, a previous study reported a relatively low antibody titer (1 : 128) in 2 dogs with PCR-confirmed IE due to *B vinsonii berkhoffii.*[22] A low level of cross-reaction with *C burnetii* also has been reported in *Bartonella* infections.[27] However, none of the dogs that had a high serum antibody titer to *Bartonella* were seroreactive for *C burnetii* in this study. Sensitivity could not be determined because the affected valves of all dogs with IE in the current study were not available for PCR analysis of *Bartonella.*

In humans, a high serum *Bartonella* antibody titer is an

accurate method of diagnosing IE due to *Bartonella*, where a titer of >1:800 is highly predictive (.955 positive predictive value) and highly sensitive (90%) for IE due to *Bartonella*.[21] Only 1 (2%) of 48 people diagnosed with IE due to *Bartonella* was seronegative for *Bartonella* sp. in 1 study.[13]

*Bartonella* seroepidemiology has been studied in sick and healthy dogs as well as in coyotes of California.[28,29] During 2001, <3% of over 2,000 dogs presented to UC Davis VMTH were seroreactive (>1:64) for *Bartonella*, and none had a titer ≥1:512 (Brady et al, unpublished data). Therefore, although *Bartonella* was an important cause of IE in dogs seen at the VMTH during the current study, *Bartonella* did not appear to be a prevalent cause of active disease across this hospital population. Similarly, seroreactivity to *B vinsonii* subsp. *berkhoffii* was found in 3.6% of sick dogs presented to North Carolina State University College of Veterinary Medicine, whereas 93% of 27 sick, heavily tick-infested Walker Hounds living in a kennel in North Carolina were seroreactive.[29,30] The high prevalence of seroreactivity in the kennel likely reflects increased exposure to a tick vector. *Bartonella* seroreactivity in healthy military dogs ranged from 5 to 65% in 1 study, where the highest seroreactivity occurred in tropical climates.[31] In the current study, the majority of dogs with IE due to *Bartonella* lived in the northern Pacific Coast region of California, where ticks are endemic. In this same Pacific Coast region, 64% of coyotes were seroreactive for *B vinsonii* subsp. *berkhoffii*, yet <10% had a high antibody titer. In endemic areas, the coyote may serve as a reservoir host for *Bartonella*.[28]

Several epidemiologic studies have suggested that *Rhipicephalus sanguineus* and other ticks may be vectors for *Bartonella*.[29,32] Twenty percent of adult *Ixodes pacificus* ticks living in a *Bartonella*-endemic area of the Pacific Coast region of California contained *Bartonella* DNA.[32] Additional supporting evidence that *Bartonella* is transmitted to dogs via ticks is the high prevalence of other tick-borne diseases in *Bartonella* seroreactive dogs.[17,29,30,33] In fact, 7 of 12 dogs from the southeastern United States, which were seroreactive to *E canis* antigens had *B vinsonii* subsp. *berkhoffii* identified by PCR from their blood.[17] In the present study, every dog with IE due to *Bartonella* was seroreactive for *Anaplasma phagocytophilum*, and 3 dogs were concurrently seroreactive for other tick-transmitted pathogens, including *Rickettsia rickettsii*, *Ehrlichia canis*, and *Borrelia burgdorferi*. Because dogs with IE frequently had immune-mediated polyarthritis, it is difficult to separate clinical signs due to *Bartonella* IE in dogs from clinical signs caused by coinfection with other similar tick-borne diseases. The true prevalence of immune-mediated polyarthritis in dogs with IE was likely overestimated. Joint fluid was only obtained in lame dogs, and we were unable to evaluate the prevalence of immune-mediated polyarthritis in dogs with IE.

*Bartonella* evades the humoral immune system by living within red blood cells and endothelial cells of the mammalian host.[34] Chronic experimental infections of *B. vinsonii* subsp. *berkhoffii* in dogs caused impaired immune defenses by reducing the number of CD8+ lymphocytes and their cell adhesion molecule expression.[35] In 1 study, an expanded population of naive CD4+ T lymphocytes was found, but B cells had less MHC II expression, implicating impaired antigen presentation to helper T cells within the lymph node.[35] These changes may impair the host's ability to clear intracellular *Bartonella*. In people, *Bartonella quintana* bacteremia caused increased IL-10 secretion from mononuclear cells, which resulted in an attenuation of the inflammatory response.[36] Chronic bartonellosis may contribute to immune suppression and development of systemic illnesses.

The prognosis was grave for dogs with IE due to *Bartonella* in the present study. Dogs often developed severe aortic insufficiency, resulting in rapid development of CHF and death. Sudden death, most likely due to fatal cardiac arrhythmia, also was observed. In people, IE due to *Bartonella* also confers a poor prognosis, which is likely related to the severe aortic valvular damage and the delay in diagnosis in many cases.[4] The aortic valve was solely infected in almost 60% of humans with IE due to *Bartonella* and over 80% of cases involved the aortic valve in addition to other cardiac valves in 1 study.[37] Humans with IE due to *Bartonella quintana* were more likely to survive if they received long-term treatment (>2 weeks duration) of aminoglycoside antibiotics.[37] No studies, however, have been performed to determine the efficacy of antibiotic therapy for treatment of *Bartonella* infections in dogs. By extrapolating from data in other species, chronic administration of doxycycline or tetracycline may reduce bacteremia.[38] All dogs with IE due to *Bartonella* in the current study had infected aortic valves and it is impossible to separate the effect of the organism from the effect of the diseased aortic valve on survival. In a series of 24 dogs with aortic IE due to conventional bacterial isolates, one third of dogs died or were euthanized within the first week and 87% of the remaining dogs died or were euthanized within 6 months.[1] Although 1 investigator suggested that aortic valve IE may be associated with a higher incidence of CHF, the current study did not identify a marked difference in the incidence of CHF between dogs with IE involving the mitral valve and those with aortic valves involvement.[2]

In conclusion, this study documented that *Bartonella* is an important cause of IE in dogs living in northern California and determined that a large number of culture-negative cases were due to *Bartonella* infections. *Bartonella* preferentially infected the aortic valve, where it caused extensive valve destruction and severe aortic insufficiency. Patients often rapidly succumbed to severe CHF or cardiac arrhythmias. A high (>1:512) antibody titer against *Bartonella* coupled with a characteristic echocardiographic lesion was highly specific for the diagnosis of IE due to *Bartonella*.

## Footnotes

[a] Lyme Reference Laboratory, Cornell University, Ithaca, NY
[b] Vector Borne Diseases Diagnostic Laboratory, North Carolina State University, Raleigh, NC
[c] Fuller Labs, Fullerton, CA
[d] Isostat microbial system, Wampole Laboratories, Cranbury, NJ
[e] BBL Septi-chek, Becton Dickinson, Le Pont de Claix, France

[f] $K_2$EDTA blood tubes, Becton Dickinson VACUTAINER Systems 1136601, Franklin Lakes, NJ
[g] Hewlett Packard, Palo Alto, CA
[h] Epi-Info, Center for Disease Control and Prevention, Division of Public Health Surveillance and Informatics, Atlanta, GA
[i] SPSS software, SPSS Inc, Chicago, IL

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