Infective Endocarditis in Dogs: Diagnosis and Therapy

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KEYWORDS

- Bacterial endocarditis • Bartonella • Echocardiography
- Congestive heart failure • Mitral regurgitation
- Aortic insufficiency

OVERVIEW

Infective Endocarditis (IE) is a deadly, difficult-to-diagnose disease caused by microbial invasion into the endothelium of heart valves or endocardium. Although the reported prevalence is low (0.09%–6.6%) in dogs presenting to a tertiary referral center, the true prevalence in the general population is likely to be highly underestimated because of the nebulous clinical signs and difficulty in diagnosis. IE in cats is extremely rare. Acute congestive heart failure is the most common pathophysiologic consequence of IE. Other sequelae include immune-mediated disease (glomerulonephritis, immune-mediated polyarthritis), thromboembolic disease, septic polyarthritis, and arrhythmias. The mitral and aortic valves are the most affected in small animals. The most common microbiologic causes include *Staphylococcus* spp, *Streptococcus* spp, and *Escherichia coli*. The most common cause of culture negative IE is *Bartonella*. IE is diagnosed by using a modified set of criteria including echocardiographic diagnosis of an oscillating vegetative lesion on a cardiac valve. Long-term treatment (8–12 weeks) is needed with broad-spectrum antibiotics, optimally including at least 1 week of intravenous antibiotics. Overall prognosis is poor, and survival depends on the type of valve that is infected. Dogs with IE of the aortic valve have a grave prognosis, with median survival time (MST) of 3 days compared with dogs with IE of the mitral valve that have significantly longer lives (MST 476 days).

This article reviews the key aspects of pathophysiology and sequelae, diagnosis using a modified criteria scheme, and appropriate treatment options for IE.

PATHOGENESIS OF IE

The normal endothelial surface of the heart and valves is naturally resistant to microbial invasion, but becomes susceptible when the surface is damaged. Formation of IE

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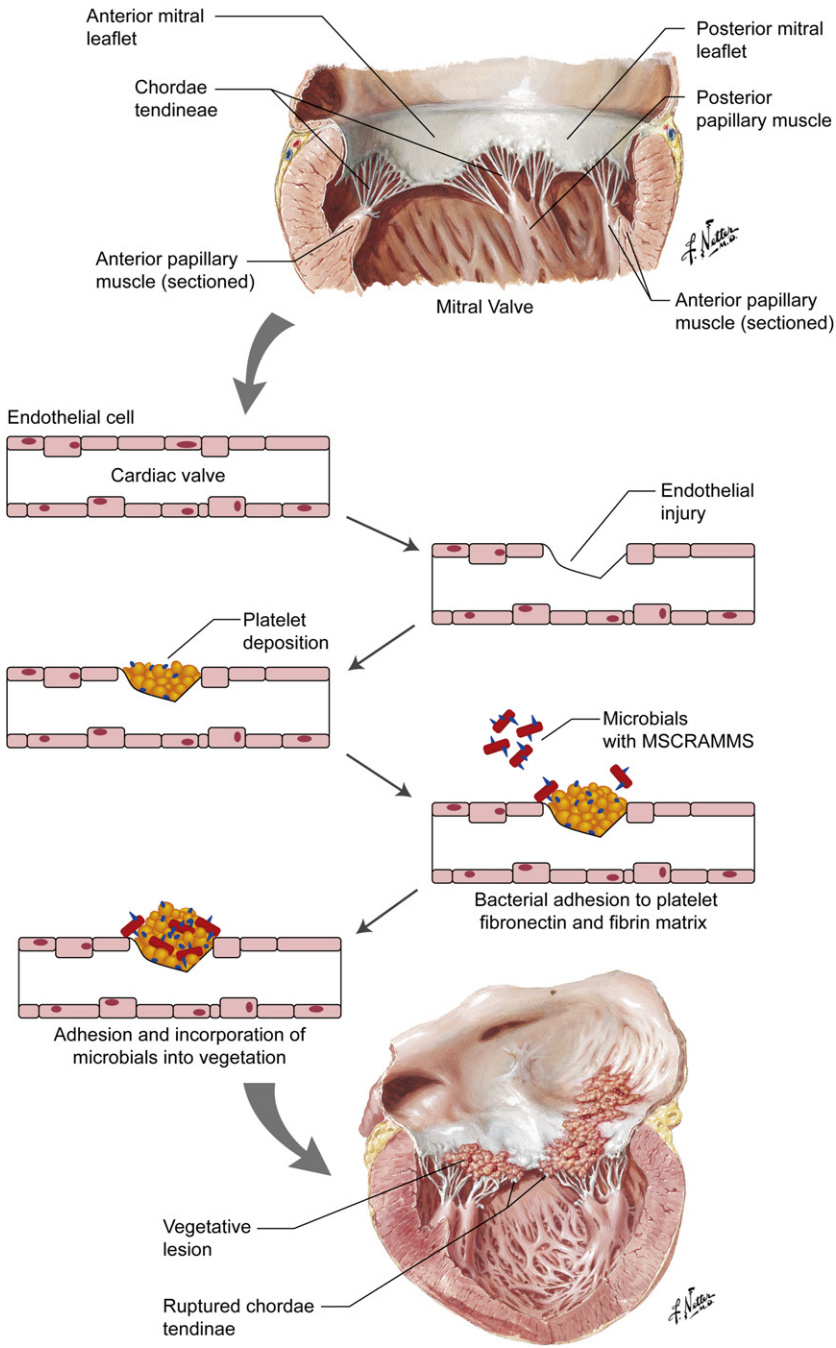
is triggered by endothelial damage, followed by platelet-fibrin deposition that provides a milieu for bacterial colonization, and finally bacterial adherence to the coagulum (**Fig. 1**). Mechanical lesions (ie, subaortic stenosis or cardiac catheterization procedure) or inflammatory lesions can promote bacterial seeding within the endothelium.



Lesions of IE develop on the ventricular side of the aortic valve, and the atrial side of the mitral valve, in regions of the most significant blood flow injury (**Fig. 2**).[1] During disruption of the endothelium, extracellular matrix proteins, thromboplastin, and tissue factor trigger coagulation, and a coagulum forms on the damaged endothelium. This coagulum contains fibrinogen, fibrin, and platelet proteins, and avidly binds bacteria. Inflammation induces endothelial cell expression of integrins that bind bacteria and fibronectin to the exposed extracellular matrix. Fibronectin facilitates adherence of bacteria to the vegetation. Bacteremia must be present and the bacteria must be able to adhere to the coagulum for colonization to occur. This adherence is mediated by microbial surface components recognizing adhesive matrix molecules (MSCRAMMS) that are expressed on the surface of some bacteria. Organisms that commonly cause IE possess receptors for MSCRAMMS and have the greatest ability to adhere to damaged valves, including *Staphylococcus* spp and *Streptococcus* spp. These virulent bacteria can trigger tissue factor production and induce platelet aggregation, thereby building a larger vegetative lesion. *Streptococcus* spp produce surface glucans and dextran, which avidly bind to the coagulum on damaged valves. The fibrinous vegetative lesion shields bacteria from the blood stream and host defenses, and provides a formidable obstacle for antibiotic penetration (see **Fig. 2**). Extremely high concentrations of bacteria (10^9–10^{11} bacteria per gram of tissue) may accumulate within the vegetative lesion.[2] Bacteria also excrete enzymes that lead to destruction of valve tissue and rupture of chordae tendinae. Bacteria have also developed other mechanisms to evade the host. Although platelets release bactericidal proteins, most bacteria that cause IE are resistant to these proteins. Bacteria such as *Staphylococcus aureus* and *Bartonella* may become internalized within the endothelial cells and escape detection by the immune system. *Bartonella* also evade the immune system by colonizing red blood cells without causing hemolysis.

CAUSATIVE AGENTS

The most common causes of IE include *Staphylococcal* spp (*aureus*, *intermedius*, coagulase positive, and coagulase negative), *Streptococcus* spp (*canis*, *bovis*, and β-hemolytic), and *E coli* in order of frequency (**Table 1**). Less common bacterial isolates include *Pseudomonas*, *Erysipelothrix rhusiopathiae*, *Enterobacter*, *Pasteurella*, *Corynebacterium*, and *Proteus*. Rare causes of IE include *Bordetella avium*–like organism, *Erysipelothrix tonsillarum*, and *Actinomyces turicensis*.

IE CAUSED BY *BARTONELLA*

Bartonella has now been recognized as an important cause of culture-negative IE in people, and is more commonly screened for in dogs with systemic diseases including

Fig. 1. Pathogenesis of IE. A normal mitral valve (including leaflets and chordae tendinae) is represented (*top*) and a magnified view shows intact normal endothelium (*bottom*). The initiating step in development of IE is an injury to the endothelium, which exposes extracellular matrix proteins. A coagulum of platelets (*yellow*), fibrinogen, fibronectin, and fibrin develops. The fibronectin receptor (*blue*) on platelets and extracellular matrix proteins avidly bind bacteria that contain MSCRAMMS. The microorganism becomes embedded and incorporated into the vegetative lesion, and multiplies. The vegetative lesion may extend to chordae tendinae, opposing leaflet, or atrial endothelium, and may cause rupture of chordae tendinae. The end result is severe mitral regurgitation and congestive heart failure. (Netter Anatomy Illustration Collection, © Elsevier, Inc. All Rights Reserved. Labels revised with permission.)

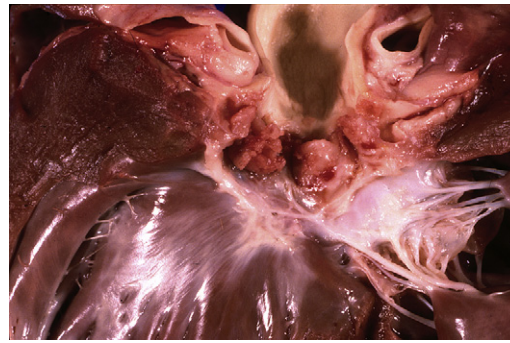


Fig. 2. Gross pathology of a dog with IE of the aortic valve. Vegetative lesions of the aortic valve appear as shaggy, thickened lesions (cauliflower-like appearance) that are also erosive to the underlying valve. This causes severe aortic insufficiency, which is a high-velocity jet that damages the endothelial surface of the interventricular septum and causes a fibrotic jet lesion. Subaortic stenosis is also seen as a fibrotic ring below the aortic cusp, which likely predisposed this dog to developing IE.

IE. In a recent case series of IE in 18 dogs living in Northern California, *Bartonella* was the most common causative agent in 28% of dogs, including 45% of dogs with negative blood cultures.[3] This may be an unusually high prevalence of IE caused by *Bartonella* compared with other parts of the country, but highlights the importance of testing for bartonellosis in dogs with IE. *Bartonella vinsonii* subsp *berkhoffii* is the most important species of *Bartonella* causing IE in dogs.[3,4] Other less common *Bartonella* species that cause IE in dogs include *B clarridgeiae*, *B washoensis*, *B quintana*, *B rochalimae*, *B clarridgeiae*–like, and *B koehlerae*.[5,6]

Bartonella primarily affects the aortic valve, and less commonly affects the mitral valve in dogs and causes unique valvular lesions characterized by fibrosis, mineralization, endothelial proliferation, and neovascularization.[7] *Bartonella* evades the immune system by colonizing red blood cells and endothelial cells, and also impairs the immune system by reducing the number of CD8+ lymphocytes and their cell adhesion

Table 1
Suggested criteria for diagnosis of IE in dogs

Major Criteria	Minor Criteria	Diagnosis
Positive echocardiogram	Fever	Definite
Vegetative, oscillating lesion	Medium to large dog (>15 kg)	Pathology of valve
Erosive lesion	Subaortic stenosis	2 Major criteria
Abscess	Thromboembolic disease	1 major and 2 minor
New valvular insufficiency	Immune-mediated disease	Possible
>Mild AI in absence of subaortic stenosis or annuloaortic ectasia	Polyarthritis	1 major and 1 minor
	Glomerulonephritis	3 minor
Positive blood culture	Positive blood culture not meeting major criteria	Rejected
≥2 positive blood cultures	*Bartonella* serology ≥1:1024	Firm alternative Dx
≥3 with common skin contaminant		Resolution <4 days of Rx
		No pathologic evidence

Abbreviations: AI, aortic insufficiency. Dx, diagnosis. Rx, treatment.

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molecule expression, inhibition of monocyte phagocytosis, and impairment of B-cell antigen presentation within lymph nodes.[8] The clinical characteristics of dogs with IE due to *Bartonella* are no different to dogs with IE due to traditional bacteria. In the author's experience, dogs with IE due to traditional bacteria do not have coinfections with *Bartonella*.[3,7] Several epidemiologic studies have suggested that ticks and fleas may be vectors for *Bartonella*. Concurrent seroreactivity to *Anaplasma phagocytophilum*, *Ehrlichia canis*, or *Rickettsia rickettsii* is common in dogs with IE due to *Bartonella*, and titers should be submitted for tick-borne diseases in dogs that are seroreactive to *Bartonella* antigen.[3,9]

PREDISPOSING FACTORS

Presence of bacteremia and endothelial disruption are necessary for development of IE. The most common underlying cardiac defect in dogs with IE is subaortic stenosis, which creates turbulent blood flow and damage to the ventricular aspect of the aortic cusps.[10,11] No other cardiac diseases have been statistically shown to predispose dogs to IE.[11] Myxomatous valve degeneration is the most common heart disease in dogs, and occurs most commonly in small-breed aged dogs, who virtually never develop IE. Therefore, it is unlikely that myxomatous valve degeneration is a predisposing factor for development of IE. Common sources of bacteremia in dogs include diskospondylitis, prostatitis, pneumonia, urinary tract infection, pyoderma, periodontal disease, and long-term indwelling central venous catheters. The role of immunosuppression as a predisposing factor for IE is controversial. In a recent study of IE in dogs, only 1 of 18 dogs (5%) had been recently administered immunosuppressive therapy for treatment of pemphigus foliaceus.[3] However, an earlier study found that 17 of 45 dogs (38%) with IE received corticosteroids at some time during the course of disease.[12] Dental prophylaxis as a predisposing factor for development of IE in dogs has long been anecdotally touted as a clinical truth without any statistical evidence. A well-designed study has recently rejected the notion that dental prophylaxis predisposes dogs to develop IE, because it did not find any association between IE and dental procedures, oral surgical procedures, or oral infection in the preceding 3 months.[11] To echo this finding, the American Heart Association revised guidelines in 2007 for antibiotic dental prophylaxis to include only patients with prosthetic heart valve, a history of IE, certain forms of congenital heart disease, and valvulopathy after cardiac catheterization, and only before procedures that involve manipulation of gingival tissue or the periapical region of teeth.[13] Routine dental cleaning is excluded.

PATHOPHYSIOLOGY OF IE

Congestive Heart Failure

Congestive heart failure is the most common sequela of IE, and is the most common cause of death. Acute heart failure is a common feature of this rapidly progressive and virulent disease. IE of the aortic valve causes massive aortic insufficiency, which increases left ventricular end-diastolic volume and pressure. Similarly, IE of the mitral valve causes severe mitral regurgitation secondary to the large vegetative lesion causing a large gap in valve coaptation, rupture of chordae tendinae, and valvular erosion, which increases left ventricular end-diastolic pressure. Cardiogenic pulmonary edema develops once the left ventricular end-diastolic pressure (and pulmonary capillary wedge pressure) exceed 20 to 25 mm Hg.[14] Early edema formation occurs in the pulmonary interstitium, and appears as interstitial infiltrates in the perihilar region of the lungs. However, most cases of IE are rapid and severe, and cause fulminant pulmonary edema with alveolar flooding. Acute and fatal increase in the left ventricular

diastolic pressure often occurs before the development of left atrial dilation. Pulmonary veins are typically distended despite the lack of marked cardiomegaly. If the animal is able to survive for weeks to months with severe aortic insufficiency, systolic myocardial failure develops secondary to marked increase in the left ventricular systolic wall stress. Chronic severe aortic insufficiency and mitral regurgitation secondary to IE cause volume overload to the left heart, and increased left ventricular end-diastolic diameter and left atrial diameter. Fractional shortening is often increased in dogs with chronic mitral regurgitation as long as the systolic function is preserved, but may normalize in dogs with secondary myocardial failure.

Immune-Mediated Disease

Patients with IE tend to develop high titers of antibodies against causative microorganisms, and there is continuous formation of circulating immune complexes.[15] Immune complexes consist of IgM, IgG, and C3 (complement). Factors such as rheumatoid factor may impair the ability of complement to solubilize immune complexes, and may lead to formation of large immune complexes. Extracardiac disease manifestations are caused by immune complex deposition and further complement activation and tissue destruction in the glomerular basement membrane, joint capsule, or dermis. Shortly after antibiotic therapy in people with IE, the circulating immune complexes are greatly reduced . Immune-mediated diseases including polyarthritis and glomerulonephritis are commonly seen in dogs with IE (75% and 36%, respectively).[3] Joint fluid analysis and culture should be performed in dogs with lameness to evaluate for immune-mediated polyarthritis or septic arthritis. Urine protein:creatinine ratio (UPC) should be evaluated in dogs with proteinuria to support the diagnosis of glomerulonephritis.

Thromboembolism

Thromboembolism (septic and aseptic) commonly occurs in 70% to 80% of dogs with IE examined at pathology.[3] Like people, dogs are more likely to suffer from thromboembolic disease with mitral valve IE.[16] In people, risk of thromboembolic disease is greatest with mitral valve IE, large mobile large vegetative lesions greater than 1 to 1.5 cm in size, or with increasing lesion size during antibiotic therapy.[17,18] Infarction of the kidneys and spleen are most common in dogs, followed by infarction of the myocardium, brain, and systemic arteries. Vascular encephalopathy occurs in approximately one-third of people with IE, and is uncommon in dogs. Recently a case series of 4 dogs with IE and vascular encephalopathy was described.[19] Thromboembolism most commonly occurs in the middle cerebral artery in both people and dogs, and results in brain ischemia and possible ischemic necrosis if persistent. A mycotic aneurysm is caused by a septic thromboembolus that lodges in a peripheral artery, often at a branch point, and causes destruction of the arterial wall and a localized, irreversible arterial dilatation. Mycotic aneurysms are often described in the cerebral vasculature of people with IE, which account for approximately 15% of neurologic complications.[2] The clinical syndrome in people ranges from a slow leak that produces only mild headache and meningeal irritation, to sudden intracranial hemorrhage and major neurologic deficits.

Other Uncommon Pathophysiologic Sequelae

Hypertrophic osteopathy is a rare sequela to IE in dogs.[20,21] Hypertrophic osteopathy is caused by increased blood flow to the extremities, triggering overgrowth of vascular connective tissue and subsequent fibrochondroid metaplasia and subperiosteal new bone formation. One potential mechanism of hypertrophic osteopathy associated with IE is that platelet clumps that detach from the vegetative endocardial lesion obstruct

a peripheral artery. Platelets release platelet-derived growth factor, which increases vascular permeability and is chemotactic for neutrophils, monocytes, and fibroblasts. The end result is increased connective tissue and fibrochondroid metaplasia, starting in the metacarpals and metatarsals, and progressing proximally.

History and Presenting Complaint

Dogs with IE often have an ill-defined history of nonspecific signs of extracardiac systemic illness including lethargy, weakness, and weight loss. In a case series of 18 dogs, lameness was the most common presenting complaint in 44% of dogs diagnosed with IE.[3] Other common nonspecific signs include lethargy, anorexia, respiratory abnormalities, weakness, and collapse. Less common presenting complaints include neurologic abnormalities, vomiting, and epistaxis. An identifiable recent precipitating factor such as a surgical or dental procedure, catheterization, or trauma is usually absent. Dogs with *Bartonella* IE often have a history of ectoparasite infestation with fleas and ticks, and live in endemic areas for bartonellosis. Although widely expected, the pathognomonic history of a large-breed dog with a new murmur, fever, shifting leg lameness, and a predisposing factor for bacteremia is overemphasized and is not the norm. In a study of 18 dogs, less than half of the dogs diagnosed with IE had identifiable predisposing causes.[3] Fever may be masked by concomitant antibiotics or anti-inflammatory medications. Most dogs (80%) diagnosed with IE in one study were currently receiving antibiotics, with a majority (64%) receiving fluoroquinolones alone or in combination with other antibiotics.[3]

Signalment

Medium- to large-breed (median weight in one study was 35 kg, range 13–57 kg), middle-aged to older male dogs are most commonly affected with IE.[3] German Shepherd dogs were predisposed to develop IE in a postmortem study.[22]

Cardiovascular Examination

A murmur is ausculted in a majority of dogs with IE (89%–96%).[3,10] Presence of a new or changing (ie, increased intensity) murmur is the prototypical auscultation abnormality, but in one study only 41% of dogs with IE had a new murmur.[12] Mitral valve IE causes mitral regurgitation and a left apical systolic murmur, with the intensity roughly paralleling the severity of the regurgitation. Aortic valve IE causes aortic insufficiency, which is much more challenging to auscult. Aortic insufficiency creates a soft, diastolic murmur at the base of the heart, which can often be masked by increased respiratory noises or lack of experience. Often there is a systolic basilar ejection murmur in dogs with aortic IE, secondary to underlying subaortic stenosis, narrowed aortic lumen because of presence of a vegetative lesion, or increased stroke volume as a result of massive aortic insufficiency. A diastolic murmur is almost always present in conjunction with a systolic murmur (69%), and rarely alone (8%).[16] The combination of increased systolic turbulence at the aortic valve and diastolic leak in the aortic valve creates a ''to-and-fro'' murmur that may be confused with a continuous murmur of a patent ductus arteriosus. Clinical findings of a diastolic left basilar murmur and bounding femoral pulses should trigger a high level of suspicion of aortic valve IE, and further diagnostics should be immediately pursued as outlined later in this article. Bounding femoral arterial pulses occur in dogs with severe aortic insufficiency and reflect a widened pulse pressure caused by low diastolic pressure from the diastolic run-off of aortic insufficiency and potentially increased systolic pressure. Mucous membranes may appear injected in bacteremic, septic patients, or may appear pale in patients with low-output heart failure. Respiratory abnormalities including

tachypnea, dyspnea, cough, or adventitious lung sounds are common, given the high frequency (50%) of heart failure in dogs with IE. Fever is often present (50%–74%), but may be episodic.

Other common physical examination abnormalities include lameness, joint pain, and swelling. In one study 57% of dogs were recumbent, reluctant to stand, and were stiff, lame, or weak.[16] Neurologic abnormalities are not uncommon (23% of dogs in one study) and include ataxia, deficits of conscious proprioception, obtundation, cranial nerve deficits, and vestibular signs.[16] Arterial thromboembolism occurs most frequently in the right thoracic limb or pelvic limbs and causes clinical abnormalities of cold extremities, cyanotic nail beds, pain and lameness, absence pulses, and firm musculature of the affected limb.

Electrocardiogram

Arrhythmias are present in 40% to 70% of dogs, and include in order of incidence ventricular arrhythmias, supraventricular tachycardia, third-degree atrioventricular block, and atrial fibrillation. The highest reported frequency of arrhythmias was seen in dogs with aortic IE, with 62% of dogs having ventricular arrhythmias.[10] Third-degree atrioventricular block may occur with periannular abscess formation secondary to aortic valve IE.[23]

Thoracic Radiographs

Cardiogenic pulmonary edema is present in almost half of patients, and is diagnosed by identification of perihilar to caudodorsal interstitial to alveolar pulmonary infiltrates. Acute congestive heart failure occurs in the absence of left atrial enlargement in 75% of cases of IE, which makes radiographic interpretation challenging (**Fig. 3**).[3] Often

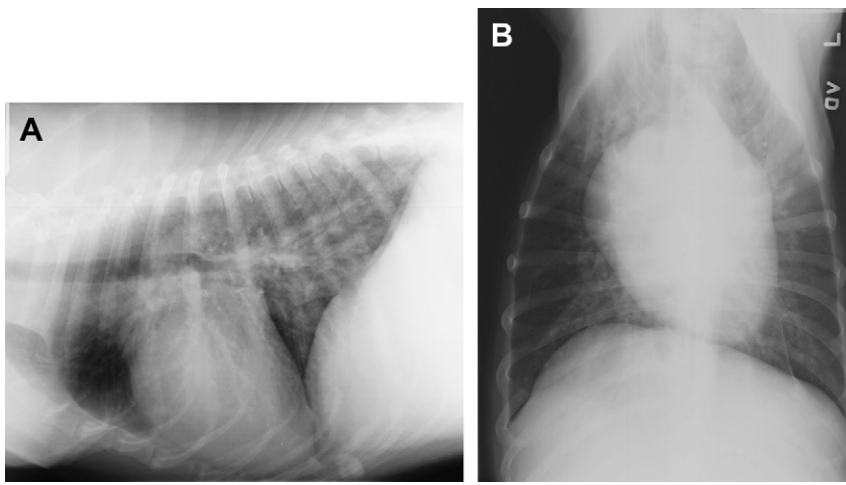


Fig. 3. Radiographs (*A*, *B*) of a dog with acute IE of the aortic valve. This dog presented for acute dyspnea, and thoracic radiographs show normal heart size and diffuse interstitial pulmonary infiltrates of the caudal lung lobes. Pulmonary veins were mildly distended. Because of the lack of cardiomegaly, there was debate whether the infiltrates were cardiogenic, and measurement of markedly elevated pulmonary capillary wedge pressure confirmed left heart failure as the cause of the infiltrates. This dog had acute aortic insufficiency from *Bartonella* IE of the aortic valve, causing acute cardiogenic pulmonary edema without overt cardiomegaly.

there is pulmonary venous distension despite unremarkable heart size. If the animal is able to survive long enough, left atrial dilation and left ventricular enlargement develop over weeks. Mitral and aortic IE equally lead to development of heart failure. Noncardiogenic pulmonary infiltrates including pneumonia or pulmonary hemorrhage are not uncommon, and occurred in approximately one-quarter of cases in one study.[3]

Clinicopathologic Abnormalities

The most common clinicopathologic abnormality is leukocytosis on a complete blood count, which occurred in 89% of dogs in a case series.[16] Typically there is a mature neutrophilia and monocytosis. Mild to severe thrombocytopenia is also commonly seen in more than half of all cases.[16] Anemia is common (52%) and is most often mild nonregenerative anemia. There is evidence of a procoagulable state in some dogs with IE, including an elevated D-dimer or fibrin degradation products in 87% of dogs in which they were measured, and hyperfibrinogenemia in 83% of dogs in which it was measured.[16] Serum chemistry often shows hypoalbuminemia (95% of dogs), elevated hepatic enzyme activity, and acidosis. Renal complications are commonly seen in at least half of dogs with IE, and may include prerenal or renal azotemia. Moderate to severe renal failure was present in approximately 33% of dogs in a case series.[3] Other significant abnormalities may include glomerulonephritis, pyelonephritis, and renal thrombosis. The most common abnormalities on urinalysis include cystitis (60% of dogs), proteinuria (50%–60%), and hematuria (18%–62%). A urine culture should always be obtained in an effort to identify a possible source of bacteremia and obtain a minimum inhibitory concentration (MIC) to guide appropriate antibiotic therapy. UPC is a necessary test in dogs with proteinuria to establish if there is excess protein loss from the kidneys, which may lead to a hypercoagulable state by loss of antithrombin III. An increased UPC ratio was present in 77% of dogs with IE, in which it was measured, and was moderate or severely elevated in 58% of these dogs.[16]

Joint Fluid Analysis

Arthrocentesis, cytologic analysis of joint fluid, and culture of the joint fluid are necessary in dogs with lameness or joint effusion. In a study of 71 dogs with IE, 35% of dogs had joint fluid analyzed, and 84% of these dogs had suppurative effusion.[16] Septic inflammation is less common than immune-mediated polyarthritis.

Diagnosis

Diagnosis of IE is challenging and elusive, and includes clinical abnormalities compatible with IE, blood culture, and echocardiographic evidence of characteristic oscillating vegetative lesions on a cardiac valve and valvular insufficiency. Definitive diagnosis of IE depends on identification of a vegetative or erosive lesion by echocardiography or by pathology. Because transthoracic echocardiography is relatively insensitive in humans for detection of IE, there is reliance on other major and minor criteria to determine a possible diagnosis.[15] In human medicine, the Modified Duke scoring system has been devised to quantify whether IE is unlikely or highly probable. Proposed veterinary criteria modeled on the human Modified Duke criteria may be useful to identify probable cases of IE in dogs (see **Table 1**).

Blood culture

Blood culture before treatment with antibiotics is an essential diagnostic tool to support the diagnosis of IE and to aid in proper selection of antimicrobial treatment. From different venous sites, 3 or 4 blood samples (5–10 mL each) should be

aseptically collected at least 30 minutes to 1 hour apart and submitted for aerobic and anaerobic culture. Lysis centrifugation tubes (Isolator, Isostat microbial system, Wampole Laboratories, Cranbury, NJ, USA) may increase diagnostic yield. Adequate volumes of blood must be collected (if clinically appropriate based on patient size), because the concentration of bacteria in blood is very low (<5–10 bacteria/mL).[24] *Bartonella* is a fastidious organism that is rarely grown on culture medium, so routine culture is not recommended. Unfortunately, many patients (78% in one study) have been treated with antibiotics prior to blood culture, thus reducing the likelihood of a positive blood culture. Not surprisingly, there is a high incidence of negative blood cultures in dogs with IE, ranging from 60% to 70%.[3,10] In dogs already receiving antibiotics, collection of blood is ideally done during the trough level of the antibiotic. The most common bacterial isolates are *Staphylococcus* spp (*aureus*, *intermedius*, coagulase positive and coagulase negative), *Streptococcus* spp (*canis*, *bovis*, and β-hemolytic), and *E coli* (**Table 2**). Other lesser isolates include *Pseudomonas*, *Erysipelothrix rhusiopathiae*, *Enterobacter*, *Pasteurella*, *Corynebacterium*, *Proteus*, and rarely, *Bordetella avium*–like organism, *Erysipelothrix tonsillarum*, and *Actinomyces turicensis*.

Testing for Bartonella

Serologic testing for *Bartonella* spp is the main diagnostic method to determine if IE is highly likely to be caused by *Bartonella*. Because *Bartonella* is an extremely fastidious intracellular bacterium, it is rarely cultured from blood or body tissues even using specialized culture medium and long incubation periods. Therefore, diagnosis is limited to polymerase chain reaction (PCR) of the blood (fraught with false negatives) or cardiac valve on postmortem (gold standard), or probable cause is determined if there is a markedly elevated serologic titer against *Bartonella*. In one study, dogs with PCR evidence of *Bartonella* on infected heart valves were highly seroreactive to *Bartonella* spp, and all titers were greater than 1:1024.[3] There is cross-reactivity to different *Bartonella* species as well as to *Chlamydia* and *Coxiella burnetii*.

Based on the veterinary literature, high seroreactivity to *Bartonella* (>1:1024) may be an additional minor criterion for diagnosis of IE due to *Bartonella* in dogs (see **Table 1**). High seroreactivity to *Bartonella* spp has been recently proposed as a minor criterion for diagnosis of IE in people. A titer greater than 1:800 for IgG antibodies to *Bartonella henselae* or *B quintana* had a positive predictive value of 0.96 for detection of *Bartonella* infection in people with IE, and confirmed the diagnosis in 45 of 145 people (31%) with culture-negative IE with 100% sensitivity.[25] PCR on serum from people with confirmed IE due to *Bartonella* is relatively insensitive (58%) but specific (100%).[26]

Echocardiography

Echocardiography is the most important tool to diagnose IE. The pathognomonic lesion is a hyperechoic, oscillating, irregular-shaped (ie, shaggy) mass adherent to, yet distinct from, the endothelial cardiac surface (**Figs. 4** and **5**). The term ''oscillating'' means that the lesion is mobile with high-frequency movement independent from the underlying valve structure, and highly supports an echocardiographic diagnosis of vegetation. The mitral and aortic valves are almost exclusively affected in small animals. Erosive and minimally proliferative lesions are less uncommon and may be challenging to visualize. Valvular insufficiency of the affected valve is always present, and most often is moderate or severe (see **Figs. 4** and **5**). Valvular insufficiency is identified as a turbulent regurgitant jet on color flow Doppler investigation of the affected valve, including a retrograde systolic turbulent jet from the left ventricle into the left atrium with mitral regurgitation, or a turbulent jet arising from the aortic valve and leaking backward into the left ventricle in diastole with aortic insufficiency. Left atrial

Table 2
Common causative agents, typical antimicrobial sensitivity profiles, and treatment recommendations for dogs with IE

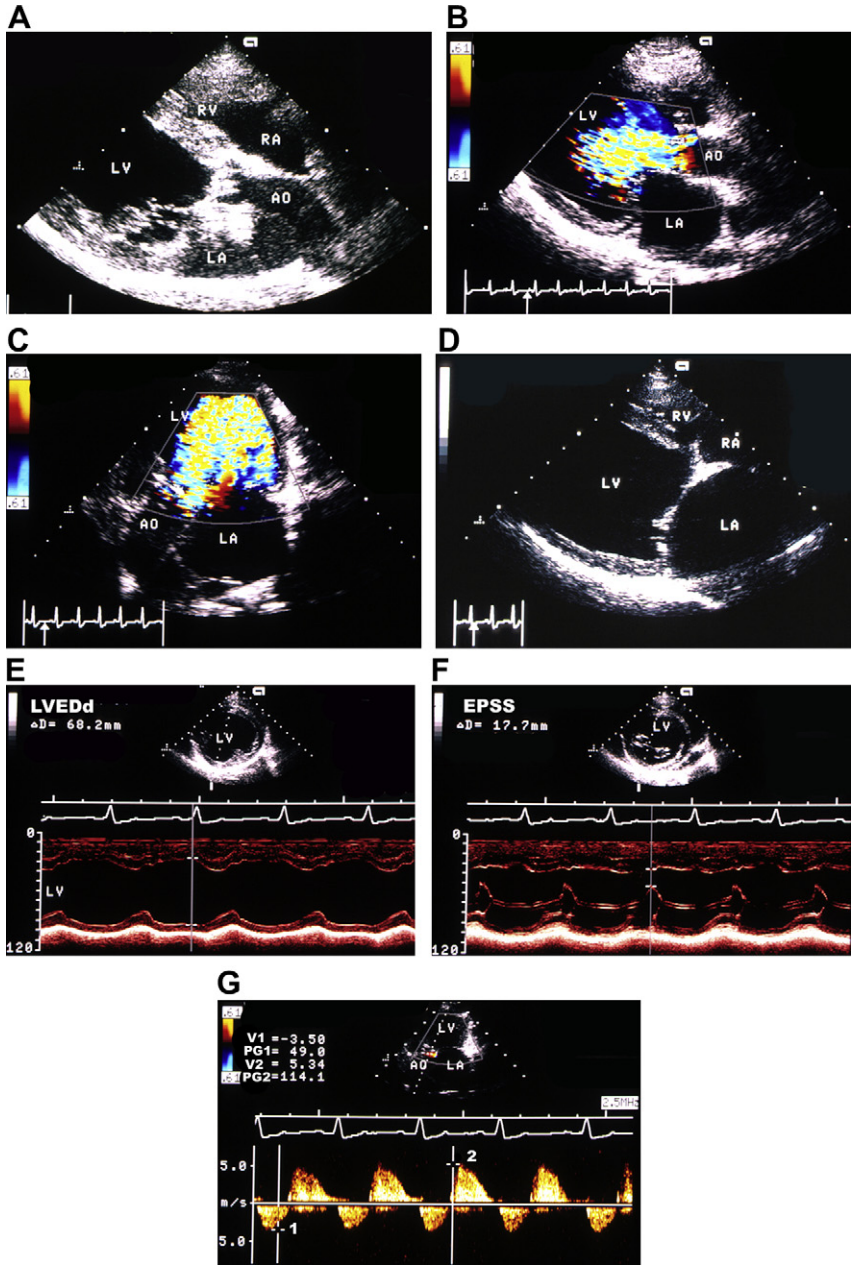
Causative Agent and Bacteremia Source	Typical Sensitivity Profile	Recommended Antibiotic
Staphylococcus intermedius Pyoderma	Usually sensitive	Acute: Timentin 50 mg/kg IV QID, or Enrofloxacin 10 mg/kg IV BID Chronic: Clavamox 20 mg/kg PO TID or Enrofloxacin 5–10 mg/kg PO BID × 6–8 wk
Staphylococcus aureus	Often resistant; if methicillin resistant, avoid β-lactams treatment	Individually dependent, evaluate MIC Acute: Amikacin or Vancomycin and Oxacillin, Nafcillin, or Cefazolin IV × 2 wk Chronic: If not methicillin resistant, high-dose first-generation cephalosporin PO 6–8 wk
Streptococcus canis Urogenital system, skin, respiratory tract	Usually sensitive	Acute: Ampicillin 20–40 mg/kg IV TID–QID or Ceftriaxone 20 mg/kg IV BID × 2 wk. If resistant, amikacin and high-dose penicillin Chronic: Amoxicillin or Clavamox PO 6–8 wk
Escherichia coli Gastrointestinal tract, peritonitis, urinary tract	Often resistant (β-lactamase), need extended MIC	Individually dependent, evaluate MIC Acute: Amikacin and/or Imipenem 10 mg/kg IV TID Chronic: Imipenem 10 mg/kg SQ TID 6–8 wk
Pseudomonas Chronic wounds, burns	Resistant, need extended MIC	Individually dependent, evaluate MIC Acute: Amikacin, Timentin, or Imipenem Chronic: Imipenem SQ or Clavamox PO
Bartonella Vector-borne disease	MIC not predictive of MBC	Acute: Amikacin 20 mg/kg IV × 1–2 wk, and Timentin 50 mg/kg IV QID × 1–2 wk Chronic: β-lactam PO × 6–8 wk or Doxycycline 5 mg/kg PO every 24 h × 6–8 wk or Azithromycin 5 mg/kg PO every 24 h × 7 d, then EOD
Culture negative	Unknown	Acute: Amikacin and Timentin IV × 1–2 wk Chronic: Clavamox 20 mg/kg TID × 6–8 wk and Enrofloxacin 5–10 mg/kg PO BID × 6–8 wk

Typical MIC profiles derived from UC Davis VMTH microbial service database of antimicrobial sensitivity of cultured microorganisms. Recommended antibiotics for particular bacteria were chosen based on greater than 90% sensitivity of the cultured isolates to the particular antibiotic.

Abbreviations: BID, twice a day; EOD, every other day; IV, intravenous; MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration; PO, by mouth; QID, 4 times a day; SQ, subcutaneous; TID, 3 times a day.

enlargement or eccentric hypertrophy of the left ventricle may not be present if the IE is acute in nature. A myocardial abscess may appear as a heterogeneous, thickened region or mass in the myocardium or annulus. A fistula or septal defect may be seen between 2 chambers if the abscess has ruptured.

Presence of moderate or severe aortic insufficiency on color flow Doppler should greatly raise the suspicion of aortic IE, and careful examination of the aortic cusps



in several views is necessary. Subaortic stenosis is often present, and can be diagnosed by 2-dimensional evidence of fibrotic narrowing of the left ventricular outflow tract; severity may be determined by measurement of aortic blood flow velocity by continuous wave Doppler using the left apical 5-chamber view. Severity of aortic insufficiency may be estimated by the length of the insufficiency jet on color flow Doppler and the slope of the aortic insufficiency on continuous wave Doppler of the left apical 5-chamber view (ie, steep slope, severe aortic insufficiency) (**Fig. 4**). Chronic, severe aortic insufficiency leads to development of left ventricular eccentric hypertrophy, mild to moderate secondary myocardial failure, and left atrial dilation.

The main differential for echocardiographic diagnosis of IE of the mitral valve is myxomatous valve degeneration, which confers a dramatically better prognosis. Patient signalment is often helpful because dogs with marked myxomatous mitral valve degeneration are small breeds that rarely develop IE, and dogs with IE are medium to large breeds that do not commonly develop marked valvular thickening as a result of myxomatous valve degeneration. Large-breed dogs may develop myxomatous mitral valve degeneration, which is more subtle in structure with less proliferative valve thickening and minimal prolapse. Myxomatous valve degeneration appears in an echocardiograph as a thickened valve that often prolapses into the left atrium. Unlike IE, myxomatous valve degeneration does not cause an appearance of an oscillating shaggy mass–type lesion that moves independently from the endocardium.

Dogs with a high clinical suspicion of IE without characteristic lesions on transthoracic echocardiography should undergo transesophageal echocardiography to better evaluate the valve morphology, or transthoracic echocardiography should be repeated in a few days.

Treatment

Long-term bactericidal antibiotics are the cornerstone of therapy for IE. Empirical broad-spectrum antibiotic therapy is started while cultures are pending, and may be continued in cases with no identifiable pathogen. High serum concentration of

Fig. 4. (*A*) Echocardiogram of a dog with IE of the aortic valve. Using the right parasternal long-axis left ventricular outflow tract view, the aortic valve is visualized and is severely thickened with a hyperechoic, shaggy, oscillating mass lesion consistent with IE. (*B*, *C*) Color flow Doppler investigation of the aortic valve from the right parasternal long-axis left ventricular outflow tract view and the left apical 5-chamber view show severe aortic insufficiency, which is turbulent blood flow leaking back into the left ventricle from the aorta in diastole. (*From* MacDonald KA, Chomel BB, Kittleson M, et al. A prospective study of canine IE in northern California (1999–2001): emergence of Bartonella as a prevalent etiologic agent. J Vet Intern Med 2004;18:56–64; with permission.) (*D*) Severe aortic insufficiency causes a severe volume overload and eccentric hypertrophy of the left ventricle. (*E*) M-mode of the left ventricle shows severe left ventricular eccentric hypertrophy with a severely increased end-diastolic diameter (LVEDd) and mildly increased end-systolic diameter consistent with secondary myocardial failure. Fractional shortening was normal. (*F*) E-point to septal separation (EPSS) was markedly increased, which also indicates significant myocardial failure. (*G*) Continuous-wave Doppler measurement of the aortic blood flow velocity shows high-velocity turbulent systolic flow out of the aorta that is consistent with moderate subaortic stenosis (1), and high-velocity turbulent flow backward into the left ventricle during diastole (2) consistent with aortic insufficiency. The aortic insufficiency is severe, which leads to a rapid decrease in the aorta to left ventricular pressure gradient through diastole, which is visualized as a steep slope rather than a flat plateau of the aortic insufficiency jet. LA, left atrium; LV, left ventricle; AO, aorta; RA, right atrium; RV, right ventricle; V, velocity (m/s); PG, pressure gradient (mm Hg).

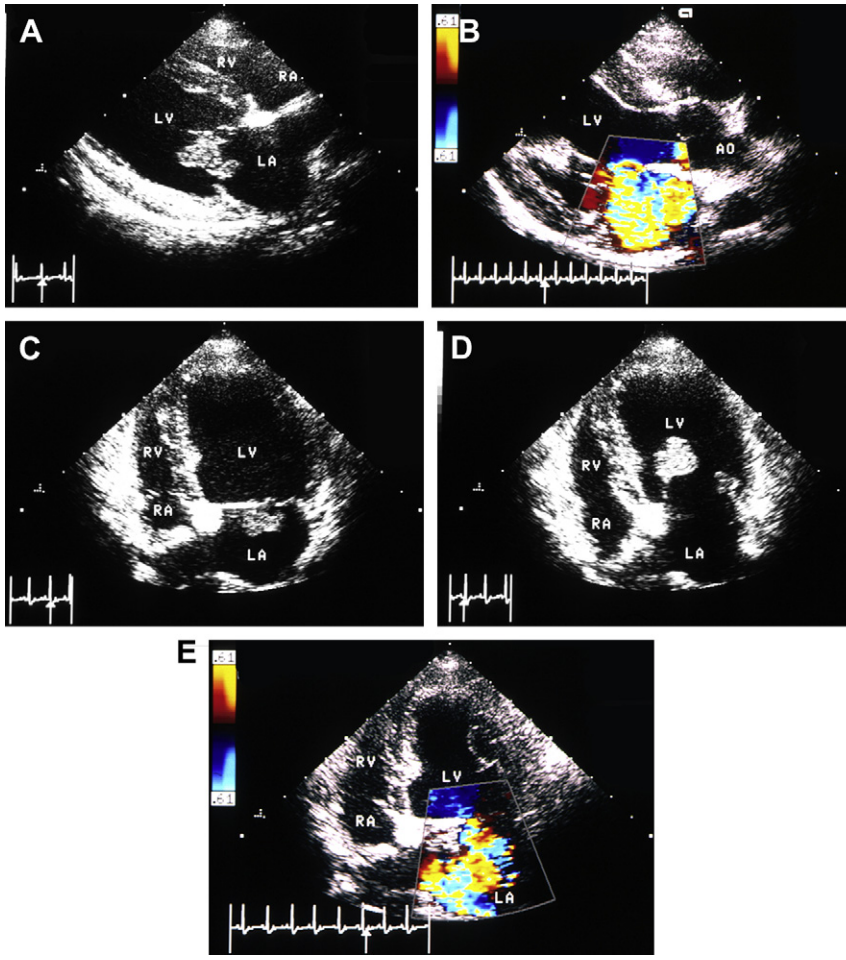


Fig. 5. (*A*) Echocardiogram of a dog with IE of the mitral valve. This right parasternal long-axis 4-chamber view shows a large, hyperechoic, vegetative lesion on the anterior mitral leaflet. (*B*) Color flow Doppler investigation of the mitral valve shows severe mitral regurgitation. (*C*, *D*) From the left apical 4-chamber view, the vegetative lesion is mobile (ie, oscillating), and prolapses into the left atrium during systole (*D*) and into the left ventricle during diastole (*C*). The left atrium is dilated secondary to severe mitral regurgitation. (*E*) Color flow Doppler of the mitral valve shows severe mitral regurgitation and a filling defect in the left atrium caused by the large vegetative lesion. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

antibiotics with good tissue and intracellular penetrating properties are needed to penetrate within the vegetative lesion to kill the bacteria. Antibiotic doses used are typically on the high end of the range to achieve high blood levels. The optimal antibiotic treatment depends on culture of the microorganism and MIC of the antibiotics, which is often impossible as a result of previous antibiotic use. Common causative agents, their typical sensitivity profile, and therapeutic regimens are included in **Table 2**. Therapeutic recommendations were derived from the UC Davis VMTH microbial service database of antimicrobial sensitivity of microorganisms. Recommended antibiotics for particular

bacteria were chosen based on sensitivity of greater than 90% of the cultured isolates to the particular antibiotic. However, general antibiotic sensitivities and resistance profiles may vary depending on the hospital, and may be more challenging in secondary or tertiary referral hospitals. There is significant resistance of many bacteria isolated from IE cases in the author's hospital to enrofloxacin and ampicillin, and they therefore cannot be recommended as an empirical, acute first line of defense when an MIC is unavailable. Patients should be supported with fluid therapy if aminoglycosides are given. Furosemide may potentiate nephrotoxicity of aminoglycosides, hence they are contraindicated in patients with congestive heart failure receiving diuretic therapy because furosemide may potentiate renal toxicity of aminoglycosides.

Intravenous antibiotic therapy for 1 to 2 weeks is necessary for acute aggressive treatment of IE. This therapy may be challenging (financially and emotionally for owners) as it involves long-term hospitalization and monitoring for this period of time. Placement of an indwelling long-term vascular access port is an option in these patients that ideally should be treated with intravenous antibiotics for several weeks. After the first 1 to 2 weeks of intravenous antibiotics, long-term oral antibiotics are needed for 6 to 8 weeks or longer. Some clinicians have suggested subcutaneous administration of antibiotics on an outpatient basis rather than oral antibiotics, but there is no clear advantage of subcutaneous antibiotic treatment over long-term oral antibiotic treatment with high bioavailability and blood levels. One exception is in the long-term treatment of resistant infections using imipenem administered subcutaneously after an initial 1- to 2-week course administered intravenously, although subcutaneous administration may cause discomfort with this drug.[27]

It is challenging to decide when long-term antibiotic therapy may be discontinued, because the affected valve often has residual thickening even with a sterile lesion. Serial monitoring of echocardiograms, and other parameters such as complete blood count, recheck urine or blood cultures (if previously positive), and body temperature are needed to follow the response to antibiotics. Lack of improvement in an oscillating vegetative lesion after the first week of antibiotic therapy in an animal without a previous bacterial isolate and MIC may indicate a more aggressive, resistant bacterium that may require switching antibiotics or adding additional antibiotics. During long-term therapy, the presence of an oscillating mass, recurrent fever, leukocytosis, or positive follow-up urine or blood cultures necessitates continued long-term therapy, possibly with a different antibiotic combination.

The superior antibiotic for treatment of *Bartonella* infections in dogs has not been defined, but acceptable choices include doxycycline, azithromycin, or fluoroquinolones. However, contrary to clinical experience, an in vitro study found that only gentamicin, and not ciprofloxacin, streptomycin, erythromycin, ampicillin, or doxycycline, exerted bactericidal activity against *Bartonella*.[28] Treatment with at least 2 weeks of aminoglycosides has been shown to improve survival in people with *Bartonella* IE.[29] In dogs with severe life-threatening IE due to *Bartonella*, aggressive treatment with aminoglycosides may be necessary, with careful monitoring of renal values and supportive intravenous fluid administration. In 24 dogs with various systemic manifestations secondary to bartonellosis, treatment with the following antibiotics resulted in clinical recovery and negative post-treatment titers: doxycycline, azithromycin, enrofloxacin, and amoxicillin/clavulanate.[30] Azithromycin achieves high intracellular concentrations and may be given with careful monitoring of the hepatic enzymes, as it may cause hepatotoxicity with long-term therapy.

At present, anticoagulant therapy is not recommended as a result of a trend in increased bleeding episodes and absence of benefit in vegetation resolution or reduced embolic events in humans with IE treated with aspirin.[15]

TREATMENT OF CONGESTIVE HEART FAILURE

Acute Heart Failure

Because of the often acute nature of IE, aggressive treatment of congestive heart failure is essential. These patients require 24-hour critical care and monitoring. High doses of parenteral furosemide (4–8 mg/kg intravenously every 1–4 hours or continuous-rate infusion of 1 mg/kg/h) are needed in the acute phase of fulminant pulmonary edema, and dose and frequency of administration should be rapidly tapered when respiratory rate and effort improve. A combination of positive inotropic therapy with dobutamine (5–10 μ/kg/min) and the potent balanced vasodilator nitroprusside (1–10 μg/kg/min) may be needed in dogs with refractory heart failure. Oxygen supplementation of 50% to 70% fractional inspired oxygen concentration for the first 12 hours, then reducing it to less than 50% helps increase arterial partial pressure of oxygen. In dogs with severe aortic insufficiency, acute afterload reduction with nitroprusside or hydralazine is indicated to lessen the severity of aortic insufficiency. Open heart surgery and valve replacement is a mainstay treatment for acute life-threatening IE in people, but is rarely done in dogs.[31]

Chronic Heart Failure

Once the dog has stabilized and pulmonary edema has been cleared by aggressive parenteral medications, multipharmacy long-term oral therapy may be started. Furosemide doses are often higher during the first week of chronic therapy and then tapered to the lowest effective dose. Typical initial furosemide doses may be 2 to 4 mg/kg orally three times a day, then tapered to twice a day. Pimobendan (0.25 mg/kg orally twice a day) is an inodilator that increases contractility and dilates systemic and pulmonary vasculature, and is an essential treatment for dogs with heart failure. In dogs with moderate or severe aortic insufficiency, addition of an arterial vasodilator (ie, afterload reducer) may lessen the severity of the aortic insufficiency. Afterload reduction is also necessary in dogs with severe or refractory heart failure secondary to mitral valve IE. Amlodipine (0.1–0.5 mg/kg orally every 24 hours to twice a day) is most effective and well-tolerated afterload reducer used for long-term oral therapy. Systolic blood pressure should be maintained less then 140 mm Hg (but >95 mm Hg), and 10 to 15 mm Hg lower than baseline blood pressure. Angiotensin-converting enzyme inhibitors are used for adjunctive heart failure therapy, and may be started once the dog is home and eating and drinking. Antiarrhythmic treatment may be necessary, especially if there are high-grade ventricular arrhythmias. A permanent pacemaker may be needed in dogs with third-degree atrioventricular block secondary to myocardial abscess spreading from aortic valve IE, although these patients are poor pacemaker candidates with a grave prognosis.

Follow-up

In patients with positive cultures (blood or urine), a repeat culture is recommended 1 week after starting antibiotic therapy and 2 weeks following termination of antibiotic therapy. An echocardiogram should be performed after 1 to 2 weeks of antibiotic treatment, in 4 to 6 weeks, and 2 weeks following termination of antibiotic therapy to assess size of vegetative lesion and severity of valvular insufficiency. Thoracic radiographs, blood pressure, and blood chemistry are needed to assess response to heart failure therapy and help tailor continued long-term therapy. In patients affected with *Bartonella*, repeat serology should be performed a month after initiation of treatment, and titers should be reduced. If titer values are persistently elevated, a different antibiotic may be needed.

Antibiotic Prophylaxis

Prophylactic perioperative antibiotics such as β-lactam or cephalosporin are indicated in dogs with subaortic stenosis, and may be indicated in other congenital heart diseases such as pulmonic stenosis or tetralogy of Fallot. Antibiotics should be given 1 hour before surgery or dentistry and 6 hours after the procedure. Clindamycin may be useful as a prophylactic antibiotic for dental procedures. The American Heart Association revised guidelines in 2007 for more stringent use of antibiotic dental prophylaxis to include only patients with prosthetic heart valve, a history of IE, certain forms of congenital heart disease, or valvulopathy after cardiac catheterization, and only before procedures that involve manipulation of gingival tissue or the periapical region of teeth, and not for routine dental cleaning.[13] Often veterinarians are saddled with the fear of risking a fatal disease versus empirical prophylactic antibiotics. However, even in human medicine the data are insufficient to substantiate efficacy of antibiotics in preventing endocarditis in patients undergoing dental procedures.[32] Likewise, there is no evidence that dogs with myxomatous valve degeneration have an increased risk of IE, or evidence of an association between a recent dental procedure and development of IE.[11] Therefore, the use of prophylactic antibiotics prior to dental procedures for dogs with myxomatous valve degeneration is controversial and needs to be reevaluated.

Prognosis

Dogs with aortic IE have a grave prognosis, and in one study median survival was only 3 days compared with a median survival of 476 days for dogs with mitral valve IE (**Fig. 6**).[3]

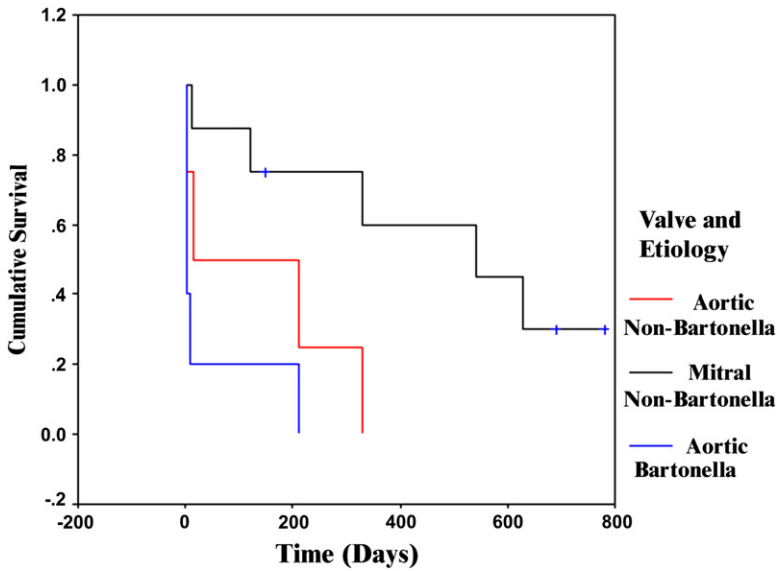


Fig. 6. Survival curve of 18 dogs diagnosed with IE with IE. Kaplan-Meier curve of the mitral and aortic valves.[3] Dogs with mitral valve endocarditis (*black line*) lived longer than dogs with aortic endocarditis from traditional bacteria (*red line*) ($P = .004$) or *Bartonella* (*black line*) ($P = .002$) (median survival time: mitral: 540 days; aortic: *Bartonella*, 3 days; non-*Bartonella*, 14 days). (*From* MacDonald KA, Chomel BB, Kittleson M, et al. A prospective study of canine IE in northern California (1999–2001): emergence of Bartonella as a prevalent etiologic agent. J Vet Intern Med 2004;18:56–64; with permission.)

Likewise, dogs with *Bartonella* IE have short survival times because the aortic valve is almost exclusively affected. Another case series of dogs with aortic IE reported similar outcomes, including 33% mortality in the first week and 92% mortality within 5 months of diagnosis.[10] Other risk factors for early cardiovascular death include glucocorticoid administration before treatment, presence of thrombocytopenia, high serum creatinine concentration, renal complications, and thromboembolic disease.[12,16] Short-term death is often a result of congestive heart failure or sudden death. Likewise, the presence of congestive heart failure has the greatest impact on poor prognosis in people with IE. Other causes of death within the first week of treatment in dogs with IE include renal failure, pulmonary hemorrhage, and severe neurologic disease.

SUMMARY

IE is an uncommon, deadly, and elusive disease to diagnose in dogs. IE primarily affects the mitral and aortic valves, and leads to severe valvular insufficiency and congestive heart failure. Other severe clinical sequelae include thromboembolism, immune-mediated disease (ie, immune-mediated polyarthritis and glomerulonephritis), arrhythmia, renal disease, and cerebral vasculopathy. The most common causative agents include *Staphylococcus* spp, *Streptococcus* spp, *E coli*, *Bartonella*, and *Pseudomonas*. Diagnosis is made by identification of a vegetative valvular lesion and valvular insufficiency on echocardiogram, and may be supported by other clinicopathologic abnormalities. Blood and urine cultures are needed to identify the offending microbial organism, although most cases are culture negative. Aggressive treatment with long-term broad-spectrum antibiotics is needed, ideally including 1 to 2 weeks of intravenous antibiotics followed by 6 to 8 weeks of oral antibiotics. Prognosis is grave for dogs with aortic valve IE, with a MST of 3 days in one study, and poor to fair in dogs with mitral valve IE, with a median survival time of 476 days.

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REFERENCES

1. Miller MW, Fox PR, Saunders AB. Pathologic and clinical features of infectious endocarditis. J Vet Cardiol 2004;6:35–43.
2. Bashore TM, Cabell C, Fowler V Jr. Update on IE. Curr Probl Cardiol 2006;31: 274–352.
3. MacDonald KA, Chomel BB, Kittleson M, et al. A prospective study of canine IE in northern California (1999-2001): emergence of *Bartonella* as a prevalent etiologic agent. J Vet Intern Med 2004;18:56–64.
4. Breitschwerdt EB, Atkins CE, Brown TT, et al. *Bartonella vinsonii* subsp. *berkhoffii* and related members of the alpha subdivision of the Proteobacteria in dogs with cardiac arrhythmias, endocarditis, or myocarditis. J Clin Microbiol 1999;37:3618–26.
5. Chomel BB, Kasten RW, Williams C, et al. *Bartonella endocarditis*: a pathology shared by animal reservoirs and patients. Ann N Y Acad Sci 2009;1166:120–6.
6. Ohad DG, Morick D, Avidor B, et al. Molecular detection of *Bartonella henselae* and *Bartonella koehlerae* from aortic valves of Boxer dogs with IE. Vet Microbiol 2010;141(1–2):182–5.
7. Pesavento PA, Chomel BB, Kasten RW, et al. Pathology of *Bartonella endocarditis* in six dogs. Vet Pathol 2005;42:370–3.

8. Pappalardo BL, Brown TT, Tompkins M, et al. Immunopathology of *Bartonella vinsonii* (berkhoffii) in experimentally infected dogs. Vet Immunol Immunopathol 2001;83:125–47.
9. Breitschwerdt EB, Hegarty BC, Hancock SI. Sequential evaluation of dogs naturally infected with *Ehrlichia canis*, *Ehrlichia chaffeensis*, *Ehrlichia equi*, *Ehrlichia ewingii*, or *Bartonella vinsonii*. J Clin Microbiol 1998;36:2645–51.
10. Sisson D, Thomas WP. Endocarditis of the aortic valve in the dog. J Am Vet Med Assoc 1984;184:570–7.
11. Peddle GD, Drobatz KJ, Harvey CE, et al. Association of periodontal disease, oral procedures, and other clinical findings with bacterial endocarditis in dogs. J Am Vet Med Assoc 2009;234:100–7.
12. Calvert CA. Valvular bacterial endocarditis in the dog. J Am Vet Med Assoc 1982; 180:1080–4.
13. Wilson W, Taubert KA, Gewitz M, et al. Prevention of IE: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 2007; 116:1736–54.
14. Guyton AC, Lindsey AW. Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. Circ Res 1959;7:649–57.
15. Baddour LM, Wilson WR, Bayer AS, et al. IE: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation 2005;111:e394–434.
16. Sykes JE, Kittleson MD, Chomel BB, et al. Clinicopathologic findings and outcome in dogs with IE: 71 cases (1992-2005). J Am Vet Med Assoc 2006; 228:1735–47.
17. Mugge A, Daniel WG, Frank G, et al. Echocardiography in IE: reassessment of prognostic implications of vegetation size determined by the transthoracic and the transesophageal approach. J Am Coll Cardiol 1989;14:631–8.
18. Macarie C, Iliuta L, Savulescu C, et al. Echocardiographic predictors of embolic events in IE. Kardiol Pol 2004;60:535–40.
19. Cook LB, Coates JR, Dewey CW, et al. Vascular encephalopathy associated with bacterial endocarditis in four dogs. J Am Anim Hosp Assoc 2005;41:252–8.
20. Dunn ME, Blond L, Letard D, et al. Hypertrophic osteopathy associated with IE in an adult boxer dog. J Small Anim Pract 2007;48:99–103.
21. Vulgamott JC, Clark RG. Arterial hypertension and hypertrophic pulmonary osteopathy associated with aortic valvular endocarditis in a dog. J Am Vet Med Assoc 1980;177:243–6.
22. Anderson CA, Dubielzig RR. Vegetative endocarditis in dogs. J Am Anim Hosp Assoc 1984;20:149–52.
23. Chomel BB, Mac Donald KA, Kasten RW, et al. Aortic valve endocarditis in a dog due to *Bartonella clarridgeiae*. J Clin Microbiol 2001;39:3548–54.
24. Peddle G, Sleeper MM. Canine bacterial endocarditis: a review. J Am Anim Hosp Assoc 2007;43:258–63.

25. Fournier PE, Mainardi JL, Raoult D. Value of microimmunofluorescence for diagnosis and follow-up of *Bartonella endocarditis*. Clin Diagn Lab Immunol 2002;9: 795–801.
26. Zeaiter Z, Fournier PE, Greub G, et al. Diagnosis of *Bartonella endocarditis* by a real-time nested PCR assay using serum. J Clin Microbiol 2003;41:919–25.
27. Barker CW, Zhang W, Sanchez S, et al. Pharmacokinetics of imipenem in dogs. Am J Vet Res 2003;64:694–9.
28. Rolain JM, Maurin M, Raoult D. Bactericidal effect of antibiotics on *Bartonella* and *Brucella* spp.: clinical implications. J Antimicrob Chemother 2000;46:811–4.
29. Raoult D, Fournier PE, Vandenesch F, et al. Outcome and treatment of *Bartonella endocarditis*. Arch Intern Med 2003;163:226–30.
30. Breitschwerdt EB, Blann KR, Stebbins ME, et al. Clinicopathological abnormalities and treatment response in 24 dogs seroreactive to *Bartonella vinsonii (berkhoffii)* antigens. J Am Anim Hosp Assoc 2004;40:92–101.
31. Arai S, Wright BD, Miyake Y, et al. Heterotopic implantation of a porcine bioprosthetic heart valve in a dog with aortic valve endocarditis. J Am Vet Med Assoc 2007;231:727–30.
32. Kim A, Keys T. IE prophylaxis before dental procedures: new guidelines spark controversy. Cleve Clin J Med 2008;75:89–92.