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Infective Endocarditis

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Endocarditis refers to inflammation of the endocardial surface of the heart. Infective endocarditis is defined as a microbial infection of the endocardial surface. Vegetative endocarditis refers to a specific form of endocarditis in which structures (vegetations) composed of platelets, fibrin, microorganisms, and inflammatory cells are found adhered to heart valves or occasionally clinging in the vicinity of septal defects, chordae tendineae, or the mural endocardium. Endocarditis is currently classified as either acute or subacute-chronic, based on the duration, rate of progression, and severity of the clinical signs. Endocarditis (both the term and the disease) is pathophysiologically and epidemiologically unrelated to the most common form of chronic valvular heart disease in dogs known as endocardiosis.

EPIDEMIOLOGY AND PREDISPOSING FACTORS

The epidemiology of endocarditis in companion animals has not been extensively studied. Based on reports of case series from referral centers, it is not a common disease in dogs, and it is a rare disease in cats. Based on the author's experiences and discussions with other veterinary cardiologists, significant geographic differences in the prevalence of infective endocarditis probably exist in the US, with significantly more cases recognized in warmer climates (specifically the Southern and Western states). Males are more commonly affected than females, and large breed dogs are affected more commonly than small. In the dog, the left-sided heart valves (aortic and mitral) are by far the most frequently affected (although transvenous pacemaker lead wires are occasionally involved in tricuspid valve endocarditis in dogs).

Predisposing factors for canine infective endocarditis include congenital aortic valve disease (e.g., subaortic stenosis) and probably other congenital heart diseases that cause disturbances of blood flow and subsequent changes in the endocardium. Steroid use is an important predisposing factor in dogs, and many cases of endocarditis appear to have a nosocomial origin. Infected intravenous catheters, prosthetic heart valves, open-heart surgery, and interventional cardiac catheterization (e.g., aortic balloon valvuloplasty) all appear to enhance the risk of endocarditis in dogs. Infection with potentially immunosuppressive organisms (e.g., *Bartonella* sp., *Ehrlichia* sp.) appears to enhance the risk of endocarditis in dogs. Interestingly, chronic valvular heart disease (endocardiosis) does not appear to predispose to infective endocarditis. There is actually little evidence that periodontal disease is a frequent source of infective endocarditis in dogs, in apparent contrast to humans. Other predisposing factors for endocarditis in dogs include other chronic sources of bacteremia (e.g., urinary tract infection, diskospondylitis) or systemic illness that facilitates bacterial infection (e.g., diabetes mellitus, Cushing's disease).

MICROBIOLOGIC FEATURES

Staphylococci sp., *Streptococci* sp., *Erysipelothrix* sp., *Corynebacteria* sp., and *Escherichia coli* sp. have been the most common bacterial isolates in canine infective endocarditis.[1,2] In recent years, *Bartonella* sp. have been isolated with increasing frequency from dogs with infective endocarditis. In clinical settings where the index of suspicion for *Bartonella* sp. is high and facilities for Bartonella culture, reliable serologic investigation, or other means of positive identification (e.g., polymerase chain reaction on tissues) are available, this organism is becoming a frequently recognized cause of infective endocarditis in dogs.[3,4,5] A wide variety of other organisms have been cultured from isolated individual cases, with many nosocomial cases involving *Pseudomonas* sp., *Proteus* sp., or other unusual (and often highly antibiotic resistant) isolates. Anaerobic bacteria (e.g., *Bacteroides* sp.) also occasionally cause infective endocarditis.[6]

CLINICAL MANIFESTATIONS

The clinical presentation of infective endocarditis often includes extracardiac manifestations of systemic infection and inflammation. Fever is the most common sign, although it may be intermittent, minimal, or even absent in patients with less virulent organisms (e.g., *Bartonella* sp., some gram-positive organisms) and in those who are severely debilitated or in congestive heart failure. The use of anti-inflammatory drugs (steroids or nonsteroidal drugs) may mask fever. Other common systemic signs of subacute infective endocarditis include lethargy, anorexia, weight loss, reluctance to move (back pain, polyarthritis), and intermittent lameness (muscle embolization, polyarthritis).

The presence of heart failure at presentation usually indicates extensive valve damage and a commensurately poor long-term prognosis. Syncope or episodic weakness is an infrequent presenting sign that may be caused by high-grade atrioventricular (AV) block (associated with extension of aortic valvular endocarditis into the adjacent tissues, which include the AV node and bundle of His), or less often, sustained ventricular or even supraventricular tachyarrhythmia, or neurologic sequelae of bacterial embolization. Almost all patients diagnosed with infective endocarditis have a heart murmur, and presumably most patients with endocarditis have a murmur. The murmur may be new, or may be newly recognized because of changes in intensity, quality, timing, or duration. Many animals with endocarditis have a preexisting heart murmur, e.g., from mild subaortic stenosis. The presence of a diastolic murmur in a systemically ill animal should dramatically raise the index of suspicion for infective endocarditis. These murmurs of aortic insufficiency are often low intensity, soft, blowing murmurs with a distant quality that makes them difficult to hear in noisy clinical environments. They are often heard best by placing the diaphragm of the stethoscope in the animal's left armpit with the animal lying on it's left side, such that the animal is actually lying on top of the stethoscope.

DIAGNOSIS

In part because the presenting complaints of clients whose animals have infective endocarditis tend to be vague and associated with some aspect of systemic illness, endocarditis is often difficult to diagnose. Definitive diagnosis requires the synthesis of clinical, laboratory (microbiologic), and echocardiographic data. The standard clinical database, including a complete blood count, serum biochemistry panel and urinalysis often reveals abnormalities (e.g., mild anemia, inflammatory or stress leukogram). Urinalysis results may reveal urinary tract infection or proteinuria, the latter caused by glomerulonephritis associated with chronic antigenic stimulation. These clinical laboratory abnormalities are common with other diseases and therefore nonspecific; they do not contribute independently to the diagnosis of infective endocarditis.

In human medicine, standardized criteria for assessing patients with suspected infective endocarditis have been clinically validated and recently revised by a group at Duke University.[7,8] These criteria integrate the presence of known predisposing factors for endocarditis, blood culture results, and echocardiographic findings with other clinical and laboratory information to arrive at a diagnosis. While these criteria are not directly applicable to veterinary medicine for a variety of reasons (different predisposing factors, greater access of human patients to transesophageal echocardiography, different microbiological and anatomic spectrum of human disease, etc), they provide a useful starting point for discussing current veterinary diagnostic criteria.

THE DUKE CRITERIA

Diagnostic criteria applicable to veterinary medicine can be briefly summarized (or adapted) as follows:

- **Major Criteria—Microbiologic:**
  - At least 2 separate blood cultures positive for a typical organism (see common list above), obtained by separate venipunctures an hour apart (3 cultures are usually recommended if time, money, and patient size permits, at least 2 must be positive).
  - In acutely ill patients with apparent sepsis syndrome, 3 blood cultures 5–10 minutes apart should be obtained if the patient's size permits, followed by empiric antibiotic therapy.
- **Major Criteria—Echocardiographic Evidence of Endocardial Involvement:**
  - An oscillating mass at a site of endocardial injury (i.e., a mass near a valve, but separate from the valve, whose movements are distinct from those of the valve—it is important to note that this criteria excludes valves that are merely thickened, such as those commonly seen with endocardiosis).
  - Periannular abscess.
  - New dehiscence of either a prosthetic patch (e.g., VSD patch), or a prosthetic valve.
- **Minor Criteria—Known Predisposing Factors:**
  - Previous proven endocarditis.
  - Subaortic stenosis.
  - Prosthetic valve, synthetic intracardiac patch, or transvenous pacemaker.
  - History of steroid use with any of the above conditions.
  - Prolonged IV catheterization, or infected IV catheterization site.
- **Minor Criteria—Clinical Findings:**
  - Fever (> 39.7C / 102.5 F), especially recurrent or persistent.
  - New heart murmur.
- **Minor Criteria—Microbiologic:**
  - Single positive blood culture.
  - Serologic evidence of infection.
- **Minor Criteria—Echocardiographic:**
  - Aortic insufficiency (more than just "3-pixel" garden variety common in large dogs).

Based on the Duke Criteria for definite diagnosis of infective endocarditis in humans, diagnosis in the dog might reasonably require fulfilling 2 major criteria above, or 1 major plus 3 minor criteria, or 5 minor criteria.

Patients with suspected or definite infective endocarditis should have electrocardiograms recorded (and repeated regularly during their clinical course), since the onset of AV or bundle-branch block, particularly in the setting of aortic valve endocarditis, suggests perivalvular extension of the infection. Such extension is a poor prognostic sign, suggesting that current therapy may be insufficient.

When blood cultures from suspected infective endocarditis patients remain sterile after 72 hours of incubation, the laboratory should intensify efforts to grow fastidious organisms such as *Bartonella* sp. and the clinician should initiate serologic assessment for such organisms if he or she hasn't already done so. Validated serologic testing for *Bartonella* sp. is available from NCSU by contacting Dr. Edward Breitschwerdt's laboratory, e-mail Julie_Bradley@ncsu.edu for specific sample preparation, mailing, and billing instructions.

ECHOCARDIOGRAPHY

Routine transthoracic echocardiography is quick, widely available, noninvasive, and at least in humans has excellent specificity for vegetations when performed by board certified cardiologists (98 percent).[9] The sensitivity of transthoracic echocardiography for vegetations in human patients is substantially less, in the range of 60 percent. For this reason, transesophageal echocardiography is recommended in human patients with suspected endocarditis but a negative transthoracic echo (e.g., a predisposed patient with positive blood cultures). In humans, the sensitivity of transesophageal echocardiography for detecting vegetations is reported to be 75 to 95 percent, while maintaining a high specificity. The sensitivity and specificity of transthoracic or transesophageal echocardiography has not been systematically examined in dogs. In humans, and presumably in dogs, the experience and training of the echocardiographer has a dramatic impact on the accuracy of the test. Though the following statement has the potential to appear self-serving, the author believes that the best available evidence suggests that echocardiographic investigation for infective endocarditis is usually best performed by board certified cardiologists if such expertise is available. Echocardiography is also useful to follow the response to therapy, as vegetations often shrink in response to successful therapy. Perivalvular extension of infection (abscessation) is often difficult to diagnose echocardiographically, but is a poor prognostic indicator when present.

COMPLICATIONS

Congestive heart failure, renal failure, or neurologic events are the complications that appear to have the greatest influence on the prognosis of infective endocarditis. Infection-induced valve damage, especially of the aortic valve, is the usual cause of congestive heart failure in these patients. In dogs as well as humans, aortic valve infection appears to be more often associated with congestive heart failure than mitral-valve infection.

Embolization of fragments of vegetations can cause acute infarction of a variety of organs, most commonly involving the spleen, liver, kidney, or skin in the dog. Neurologic complications occur in dogs, but generally appear less common (or less visible) in dogs than in people, where the risk of stroke is high in left-sided endocarditis. Polyarthritis, when it occurs, may be immune-complex mediated or may in fact be caused by direct infection of multiple joints with the cultured organism. Endocarditis complicates approximately 20–30% of cases of diskospondylitis in dogs, in whom pain or the onset of neurologic signs (caused by spinal cord or nerve root compression) generally signals the presence of disease. Dogs diagnosed with primary diskospondylitis should be screened echocardiographically for evidence of infective endocarditis whenever a heart murmur is detected. Many other unusual (and presumably infrequent) complications of infective endocarditis have been reported in dogs, including intrahepatic cholestasis, pneumothorax, and other complications of systemic or distant infection.

TREATMENT

Prolonged parenteral administration of a bactericidal antibiotics or combinations of antibiotics is currently recommended for the treatment of infective endocarditis in humans. Such treatment courses are generally prohibitively expensive in dogs. Treatment is usually begun with parenteral antibiotic combinations in hospitalized dogs, but once the fever has resolved and clinical improvement (return of appetite, etc.) is evident (generally not more than 3–5 days), treatment is completed on an outpatient basis with oral antibiotics. Treatment is based on blood culture and sensitivity results, but these are not available for the first, often critical, hours or days of therapy. Empiric antibiotic therapy for dogs with a clinical history and echocardiographic findings compatible with infective endocarditis are generally started on a combination of fluoroquinolone and a penicillin-based antibiotics. In our practice, parenteral Enrofloxacin (5 mg/kg IV q12h) and Amoxicillin (20 mg/kg IV q8h) are most often chosen. Therapy is generally continued for 12 weeks, and blood cultures are ideally obtained after 10–14 days (on antibiotics), and then again 1 week after stopping antibiotics. If *Bartonella* sp. are identified by culture or serology, our current antibiotic recommendation is Azithromycin, 5–10 mg/kg q24h for the first 7 days,

then every other day for 6–12 weeks. Azithromycin appears to achieve intracellular concentrations approximately 120 times higher than erythromycin. Although discussed by some veterinary authors, anticoagulation does not appear to diminish the risk of bacterial embolization in humans, and is not generally recommended.[10] Management of heart failure, if needed, is discussed elsewhere in this volume.

PROGNOSIS

The prognosis for endocarditis appears to depend primarily on the valve damage that has been done at the time of diagnosis, as well as the response to antibiotic therapy. There is not enough information available regarding the natural history of infective endocarditis in dogs to accurately correlate the infective organism, independent of other factors that influence the severity of the disease, with prognosis. Recurrence or treatment failure is likely with inadequate duration of therapy, inappropriate antibiotic selection, or owner noncompliance. Owner compliance is perhaps an even bigger issue in the treatment of endocarditis than it is with other heart diseases, and client education is critical. Despite optimal therapy and therapeutic monitoring, the cure rates for endocarditis do not appear to be especially promising in dogs, and heart failure is often the long-term result.

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KEYWORDS

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