Clinicopathologic findings and outcome in dogs with infective endocarditis: 71 cases (1992–2005)

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Objectives—To evaluate clinical, laboratory, and necropsy findings in dogs with infective endocarditis (IE).

Design—Retrospective case series.

Animals—71 dogs with possible or definite IE.

Procedures—Medical records were reviewed for signalment, clinical features, and results of clinicopathologic testing and diagnostic imaging. Yearly incidence and the effect of variables on survival were determined by use of survival curve analysis.

Results—The overall incidence of IE was 0.05%. Most affected dogs were of large breeds, and > 75% were older than 5 years. The aortic valve was affected in 36 of the 71 (51%) dogs, and the mitral valve was affected in 59%. Lameness caused by immune-mediated polyarthritis, septic arthritis, or peripheral arterial thromboembolism was observed in 53% of the dogs. Neurologic complications were diagnosed in 17 of 71 (24%) dogs. Thromboembolic disease was suspected in 31 of 71 (44%) of dogs. The mortality rate associated with IE was 56%, and median survival time was 54 days. Factors negatively associated with survival included thrombocytopenia, high serum creatinine concentration, renal complications, and thromboembolic complications.

Conclusions and Clinical Relevance—A diagnosis of IE should be suspected in dogs with fever, systolic or diastolic murmur, and locomotor problems. Dogs with thrombocytopenia, high serum creatinine concentration, thromboembolism, or renal complications may have a shorter survival time. (*J Am Vet Med Assoc* 2006;228:1735–1747)

Infective endocarditis is defined as infection of 1 or more of the endocardial surfaces in the heart[1] and almost always involves a cardiac valve. In dogs, the mitral and aortic valves are the most frequently affected.[2-8] The reported[5,8,9] incidence of IE in dogs has ranged from < 0.1% of cases examined at veterinary teaching hospitals to approximately 1% of cases examined by veterinary cardiologists. Affected dogs are typically middle-aged to older large-breed dogs such as German Shepherd Dogs, Golden and Labrador Retrievers, and Rottweilers. Males are affected approximately twice as often as females. The most commonly reported etiologic agents are streptococci, staphylococci, gram-negative bacilli, and *Bartonella* spp.[3,5,6,10] Consequences of IE include development of CHF, arrhythmias resulting from myocardial infection and infarction, and immune-mediated conditions such as polyarthritis and glomerulonephritis. Septic thromboemboli may lodge in any arterial bed, but this complication is most common in arteries supplying the spleen, kidneys, brain, and skeletal muscles and leads to a range of clinical manifestations. As a result, dogs with IE may be taken by owners to general veterinary practitioners for evaluation or to emergency and critical care veterinarians, veterinary cardiologists, internists, and neurologists.

Abbreviations

IE	Infective endocarditis
CHF	Congestive heart failure
VMTH	Veterinary Medical Teaching Hospital
ALT	Alanine aminotransferase

The published literature[2-8,11-20] regarding IE in dogs consists of several case series, review articles, and case reports in which unusual infectious agents are described. The most common clinical signs are cardiac murmurs, fever, lameness, and detection of an arrhythmia; abnormal laboratory findings include anemia, leukocytosis, thrombocytopenia, hypoalbuminemia, high serum activities of liver enzymes, and azotemia. Renal, arthritic, and neurologic complications secondary to IE have been reported,[9,21,22] and acquired septal defects secondary to IE have been described.[23,24] However, to the authors' knowledge, no large case series of IE has been published for over 2 decades, the published studies predated the widespread clinical use of echocardiography, and the true prevalence of complications is unknown.

The number of dogs with IE at the University of California VMTH in the last 5 years was high, compared with numbers in previous years, and *Bartonella* spp have been identified as an important cause of IE in this geographic area.[5,16] Whether or not these observations represent a true increase in incidence is unclear because heightened suspicion for the disease, improvements in ultrasonographic imaging capabilities, and increased use of invasive interventional procedures (such as placement of central venous catheters) may also explain the larger number of cases recognized.

The mortality rate in humans with IE remains as high as 25%,[25-28] and in the subset of patients admitted to intensive care units, an in-hospital mortality rate of 45% has been reported.[29] Clinicopathologic features that influence mortality rates include a high WBC

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count, low serum albumin concentration, high serum creatinine concentration, arthralgia, cardiac arrhythmias, CHF, neurologic complications, vegetations that are visible on echocardiographic imaging, infection with *Staphylococcus aureus*, an immunocompromised state, diabetes mellitus, and embolic events.[25-27,29-33] In dogs, infection with *Bartonella* spp adversely affects clinical outcome.[5,10] However, no investigators have evaluated other clinical or laboratory findings in dogs with IE with the objective of determining their prognostic importance. The objectives of the present study were to review the records of dogs with a diagnosis of IE at the University of California VMTH from January 1992 to August 2005 and analyze the incidence of IE over time; determine the clinical, laboratory, diagnostic imaging, and necropsy findings; and identify factors that might contribute to outcome.

Criteria for Selection of Cases

The electronic database of the University of California VMTH was searched with the terms endocarditis and canine for records generated from January 1992 to August 2005. Cases were classified as possible or definite IE on the basis of echocardiographic, microbiologic, and pathologic findings, as described in the article by Sykes et al.[10]

Procedures

Information extracted from medical records included date of initial examination at the VMTH, the clinical service that received the dog, age, breed, sex, clinical findings (ie, duration of illness before admission, owner complaints, medication history, history of underlying congenital cardiac defects, and initial and subsequent physical examination findings including presence or absence of fever and a cardiac murmur), laboratory findings (ie, results of CBC, biochemical analyses, urinalysis, urine protein-to-creatinine ratio, and clotting function assays; when there was more than 1 result, the first available result was used), results of synovial fluid analysis (ie, neutrophilic polyarthritis and whether findings were more consistent with septic or immune-mediated polyarthritis), ECG findings (ie, detection of arrhythmia and type of arrhythmia [other than sinus tachycardia] or conduction defect), echocardiographic findings (ie, description of lesions if observed, valve or valves involved, severity of valvular regurgitation, concurrent congenital or acquired cardiac defects, and cardiac chamber enlargement), results of thoracic radiography (ie, the spectrum of abnormalities observed and whether there were lesions consistent with CHF), results of abdominal ultrasonographic imaging (ie, the spectrum of abnormalities observed and whether there were lesions consistent with thromboembolism), and findings on necropsy (ie, descriptions and sites of endocarditis lesions, whether there were lesions that were consistent with CHF, descriptions and sites of lesions consistent with thromboembolism or vasculitis or both, and glomerulonephritis).

Renal complications were defined as clinicopathologic evidence of renal injury (cylinduria or azotemia with isosthenuria) or protein-losing nephropathy (urine protein-to-creatinine ratio > 5); observation of lesions consistent with renal infarction on abdominal ultrasonography; or lesions at necropsy consistent with renal infarction, vasculitis, or glomerulonephritis. Neurologic complications were defined as observation of abnormalities on neurologic examination that were temporally associated with a diagnosis of IE (with or without abnormal findings on CSF analysis) or the finding of inflammatory lesions or infarction in the CNS during necropsy. Dogs with thromboembolism had changes observed during abdominal ultrasonographic imaging that were consistent with infarction or lesions consistent with thromboembolism at necropsy. Types of neurologic and renal complications were recorded. Relationships between the following factors were evaluated: murmurs and site affected by IE, duration of signs > 2 weeks and radiographic evidence of cardiac enlargement, echocardiographic observation of mobile or vegetative lesions and thromboembolism, valve involved and thromboembolism, and valve involved and development of CHF. The cost of the first episode of hospitalization relating to IE and time to death, euthanasia, or loss to follow-up were recorded. Deaths were classified as related or unrelated to IE. For dogs that were discharged from the VMTH, information on outcome was obtained via telephone conversations with owners, referring veterinarians, or both.

Statistical analysis—Data are presented as mean ± SD where appropriate. A Fisher exact test was used to detect group differences by use of frequency data. Incidence data were compared to the general VMTH canine patient population by use of χ^2 analysis after determining the number of dogs examined at the VMTH during each quarter of every year. For survival analysis, Kaplan-Meier curves were constructed, with dogs lost to follow-up or alive at the time of writing being censored in the analysis. The associations between outcome and the following variables were determined: sex; previous treatment with glucocorticoids; concurrent congenital heart disease; affected valve (aortic or not aortic); involvement of multiple valves; high serum creatinine concentration; high serum ALT activity; serum albumin concentration < 2.5 g/dL; WBC > 25×10^9 cells/L; presence of band neutrophils; thrombocytopenia; neutrophils with toxic changes; proliferative, shaggy, or mobile lesions on echocardiography; thromboembolic, renal, and neurologic complications; CHF; neutrophilic polyarthritis; and arrhythmias. Survival curves were compared by means of the log-rank test; hazard ratios and 95% confidence intervals were also determined. All analyses were performed with statistical software.[a] Values of $P < 0.05$ were defined as significant.

Results

Incidence—The 71 dogs with IE revealed by the record search were composed of 19 dogs with possible IE and 52 dogs with definite IE, as described.[10] All dogs were examined initially by clinicians at the VMTH (no dogs were admitted for necropsy only). Forty-eight of the 71 (68%) dogs were received by the emergency service, 10 (14%) dogs each were received by the internal medicine and cardiology services, and 2 (3%) dogs were

received by the neurology service. A mean of 5 dogs with IE were examined per annum (range, 0 to 11). During the same period, 132,506 dogs were examined at the VMTH, yielding an incidence for dogs with a diagnosis of IE of 0.05% of all dogs examined. The incidence varied from year to year in a manner unrelated to the overall number of dogs examined, which progressively increased ($P = 0.004$; **Figure 1**). Thirty of the 71 (42%) dogs were examined from 2000 to 2002, during which time the annual incidence peaked at 0.1%. The incidence was lowest (0.03%) during the hottest months of the year, from July through September; this distribution differed ($P = 0.01$) from the remainder of the VMTH canine patient population, which did not decline during the hottest months of the year.

Signalment—Of the 71 dogs with a diagnosis of possible or definite IE, 65 (92%) were large-breed dogs (ie, weighed > 15 kg [33 lb]). The 6 small-breed dogs included a Chihuahua and a Miniature Schnauzer in which IE was confirmed at necropsy and a Miniature Schnauzer, Tibetan Terrier, Shetland Sheepdog, and Toy Poodle with antemortem diagnoses of IE. Large breeds represented were Labrador Retrievers and their crosses (n = 12), German Shepherd Dogs and their crosses (11), Golden Retrievers (7), Rottweilers and their crosses (6), Boxers (3), Dalmatians (3), Doberman Pinschers (3), Bullmastiffs and their crosses (3), Airedale Terriers (2), Bassett Hounds (2), Newfoundlands (2), German Shorthaired Pointers (2), and one each of Afghan Hound, Akita, Australian Shepherd, Border Collie, Great Dane, Old English Sheepdog cross, red tick hound, Saint Bernard, and Weimeraner breeds. Forty-seven of the 71 (66%) dogs were male (n = 11) or neutered males (36). Four dogs were female and 20 were spayed females. Of the 69 dogs in which age was known, 54 (78%) were 5 years of age or older, 10 dogs were 1 to 5 years of age, and 5 dogs were 1 year of age or younger; 3 of those dogs had evidence of underlying subaortic stenosis. Mean age was similar between males (7.1 years) and females (7.7 years), and age was normally distributed.

Clinical findings—Historical data were available for 70 dogs. Median duration of illness before admission was 10 days (range, 0 to 390 days; n = 68). Of the 2 dogs that had been ill for longer than 6 months, 1 had no signs except for a progressive cardiac murmur and the other had signs related to concurrent adrenal neoplasia. The most common owner complaints at initial examination were lethargy (61% [43/70]), inappetence (57% [40/70]), and locomotor problems (53% [37/70]). Locomotor problems included lameness (33% [23/70]), reluctance to move (13% [9/70]), inability to walk (13% [9/70]), and joint pain and stiffness (6% [4/70]). Lameness was characterized as shifting in 10 (14%) dogs. Other complaints were vomiting (27% [19/70]), respiratory difficulty (20% [14/70]), weight loss (13% [9/70]), coughing (13% [9/70]), swollen joints (11% [8/70]), swollen limbs (10% [7/70]), weakness (10% [7/70]), and ocular discharge (10% [7/70]). Other variables recorded for a small (< 10%) number of dogs were collapse, diarrhea, epistaxis, hypersalivation, increased drinking and urination, cool limbs, oral cavity ulceration, nasal discharge, abdominal enlargement, black feces, and hematemesis. Neurologic abnormalities were observed in 4 (6%) dogs and included head tilt with nystagmus, head tilt, nonresponsiveness, and staring. Fever had been recorded objectively by the owner or referring veterinarian in 28 (40%) dogs before admission.

A medication history was available for 57 dogs. Antimicrobials had recently been administered to 42 of those 57 (74%) dogs. Sixteen (28%) dogs had received dexamethasone, prednisone, or both. Six dogs were treated with dosages of prednisone in excess of 2 mg/kg/d (0.9 mg/lb/d) for presumed immune-mediated polyarthritis; 3 of those dogs were also treated with azathioprine. Three dogs were receiving long-term prednisone treatment for dermatitis, chronic bronchitis, and hepatopathy. Musculoskeletal pain had prompted treatment with a nonsteroidal anti-inflammatory drug (8 dogs) or butorphanol (2). Furosemide had been administered to 10 dogs, and 5 dogs had been treated with an angiotensin-converting enzyme inhibitor.

Initial physical examination findings were available for 70 dogs. For 2 dogs, temperature, pulse rate, and respiratory rate were not recorded. The most common findings were a cardiac murmur (59% [41/70]) and tachycardia (50% [34/68]). Arrhythmias were detected in 14 dogs (19%). Twenty-six of 68 (38%) dogs had fever; 5 of those dogs had no murmur, tachycardia, or arrhythmia. Fifty-seven (81%) dogs had cardiac signs (ie, a murmur, tachycardia, or arrhythmia), cardiac signs with fever, or fever alone at initial examination. Ten of the 70 (14%) dogs, all with aortic valve lesions, had bounding pulses. Weak pulses were detected in 8 (11%) dogs. Other cardiovascular abnormalities detected in a small number (< 10%) of dogs were mucosal pallor, red mucous membranes, cyanosis, and absent pulses. Physical examination abnormalities pertaining to the respiratory system were identified in 35 of the 70 (50%) dogs and consisted of tachypnea and increased lung sounds, which were each detected in 24 (34%) dogs. Neurologic abnormalities were observed in 16 (23%) dogs and included ataxia, deficits of conscious proprioception (n = 11 dogs),

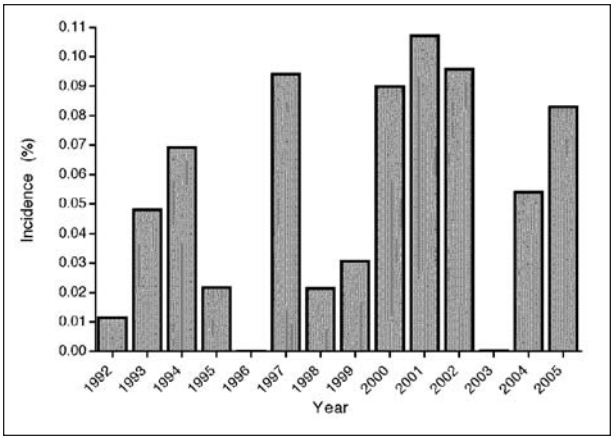

Figure 1—Annual incidence of dogs with IE evaluated at the University of California VMTH from 1992 to 2005.

strabismus (4), vestibular signs (3), obtundation and anisocoria (2), and unilateral facial nerve paresis, which was observed in conjunction with tetraparesis in 1 dog. The most common musculoskeletal signs were recumbency (30% [21/70]), swollen joints (21% [15/70]), stiffness or lameness (19% [13/70]), muscle atrophy (14% [10/70]), reluctance to stand (11% [8/70]), and muscle pain (6% [4/70]). Signs of pain in the vertebral column was observed in 7 (10%) dogs and abdominal pain in 6 (9%) dogs. Forty (57%) dogs were recumbent, reluctant to stand, stiff, lame, or weak. One dog had cold, firm, swollen pelvic limbs resulting from aortic thromboembolism. Other signs were mental dullness (27% [19/70]), dehydration (16% [11/70]), ocular discharge (14% [10/70]), thin body condition (9% [13/70]), and peripheral edema (10% [7/70]). Additional physical examination findings that affected < 10% of dogs were oral ulceration, pyoderma, abdominal enlargement, hepatomegaly, splenomegaly, icterus, cutaneous ulcers, ptyalism, conjunctivitis, uveitis, signs of prostatic pain, petechia or ecchymoses, hyphema, and mucopurulent nasal discharge.

Fever was observed historically, at the time of initial examination, or in subsequent physical examinations in 41 of 68 dogs (60%), and a cardiac murmur was detected under those same conditions in 53 of 70 (76%) dogs. The magnitude of fever was recorded (in referring veterinarians' records or in the VMTH record) for 34 of the 41 dogs. Mean ± SD rectal temperature was 104.4 ± 0.9°F (40.2 ± 0.3°C; range, 39.4°C ± 41.2°C [103°F to 106.2°F]). Fever was defined as mild (39.4°C ± 39.9°C [103°F to 103.9°F]) in 11 dogs, moderate (40°C [104°F to 104.9°F]) in 15 dogs, and severe (40.5°C [> 104.9°F]) in 8 dogs.

No associations were detected between absence of a cardiac murmur and whether the aortic or mitral valve was affected ($P = 0.21$) or whether lesions were restricted to the right side of the heart or were mural, as opposed to involvement of other sites ($P = 0.38$). A systolic heart murmur was the most frequent type of murmur detected (45/49 [92%] in dogs with murmurs for which the type of murmur was recorded). A diastolic murmur was detected in 13 of the 49 (26%) dogs, but 9 of those dogs also had a systolic murmur. Therefore, only 4 of 49 (8%) dogs had only a diastolic murmur. The intensity of diastolic and systolic heart murmurs varied from Grade I to Grade VI, although Grade I murmurs were uncommon.

Underlying congenital cardiac disease was diagnosed in 8 (11%) dogs and consisted of isolated subaortic stenosis (n = 6 dogs), subaortic and pulmonic stenosis (1), and tetralogy of Fallot (1). All dogs with subaortic stenosis had aortic valve endocarditis, and the mitral valve was also affected in 3 of those dogs. The dog with subaortic and pulmonic stenosis had IE lesions on both the aortic and the pulmonic valves, and the dog with tetralogy of Fallot had tricuspid valve endocarditis. Five dogs had moderate to severe myxomatous mitral valve degeneration. Two of those dogs had aortic valve endocarditis, 2 had mural endocarditis, and 1 had mitral valve endocarditis.

Clinicopathologic abnormalities—A CBC had been performed in 61 dogs (**Table 1**). Thirty-two (52%) dogs had anemia, usually characterized as mild and nonregenerative. However, anemia was regenerative in 7 of the 32 (22%) dogs, a determination made on the basis of an absolute reticulocyte count (in 5 dogs) or RBC morphology and indices (in 2 dogs). Regenerative anemia was considered to be secondary to gastrointestinal hemorrhage in 4 dogs and to immune-mediated destruction in 1 dog. Gastrointestinal bleeding secondary to exogenous glucocorticoid administration may have contributed to regenerative anemia in the remaining 2 dogs. Leukocytosis was observed in 54 (89%) dogs. Four of 7 dogs with a WBC count in the reference range had a high number of band neutrophils. Five of 12 dogs with a neutrophil count within reference range had a degenerative left shift. Toxic-appearing neutrophils were detected in 34 dogs, including 4 dogs with a WBC count in reference range.

Table 1—Results of clinicopathologic testing in dogs with IE in a retrospective case series.

Variable	No. tested	Mean ± SD	Range	No. (%) with high values	No. (%) with low values	Reference range
Hct (%)	61	35 ± 8	13–53	0 (0)	32 (52)	36–55
Total WBCs (cells/μL)	61	26,616 ± 14,906	7,870–81,574	54 (89)	0 (0)	6,000–13,000
Neutrophils	61	21,345 ± 12,551	4,876–61,996	49 (80)	0 (0)	3,000–10,500
Band neutrophils	61	1,483 ± 2,113	0–7,764	41 (67)	0 (0)	rare
Monocytes	61	2,010 ± 1,761	0–9,789	37 (61)	2 (3)	150–1,200
Lymphocytes	61	1,355 ± 1,118	0–6,930	1 (2)	24 (39)	1,000–4,000
Eosinophils	61	378 ± 790	0–5,166	2 (3)	0 (0)	0–1,500
Platelets	56	199,964 ± 136,234	18,000–562,000	5 (9)	28 (50)	160,000–400,000
Albumin (g/dL)	64	2.2 ± 0.5	0.9–3.2	0 (0)	61 (95)	2.9–4.2
Globulin (g/dL)	61	3.8 ± 1.0	1.0–6.4	15 (25)	3 (5)	2.3–4.4
Sodium (mmol/L)	63	146 ± 6	126–164	3 (5)	24 (38)	145–154
Potassium (mmol/L)	63	4.3 ± 0.6	3.0–5.9	5 (8)	19 (30)	4.1–5.3
Total CO_2 (mmol/L)	63	19 ± 4	10–30	2 (3)	18 (29)	16–26
Creatinine (mg/dL)	64	1.8 ± 2.4	0.2–16.1	18 (28)	4 (6)	0.5–1.6
BUN (mg/dL)	64	41 ± 49	7–206	24 (38)	1 (2)	8–31
Glucose (mg/dL)	58	104 ± 27	50–219	12 (21)	3 (5)	70–118
Alanine aminotransferase (U/L)	60	126 ± 208	9–1,309	25 (42)	1 (2)	10–70
Alkaline phosphatase (U/L)	60	475 ± 879	15–5,208	34 (57)	0 (0)	15–127
Total bilirubin (mg/dL)	59	0.8 ± 3.0	0–23.3	12 (20)	0 (0)	0–0.4
Cholesterol (mg/dL)	59	287 ± 130	70–825	14 (24)	4 (7)	135–345

Thrombocytopenia (platelet numbers < 160,000 /μL) was diagnosed in 28 of 56 (50%) dogs.

The most common serum biochemical abnormality was hypoalbuminemia (95% [61/64]). Hypoalbuminemia was mild (serum albumin concentration, 2.6 to 2.8 g/dL) in 11 dogs, moderate (2.0 to 2.5 g/dL) in 30 dogs, and severe (0.9 to 1.9 g/dL) in 20 dogs. Hyponatremia was also a common abnormality, although the serum sodium concentration was < 140 mmol/L in only 5 dogs. Hyperkalemia was detected in 5 dogs and was associated with acute renal failure in 4 dogs. Azotemia was detected in 27 of 64 (42%) dogs. Eighteen of 64 (28%) dogs had a high serum creatinine concentration; BUN concentration was within reference range in 3 of those dogs. Twenty-four (38%) dogs had a high serum BUN concentration; serum creatinine concentrations were low or within reference range in 9 of those dogs. Thus, concentrations of both BUN and creatinine were high in 15 of 64 (23%) dogs. Urine specific gravity was measured in 12 dogs with a high serum creatinine concentration, and all 12 were isosthenuric. Two of those dogs had received furosemide. High serum activities of ALT, alkaline phosphatase, or γ-glutamyltransferase were detected in 42 of 60 (70%) dogs (Table 1). Total serum bilirubin concentration was high in 12 of 59 (20%) dogs; values were > 1.0 mg/dL in 5 dogs. Only 1 dog had a total bilirubin concentration > 5.0 mg/dL; that dog had biliary obstruction secondary to severe septic pancreatitis. Hypercholesterolemia was detected in 14 of 59 (24%) dogs and was associated with protein-losing nephropathy or glomerulonephritis in 6 dogs. Serum creatine kinase activity was measured in 9 dogs and was high in 5 dogs. Three dogs had values ranging from 603 to 1,126 U/L (reference range, 46 to 320 U/L). The other 2 dogs had values > 100,000 U/L, and 1 of those dogs had aortic thromboembolism.

Results of a urinalysis were available for 52 dogs. Pyuria was observed in 31 of the 52 (60%) dogs, cylinduria in 13 (25%) dogs, hematuria in 32 (62%) dogs, bacteriuria in 5 (10%) dogs, and glucosuria in 5 (10%) dogs. Thirty-two (62%) dogs had proteinuria. The urine protein-to-creatinine ratio had been determined in 22 dogs and was high in 17 (range, 1 to 18; reference range, < 1). The magnitude of increase in ratio was mild (1 to 1.9) in 7 dogs, moderate (2 to 4.9) in 4 dogs, and severe (> 5) in 6 dogs.

Abnormalities of coagulation, including thrombocytopenia, were noted in 35 dogs. Specific coagulation testing was performed in 26 dogs. Prothrombin time was more often shortened (35%) than prolonged (8%). Partial thromboplastin time was prolonged in 23 of 26 (88%) dogs; in 13 (50%) of those dogs, the time was ≥ 25% longer than the upper limit of reference range. Plasma fibrinogen concentration was high in 15 of the 18 (83%) dogs in which it was measured. An assay for D-dimers (measured in 13 dogs) or fibrin degradation products (measured in 2 dogs) yielded positive results in 13 of 15 (87%) dogs.

ECG findings—Arrhythmias and conduction deficits were detected in 32 of 71 (45%) dogs and were characterized with an ECG in 31 dogs; an ECG was not performed in 1 dog. Ventricular arrhythmias were detected in 24 of the 31 (77%) dogs, and an atrial arrhythmia was detected in 10 (32%) dogs. Ventricular arrhythmias recorded included ventricular premature complexes (11 dogs), ventricular tachycardia (8), ventricular bigeminy or trigeminy (2), accelerated idioventricular rhythm (2), and ventricular fibrillation (1). Atrial arrhythmias included supraventricular tachycardia (5 dogs), atrial fibrillation (4), and supraventricular premature complexes (1). Six dogs had atrioventricular block, which was characterized as first degree in 4 dogs and third degree in 2 dogs. Findings of an arrhythmia were poorly correlated with observation of pathologic cardiac changes at necropsy. Fourteen dogs had evidence of myocardial injury at necropsy, but an arrhythmia had been detected antemortem in only 6 of those dogs. Four dogs with an arrhythmia had no evidence of myocardial pathology at necropsy. One of the dogs with third-degree atrioventricular block had necrotizing myocarditis at necropsy, and the other had extension of proliferative tissue from valvular lesions into the region of the atrioventricular node.

Diagnostic imaging—Echocardiographic imaging had been performed in 59 of the 71 (83%) dogs, and results were consistent with a diagnosis of IE in 57. In the remaining 14 (20%) dogs, IE was diagnosed at necropsy. In 2 dogs, IE was not suspected on the basis of echocardiographic findings but was confirmed within 3 days of echocardiographic imaging at necropsy.

For the 28 dogs in which the location of lesions on the mitral valve was recorded, the septal leaflet alone was affected in 14 (50%) dogs, the mural leaflet alone was affected in 1 (4%) dog, and both leaflets were affected in 13 (46%) dogs. For the 19 dogs in which the location on the aortic valve was recorded, each cusp was equally involved; only a single cusp was affected in 9 (47%) of those dogs. Valvular abnormalities included the following: valvular hyperechogenicity (n = 29 dogs), thickening (23), and irregularity (7); proliferative or vegetative lesions (20); vegetations that were oscillating, vibratory, or mobile (9); lesions with a shaggy, moth-eaten, or fluffy appearance (9); nodular changes (7); and focal or discrete lesions (3). Lesions were designated as some combination of proliferative, mobile, and shaggy in appearance in 32 of the 59 (54%) dogs. The severity of accompanying valvular regurgitation or insufficiency was reported for 41 dogs (48 valves) and was categorized as absent (n = 3 dogs), mild or trivial (20), moderately severe (10), and severe (14). Mild-to-moderate left atrial enlargement was reported for 13 dogs. Left ventricular eccentric hypertrophy and chamber dilatation were observed in 11 dogs, and mural hyperechogenicity was observed in 2 dogs. Other complications resulting from IE were valve prolapse (n = 6 dogs), acquired valve stenosis (3), defects in mitral valve leaflets and aortic valve cusps (2), ruptured mitral valve chorda tendineae (2), acquired interventricular septal defect (1), avulsion of the noncoronary cusp of the aortic valve (1), and mild pericardial effusion (2). Follow-up echocardiographic imaging results were available for 23 dogs from 1 week to 28 months after initial diagnosis. Median duration of the longest follow-up time was 90 days. Partial (n = 8 dogs) or complete (7) resolution of valve lesions was observed in 15 dogs. In 2 of those dogs, severe aortic

insufficiency persisted. One dog developed aortic stenosis, and a fourth dog with residual mitral regurgitation developed progressive left atrial enlargement, atrial fibrillation, and rupture of a chorda tendineae 28 months after diagnosis. Resolution was generally associated with reduction in size, increase in echogenicity, and consolidation of lesions. Three dogs with mitral valve lesions developed a new lesion on the other mitral valve leaflet (2 dogs) or on the aortic valve (1) during the course of treatment. New lesions were observed as early as 7 days after initial diagnosis. Valve lesions were unchanged in 8 dogs. One of those dogs developed aortic stenosis, and in another dog, mitral regurgitation became more severe.

Affected valves were determined during echocardiographic imaging, necropsy, or both in all 71 dogs. A single valve was affected in 52 (73%) dogs (aortic valve, 22 [31%] dogs; mitral valve, 28 [39%] dogs; tricuspid valve, 2 [3%] dogs). The aortic valve was affected in 36 (51%) dogs, and the mitral valve was affected in 42 (59%) dogs. Combined mitral and aortic valvular lesions were detected in 11 (15%) dogs. Pulmonic valve IE was suspected in 2 (3%) dogs, both of which also had aortic valve IE. Tricuspid valve IE was detected in 5 (7%) dogs, 2 of which also had mitral valve involvement and 1 of which also had mitral and aortic valve involvement. Mural lesions were observed at necropsy in 6 (8%) dogs and usually involved the left ventricular wall, although 1 dog with no microbial growth on culture of blood had extensive involvement of the left atrial wall and another with *Streptococcus canis* IE had involvement of the left atrium and both ventricles as well as thrombus formation on the surface of the right atrium and cranial vena cava. Two of the 6 dogs with mural IE also had mitral valve involvement, and 1 had aortic and mitral valve involvement. Sites of mural involvement were not observed echocardiographically.

Results of thoracic radiography were available for 59 (83%) dogs. No abnormal findings were detected in 14 of those 59 (24%) dogs. In the remaining dogs, cardiopulmonary abnormalities were reported and included patchy or diffuse pulmonary interstitial or bronchointerstitial infiltrates (n = 17 dogs), the distribution of which was typical of changes associated with CHF in 3 dogs; alveolar infiltrates (10), the distribution of which suggested pneumonia in 4 dogs; generalized cardiomegaly (18); microcardia or vascular attenuation (2); left atrial enlargement (14); pulmonary venous distension (7) accompanied by infiltrates suggestive of CHF in 4 dogs; mild pleural effusion (6); and bronchiectasis (1). No correlation between duration of illness > 2 weeks and cardiac enlargement was observed.

Results of abdominal ultrasonographic imaging were available for 44 of the 71 (62%) dogs, and findings were unremarkable in 5 dogs. Hepatic lesions were detected in 13 dogs and were nonspecific in nature; findings included hepatomegaly (n = 7 dogs), diffuse hypoechogenicity (3), small cystic lesions (2), small cystic lesions and hypoechoic nodular lesions (2), and small cystic lesions and hypoechoic and hyperechoic nodular lesions (1). Hepatic vessel dilatation and free abdominal fluid suggestive of right-sided heart failure were observed in 2 dogs, neither of which had right-sided IE. Pancreatic lesions observed during imaging included hypoechoic mass lesions suggestive of pancreatitis or pancreatic neoplasia (n = 3 dogs) and mild pancreatic enlargement and hyperechogenicity (1). At necropsy, it was determined that one of the masses was caused by acute hemorrhage and another was a pancreatic adenocarcinoma. The dog with mild pancreatic enlargement had pancreatic nodular hyperplasia and fibrosis. The most common gastrointestinal lesion was intestinal wall thickening suggestive of inflammatory disease (n = 4 dogs). Free abdominal fluid was noted in 11 dogs, and volume of fluid was reported as large in 2 of those dogs. Abdominal fluid was associated with septic peritonitis in 3 dogs, a pancreatic acinar adenocarcinoma in 1 dog, and bladder necrosis (secondary to infarction) with urine leakage in another. Twelve dogs had splenic abnormalities, including splenomegaly (n = 5 dogs), a diffuse coarse or mottled echotexture (5), focal hypoechoic lesions (6), a cavitary splenic mass (1), and diffuse nodular lesions (1). Infarction was confirmed at necropsy in 2 dogs with hypoechoic lesions, and the cavitary mass in the spleen was determined to be a large hemorrhagic infarct. The dog with nodular lesions had hemangiosarcoma, which was diagnosed after splenectomy. Renal abnormalities were detected in 12 dogs. Focal hyperechoic or hypoechoic lesions suspected to be infarcts were seen in 9 dogs; histologic evaluation was performed in 2 of those dogs and confirmed infarction. Renal cortical hyperechogenicity was detected in 2 dogs. One dog with multiple small renal cystic lesions observed during ultrasonographic imaging had interstitial nephritis, glomerulonephritis, and glomerular thrombosis at necropsy, but cystic lesions were not observed. Six dogs had abdominal lymphadenopathy. The urinary bladder contained calculi in 2 dogs and echogenic debris in 3 dogs; 2 of those 3 dogs had bacterial urinary tract infections with the same organism that was causing IE, and the other had severe hematuria and hemoglobinuria associated with immune-mediated hemolytic anemia. Two dogs had large adrenal masses, 1 with bilateral involvement and vascular invasion. Iliac arterial and aortic thrombosis was detected in 2 dogs with peripheral arterial thromboembolism.

Complications—Arthrocentesis and cytologic analysis of synovial fluid was performed in 25 dogs and revealed suppurative inflammation in 21 (84%) dogs. Arthrocentesis was not performed in 10 additional dogs with lameness, swollen joints, or both. In 4 dogs, cytologic examination revealed septic inflammation with bacteria and degenerated neutrophils. Three of those dogs had *S canis* infection. In another dog with *S canis* infection, degenerated neutrophils, but not bacteria, were observed. The synovial fluid of 1 dog infected with *S canis* contained lupus erythematosus cells; that dog had concurrent evidence of protein-losing nephropathy. Five dogs had evidence of peripheral arterial thromboembolism. In 1 dog, both hind limbs and the right thoracic limb were affected and an iliac arterial embolus was confirmed during ultrasonographic examination.

Another was admitted with cool, firm hind limbs resulting from aortic thromboembolism, which was detected by use of ultrasonographic imaging. A third dog had lameness in the right thoracic and left pelvic limbs, and right cephalic vein and aortic thromboemboli were detected at necropsy. The other 2 dogs developed acute thoracic limb lameness after initial examination, and a diagnosis of peripheral arterial thromboembolism was made on the basis of clinical impression. The left limb was affected in 1 dog and the right limb was affected in the other. Another dog developed edema in all 4 limbs and gangrenous necrosis of several digits in 3 limbs, complications that were ascribed to thromboembolism or vasculitis. Hypertrophic osteopathy was observed in 1 of the dogs in which peripheral arterial thromboembolism developed after initial examination.

Renal complications were recorded in 37 of the 71 (52%) dogs. Seven dogs had moderate to severe renal failure (serum creatinine concentration > 4 mg/dL) at initial examination. One of the 7 dogs had protein-losing renal dysplasia complicated by secondary pyelonephritis. Two of the 7 dogs also had protein-losing nephropathy; histologic evaluation results were available for 1 dog and revealed severe, acute fibrinonecrotic renal vasculitis, tubulointerstitial nephritis, renal infarcts, and necrosuppurative glomerulitis. Necropsy results were available for the remaining 4 dogs with moderate to severe renal failure. One dog had renal vasculitis and membranoproliferative glomerulonephritis. Another dog had severe, multifocal acute glomerular thrombosis and interstitial nephritis; membranous glomerulonephritis; and severe, chronic plasmacytic tubulointerstitial nephritis. The third dog became oliguric terminally and had evidence of multiple acute renal infarcts at necropsy. The remaining dog had pyelonephritis secondary to *Escherichia coli* infection and bilateral renal microabscessation secondary to septicemia. Seven dogs had mild azotemia (serum creatinine concentration, 1.7 to 2.1 mg/dL) and isosthenuria at initial examination. Possible causes for these changes were identified in 6 dogs. One dog had ultrasonographic lesions consistent with infarction. Three dogs had lesions consistent with multifocal thrombosis and infarction at necropsy. One dog had histologic evidence of chronic interstitial nephritis, and the remaining dog had bilateral acute pyelonephritis. Three dogs became azotemic subsequent to initial examination. One dog developed oliguric renal failure; a severe acute infarct of the left kidney superimposed on moderate chronic interstitial nephritis was revealed at necropsy. The 2 other dogs became azotemic after furosemide administration. Four nonazotemic dogs had severe proteinuria consistent with protein-losing nephropathy at initial examination; histologic evaluation results were available for 1 of those dogs. Despite a urine protein-to-creatinine ratio of 17, that dog had only lesions consistent with multifocal renal thrombosis; glomerular lesions were absent. An additional 13 nonazotemic dogs had evidence of renal damage, either based on findings of cylinduria and proteinuria (n = 2 dogs), ultrasonographic evidence of infarction (4), or results of histologic examination of necropsy specimens (7). Renal lesions observed at necropsy were infarction (n = 11 dogs), glomerulonephritis (7; characterized as membranoproliferative in 4 dogs, necrosuppurative in 2 dogs, and membranous in 1 dog), pyelonephritis (7; chronic in 5 dogs and acute or subacute in 2 dogs), interstitial nephritis (7; chronic in 3 dogs and acute or subacute in 4 dogs), thrombosis (6), vasculitis (4), microabscesses (2), and multifocal bilateral renal tubular necrosis (2).

Seventeen (24%) dogs had neurologic complications associated with neurologic signs at the time of or subsequent to initial examination. Three additional dogs had diskospondylitis but no neurologic abnormalities. Involvement of the nervous system was diagnosed solely on the basis of neurologic examination findings in 9 dogs. Cerebrospinal fluid analysis was performed in 5 dogs, including 1 of the dogs with diskospondylitis; that dog had no abnormal findings in the CSF. Three dogs had suppurative inflammation (total nucleated cell counts 2, 120, and 23,300 cells/μL; reference range, < 1 cell/μL) and high protein (38, 69, and 1,152 mg/dL; reference range, < 25 mg/dL); the dog with the most severe changes in CSF had degenerated neutrophils and intracellular diplococci, and culture of the fluid yielded growth of *S canis*. Cerebrospinal fluid in the fifth dog contained mildly reactive mononuclear cells and high protein concentration (75 mg/dL). Six of the 17 dogs had necropsy confirmation of neurologic lesions, including 1 dog that had undergone CSF analysis. Lesions observed at necropsy were multifocal infarction (n = 2 dogs); suppurative-lymphoplasmacytic meningitis (2); and 1 dog each had suppurative-histiocytic meningitis with degenerated neutrophils, multifocal meningeal thrombosis, necrotizing vasculitis, and neutrophilic-histiocytic-lymphoplasmacytic meningoencephalomyelitis.

Development of CHF was suspected at the time of or subsequent to initial examination in 22 of 71 (31%) dogs, on the basis of results of thoracic radiography, necropsy findings, or both. Dogs with aortic valve involvement were more likely to develop CHF than dogs without aortic valve involvement ($P = 0.042$).

Pathology reports for results of valvular evaluation were available for 28 dogs, including 16 dogs that also had echocardiographic reports. At necropsy, valvular lesions ranged from thickening and nodules < 1 mm in diameter to nodules with dimensions of 2.5 × 1.5 × 1.0 cm; lesions in 13 of the 28 (46%) dogs were > 0.5 cm in diameter. Lesion measurements were not usually available in echocardiography reports, but the pathologic descriptions correlated approximately with echocardiographic descriptions in most instances. Two dogs with large lesions detected echocardiographically had only nodular lesions < 3 mm at necropsy, but in the intervening period, 1 of those dogs (with mitral valve IE) developed peripheral arterial thromboembolism in the right thoracic limb, and the other (with aortic valve IE) developed acute renal failure resulting from infarction, which was detected at necropsy. Of the 2 dogs with no abnormal echocardiographic findings, 1 dog had a large (1.2 cm) vegetation between 2 cusps of the aortic valve and both dogs had tiny coalescing nodular lesions on the mitral valve. One dog had a thrombus in the right atrium that was not detected echocardiographically. Echocardiographic imaging had

been performed in 2 dogs with mural and valvular lesions, and only the valvular lesions were recorded. At necropsy, 5 dogs had avulsion or perforation of valvular structures. One dog with CHF had a ruptured chorda tendinea. Two dogs, including 1 with CHF, had perforation of all aortic valve cusps. One dog had mitral valve leaflet perforation and an acquired ventricular septal defect, and another dog with CHF had avulsion of the noncoronary cusp of the aortic valve. Echocardiographic imaging was performed in all of those dogs except the dog with the ruptured chorda tendineae. An aortic valve leaflet perforation was suspected in 1 dog, and a septal defect was detected in another. The aortic valve avulsion was detected by use of transesophageal, but not transthoracic, echocardiographic imaging.

Histologic evaluations of necropsy specimens were recorded for 25 dogs. The most common systemic abnormalities were evidence of infarction, widespread thrombosis, and CHF. Necrotizing vasculitis was observed in the lungs, myocardium, kidney, spleen, liver, or brain in 6 of the 25 (24%) dogs. In 4 dogs, erythrophagocytosis was observed in the spleen, liver, or lymph nodes; those dogs all had gram-positive coccal infections. Only 1 of those dogs had clinically important anemia, and this was thought to result from gastric ulceration. Results of valvular pathologic evaluation have been reported elsewhere.[10]

When ultrasonographic findings and necropsy results were taken into account, thromboembolism was detected in 31 of the 71 (44%) dogs. An additional 5 dogs had localized neurologic abnormalities at initial examination; abnormal signs were suspected to be caused by thromboembolism, but further imaging or necropsy evaluation was not performed. The organs most commonly involved were the kidneys (23 [74%] dogs), spleen (10 [32%] dogs), lung (7 [23%] dogs), myocardium (6 [19%] dogs), peripheral arteries (6 [19%] dogs), and brain (4 [13%] dogs). Other sites with involvement that were detected at necropsy included the gastric mucosa (2 dogs) and urinary bladder, tongue, liver, and skin (1 dog each). Dogs with mitral valve involvement alone were more likely to have thromboembolism than dogs with aortic valve involvement alone ($P = 0.047$), but observation of proliferative, mobile, or shaggy lesions during echocardiographic imaging did not predict thromboembolism.

Outcome—Fourteen dogs died, 43 were euthanized, 12 were lost to follow-up, and 2 were alive at the time of writing. The cost of the initial visit in which endocarditis was diagnosed ranged from $2.00 (euthanasia only) to $9,237 (mean, $1,965; median, $1,483).

Of the 14 dogs that died, 7 died for reasons related to IE, and all except 1 of those dogs died within 6 days of admission. Five dogs died of unknown causes from 67 to 1,760 days (median, 665 days) after diagnosis of IE, and 1 dog died 78 days after initial examination for reasons thought to be related to underlying congenital

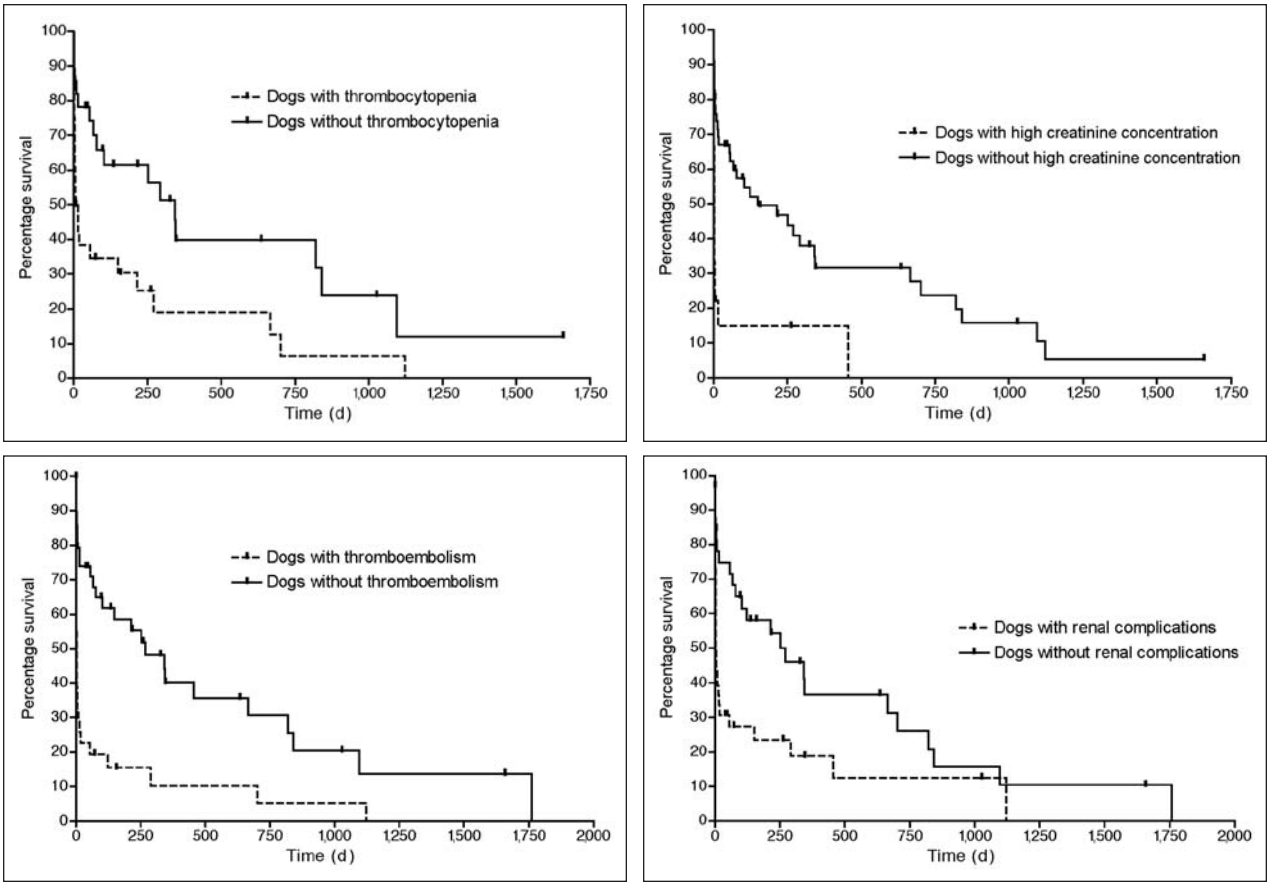

Figure 2—Kaplan-Meier analyses illustrating the effect of factors that were significantly ($P < 0.05$) associated with outcome in 71 dogs with IE.

Table 2—Factors significantly ($P < 0.05$) associated with fatality in 71 dogs with IE.

Variable	Category	No. (%)	Death or euthanasia (No.)	Hazard ratio	95% CI	*P* value
Sex	Male	47 (66)	10	1.13	0.64–2.03	0.66
	Female	24	6			
Previous glucocorticoid treatment	Yes	11 (15)	8	0.74	0.38–1.51	0.42
	No	60	47			
Serum creatinine concentration	High	18 (28)	16	3.00	2.45–13.50	< 0.001
	Normal	46	34			
Serum ALT activity	High	25 (42)	20	1.20	0.66–2.21	0.54
	Normal	35	26			
Serum albumin concentration	≤ 2.5 g/dL	44 (69)	34	1.23	0.68–2.24	0.48
	> 2.5 g/dL	20	16			
WBC count	≥ 25×10^3/L	26 (43)	18	1.16	0.63–2.18	0.61
	< 25×10^3/L	35	28			
Band neutrophils	Present	41 (67)	32	1.40	0.76–2.55	0.29
	Absent	20	14			
Toxic-appearing neutrophils	Present	34 (56)	28	1.71	0.96–3.13	0.07
	Absent	27	18			
Thrombocytopenia	Present	28 (50)	24	2.29	1.31–4.81	0.006
	Absent	28	17			
Arrhythmias and conduction defects	Present	32 (45)	29	1.25	0.73–2.19	0.39
	Absent	39	26			
Congenital heart disease	Yes	8 (11)	5	0.53	0.25–1.22	0.14
	No	63	50			
Valve involvement	Aortic	36 (51)	22	1.19	0.70–2.09	0.50
	Other	35	18			
	Multiple	16 (23)	11	0.79	0.42–1.49	0.46
	Single	55	44			
Vegetative lesion on echocardiography	Noted	27 (46)	25	1.41	0.78–2.66	0.25
	Not noted	32	18			
Neutrophilic polyarthritis	Present	21 (30)	15	0.66	0.38–1.17	0.15
	Not noted	50	40			
Thromboembolic complications	Present	31 (44)	29	2.78	1.98–6.74	< 0.001
	Not noted	40	26			
Renal complications	Present	38 (54)	31	1.98	1.23–3.83	0.007
	Absent	33	24			
Neurologic complications	Present	17 (24)	13	1.09	0.57–2.10	0.79
	Absent	54	42			
CHF	Present	22 (31)	21	1.54	0.90–3.02	0.10
	Absent	49	34			

cardiac disease. Thirty-three dogs were euthanized for reasons related to IE. One of those dogs was euthanized after concurrent splenic hemangiosarcoma was diagnosed. Common reasons for euthanasia included respiratory distress, cardiopulmonary arrest, refractory oliguria, and neurologic abnormalities. Three dogs were euthanized within 24 hours of echocardiographic diagnosis of endocarditis; 2 of those dogs had visible rents in valve leaflets. Two dogs were euthanized at the owner's request prior to diagnosis of IE. Eight dogs were euthanized for reasons unrelated to IE. Of the 12 dogs lost to follow-up, 2 dogs were discharged with antimicrobial treatment 4 to 7 days after admission, and subsequent outcome was unknown. Two dogs were doing poorly at the time of loss to follow-up because of reasons related to IE, including CHF and severe weakness (1 dog each). Two dogs were doing poorly for reasons unrelated to IE. Six dogs were doing well with static (n = 2) or resolving (2) valvular lesions; 1 dog each had persistent arrhythmia and flow abnormalities despite resolution of valvular lesions. Survival time in the dogs that died or were euthanized ranged from 0.04 to 1,659 days (mean, 197 days; median, 5 days; n = 55). In 15 dogs for which survival time was unknown, time to loss of follow-up contact or study completion ranged from 0.04 to 1,028 days (mean, 225 days; median, 136 days). Thirty-five (49%) dogs survived longer than 2 weeks. Median survival time for all dogs was 54 days. Variables found to significantly influence survival were thrombocytopenia ($P = 0.005$), high serum creatinine concentration ($P < 0.001$), renal complications ($P = 0.007$), and thromboembolic complications ($P < 0.001$; **Figure 2**; **Table 2**).

Discussion

The present study represents the largest series of IE in dogs and is the first, to the authors' knowledge, in which relationships between clinical features and outcome were studied. Most dogs were initially received by the emergency and critical care services at the VMTH, but some were initially examined by veterinary cardiologists, internists, or neurologists. Mean cost of initial treatment was approximately $2,000, but the range was wide. The costs examined in this study did not include costs of subsequent examinations that were often related to complications such as CHF and thromboembolism and that often required hospitalization. Forty dogs died or were euthanized as a result of IE, yielding a mortality rate of at least 56%, a finding that was similar to values reported[3] 2 decades ago. In the present study, findings of thrombocytopenia, high serum creatinine concentration, and renal and thromboembolic complications were negatively associated with survival. Knowledge of these factors facilitates accurate prognostication and may aid in

identification of dogs that require more aggressive treatment.

In the present study, the annual incidence of IE ranged from 0.03% to 0.1%. A large proportion (30/71 [42%]) of the diagnoses were made in the interval from 2000 to 2002, coincident with the interval in which *Bartonella* spp were recognized as an important cause of IE in dogs in this geographic region.[5] After that period, the incidence of IE decreased, as did the number of dogs with IE caused by *Bartonella* spp. Over the entire period analyzed, it was difficult to ascertain whether a true increase in the incidence of IE in dogs was occurring. It is unclear why the incidence of IE was slightly lower during the hotter months of the year, but seasonal activity of vectors that transmit *Bartonella* may have played a role.

As in previous studies,[2-5,8] large-breed middle-aged to older male or male neutered dogs were predominantly affected. Myxomatous mitral valve degeneration and underlying congenital heart disease were not important contributors to IE in small-breed dogs; those conditions were observed in only 1 dog each. It has been suggested[18] that the predisposition for IE in male dogs may be partly explained by the effects of underlying bacterial prostatitis, but this finding was observed in only 1 dog.[10] Three of 5 dogs younger than 1 year of age had underlying subaortic stenosis, suggesting that this condition may be an important contributor to IE in young dogs, although in 1 study it was found that IE was an uncommon complication in dogs younger than 2 years of age that had subaortic stenosis.[34] In human patients with IE, the mean age of affected males is 6 to 7 years older than the mean age for women.[35] In the present study, the mean age of male and female dogs was the same.

As was reported in earlier studies,[3-5,8] locomotor problems were a common clinical abnormality and were most commonly caused by neutrophilic polyarthritis, but neurologic abnormalities, peripheral arterial thromboembolism, and hypertrophic osteopathy were also described. The latter condition has only rarely been reported[6,36,37] in humans or dogs with IE. Splenomegaly and petechial hemorrhage were rare findings, whereas these findings are reported[1,35] in > 20% of human patients.

Although fever and cardiac murmurs were often detected on physical examination, the absence of those findings did not rule out IE, and fever was more often absent than present on initial physical examination. These findings were detected with a higher prevalence in other studies.[3,5,6] In the present study, fewer than 20% of dogs lacked fever and any cardiovascular abnormality on initial physical examination. Fever and a cardiac murmur were often detected on later examinations if not detected at initial examination. The absence of fever has been attributed to the effects of recent antimicrobial treatment, advanced age, uremia, CHF, and prolonged period of infection.[1,3,6,19,35] In the present study, the only variable that differed between febrile and afebrile dogs was high serum creatinine concentration ($P = 0.04$); recent antimicrobial treatment, age ≥ 10 years, CHF, and duration of signs > 14 days were not significantly different between those 2 groups. In dogs, infection with *Bartonella* may also contribute to the high number of afebrile patients.[10] In contrast to humans with IE,[1,38] in the present study there was no correlation between absence of a cardiac murmur and presence of right-sided or mural lesions. Nearly all of the dogs with a heart murmur had a systolic murmur, and although a diastolic murmur may be strongly suggestive of IE, diastolic murmurs were only detected in one fourth of the dogs with a heart murmur.

In the present study, underlying cardiac disease, as has been found in other studies,[3,6] was an uncommon predisposing factor for development of IE, being diagnosed in only 13% of dogs. Nearly all of those dogs had subaortic stenosis. In humans, underlying cardiac disease has been categorized as valvular, congenital, prosthetic, or other; prosthetic valve endocarditis, but not congenital cardiac disease, has been associated with a worse prognosis.[26] Underlying congenital cardiac disease was not associated with outcome in dogs in the present study. Prior treatment with glucocorticoids, a factor that was previously suspected to affect outcome,[3] was not associated with a poor outcome in dogs in the present study. In a study[29] in humans, an immunocompromised state was associated with a 2.9-times greater risk of adverse outcome in intensive care unit patients with IE, and in another study,[25] concurrent diabetes mellitus was an independent predictor of death. Concurrent diabetes mellitus was not a predisposing factor for IE in any of the dogs in the present study.[10]

Leukocytosis and hypoalbuminemia were more common laboratory abnormalities in dogs with IE than in humans with IE[1] and were findings observed in nearly all dogs. In contrast to findings in humans,[26,27] these conditions were not associated with mortality rate in the present study. Thrombocytopenia was detected in half of the dogs in this study, and the median survival time of dogs with thrombocytopenia was half of the median survival time of dogs that did not have thrombocytopenia. Thrombocytopenia reportedly affects only 5% to 15% of humans with IE[1] but has also been linked to poor outcome.[4] Proposed mechanisms for thrombocytopenia resulting from IE and sepsis include immune-mediated destruction, consumption of platelets during clot formation, and decreased production by the bone marrow.[39] In the present study, only 1 dog had a normal CBC; that dog had a diagnosis of possible IE, no microbial growth on culture of blood, and underlying congenital cardiac disease. Nearly one third of the dogs in the present study had a high serum creatinine concentration. Studies[27,40] in humans reveal an association between poor outcome and high serum creatinine concentration, and this was a strongly significant association in dogs of the present study as well.

Over half of the dogs had coagulation abnormalities, including thrombocytopenia. When coagulation testing was performed, results were nearly always abnormal; therefore, consideration should be given to testing all dogs with IE for coagulation function. Testing of dogs in the present study was usually performed because thromboembolism was suspected. Human patients with IE and subsequent thromboembolism have systemic coagulation activation and impaired fibrinolysis.[41]

In the present study, echocardiographic imaging was a sensitive tool for diagnosis of IE, with a sensitivity of 87.5%, compared with necropsy, which was used as the gold standard for diagnosis. Only 2 dogs had negative findings of IE on the basis of echocardiographic imaging yet positive findings at necropsy. Echocardiographic findings appeared to correlate well with those found at necropsy, and the large lesions that were observed during imaging but that were not detected at necropsy in 2 dogs most likely detached and became thromboemboli in the intervening period. In 2 dogs that had valvular and mural lesions, the mural lesions were not detected echocardiographically. Echocardiographic imaging was useful for monitoring response to treatment and detecting complications such as aortic stenosis, perforation of a valve leaflet, a ruptured chorda tendineae, or an acquired septal defect. In 1 dog, transesophageal echocardiography was necessary to detect an avulsed aortic valve cusp. Additional studies will be required to determine the value of transesophageal echocardiography for diagnosing IE in dogs, although the high sensitivity of transthoracic echocardiography in dogs, compared with that in humans, suggests that the value of the transesophageal approach is likely to be much lower.[20] In the present study, the finding of lesions that were proliferative, mobile, or shaggy in appearance and suggestive of vegetative lesions during echocardiographic imaging was not predictive of outcome. Observation of mobile lesions alone was likewise unassociated with outcome. Detection of a vegetative lesion did not predict thromboembolism, which contrasts with findings from an earlier study in humans.[42]

Preferential involvement of valves on the left side of the heart has been reported in pigs,[43] humans,[1,44] and dogs[2-8] with IE, and it has been suggested that this finding is a reflection of the degree of pressure, and thus trauma, exerted on the closed valve over a lifespan.[44] In cattle, the valves on the right side of the heart are more commonly involved, possibly as a result of introduction of bacteria by farmers or veterinarians during jugular venipuncture.[45] In most, but not all, studies[1,44] involving humans with IE, the mitral valve is reported as being more commonly affected than the aortic valve. In contrast, a predominance of aortic valve involvement has been reported in dogs.[8,18] In the present study, the mitral valve was affected slightly more often than the aortic valve, a finding that has also been reported in other canine studies.[2,3] The larger septal leaflet of the mitral valve was more commonly affected than the mural leaflet. In contrast with findings in a previous study[5] involving a subset of the patients in the present study, and in accordance with findings from human studies,[27,30,32] we did not find an association between aortic valve involvement and poor outcome. The association between aortic valve IE and CHF has been postulated by other investigators,[3] and results of the present study support such a connection.

Common complications of IE included neutrophilic polyarthritis (30% of the 71 dogs), CHF (31%), arrhythmias and conduction deficits (45%), thromboembolism (44%), and glomerulonephritis or protein-losing nephropathy (15%). Septic polyarthritis was suspected in almost one fourth of dogs with neutrophilic polyarthritis; the remainder had synovial fluid changes that were more consistent with immune-mediated disease. Neutrophilic polyarthritis, CHF, and arrhythmia were not associated with poor outcome in these dogs. Arthralgia was an independent predictor of fatality in 1 study[30] of human patients, and CHF has been found to affect fatality in some, but not all, studies of humans with IE.[30,32,33,35]

Thromboembolic disease was common and, as was reported in a study of humans,[46] was more likely to affect dogs with mitral valve involvement. Although thromboembolism and renal complications were associated with a poor outcome, this finding should be interpreted with caution because in some dogs evidence of those complications was only detected at necropsy. Abdominal ultrasonography was useful for detection of visceral infarcts and arterial thromboemboli in many dogs in the present study. Use of color Doppler interrogation to ascertain an absence of blood flow facilitated differentiation of infarcts from benign hypoechoic lesions. Studies of the effect of thromboembolism on outcome in humans have typically relied on the results of computed tomography, magnetic resonance imaging, angiography, or all 3 for diagnosis of thromboembolism. The risk of death may double in patients with thromboembolism.[47] The requirement for general anesthesia in dogs limits the use of these diagnostic modalities, but they could be considered for detection of thromboembolism in dogs with IE that are physiologically stable.

Renal complications in dogs with IE have been reported in 1 other study.[9] All 4 dogs with renal failure in that study had renal infarction detected at necropsy, and 1 dog also had membranoproliferative glomerulonephritis. Focal renal infarction is the most common renal lesion in humans with IE,[48,49] and results of the present study suggest that the same is true in dogs. Glomerular lesions in humans include vasculitic glomerulonephritis (without deposition of immunoglobulins), membranoproliferative glomerulonephritis, and acute postinfective glomerulonephritis, with deposition of IgG and complement.[49,50] Although immune-complex deposition was not studied in the dogs in this report, glomerular lesions were detected at necropsy in 7 dogs, the most common being membranoproliferative glomerulonephritis. Other renal pathologic findings in dogs of this study were interstitial nephritis, pyelonephritis, renal vasculitis, and renal cortical necrosis, all of which have been reported in human patients.[49,50] In some dogs, findings of chronic interstitial nephritis were observed and were considered to be incidental. Pyelonephritis may have been a predisposing cause of IE in some dogs.

Involvement of the CNS was detected in one fourth of the dogs in the present series and, in contrast to results of studies in humans,[28,30,35] was not necessarily associated with a poor outcome because neurologic signs resolved after treatment in several dogs. The most common causes of neurologic abnormalities identified were thromboembolism and meningeal inflammation. The brain is a common site of embolization in humans with IE, and up to 28% of human patients with IE have focal neurologic deficits, altered mentation, or headache.[28] Involvement of the CNS may have been

more prevalent in dogs of the present study than was indicated by the data because subtle changes in mentation are difficult to detect in dogs, and the CNS was not routinely evaluated at necropsy. Results of earlier studies[2-4,6] suggest that the prevalence of neurologic involvement is lower in dogs.

A number of factors limit interpretation of the results of this study. Retrospective collection of data makes comparisons with a standard treatment protocol impossible, although most dogs received aggressive treatment with parenterally administered antimicrobials in the hospital followed by long-term parenterally or orally administered antimicrobials on an outpatient basis. Factors not analyzed in the present study that have prognostic implications in humans with IE include weight loss, size of vegetative lesions, cardiac function, and septic shock.[27,29,30] These factors were not analyzed because of incomplete detail in the medical records. The rate of complications was likely underestimated because not all dogs underwent advanced imaging or necropsy evaluation, and inclusion of thromboembolism, renal, neurologic, and cardiac complications as detected during necropsy leads to a study bias toward fatality. However, neurologic complications and CHF were not associated with poor outcome despite this bias. Several dogs were lost to follow-up, and the reason for euthanasia or death was not known in many dogs. Some dogs were euthanized soon after initial examination with minimal or no treatment because of owner financial concerns. Multivariate analysis was not performed to determine independent predictors of risk, and the factors that were significant in univariate analysis (high serum creatinine concentration, renal complications, and thromboembolism) were interrelated. Nevertheless, this large case series of dogs with IE yields insight as to potential factors influencing outcome of affected dogs.

a. GraphPad Prism, version 4.00, GraphPad Software Inc, San Diego, Calif.

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