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Infective Endocarditis

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Author Disclosure
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Objectives After completing this article, readers should be able to:

1. Discuss the epidemiology and pathogenesis of infective endocarditis.
2. Describe the clinical manifestations of infective endocarditis.
3. Define the microbiology of infective endocarditis.
4. Explain issues related to the diagnosis and management of infective endocarditis.

Case Reports

Case 1

A previously healthy 4-year-old boy refuses to walk. He has a 7-day history of fever and fatigue. His temperature is 101.3°F (38.5°C), and his heart rate is 120 beats/min. He has a new systolic heart murmur. His right knee is warm and mildly swollen. He is admitted to the hospital for evaluation and treatment of possible septic arthritis and osteomyelitis. A blood culture is drawn the first day. The orthopedic surgeon drains fluid from the right knee. The next day, he remains febrile, the murmur persists, and gram-positive cocci grow from his blood and joint fluid. A cardiology consultation is requested to rule out endocarditis.

Case 2

A 12-year-old boy who has cyanosis and tetralogy of Fallot and last underwent surgery at the age of 4 years presents to the emergency department with a fever and appearing acutely ill. He has a narrowed conduit from the right ventricle to the pulmonary artery and an unrepaired ventricular septal defect. One week prior to admission, his mother pierced his ear at home. The ear subsequently became inflamed and swollen. After his initial presentation, his condition rapidly deteriorates, and he requires intubation and inotropic support. An echocardiogram demonstrates a mobile mass within the homograft conduit. Multiple blood cultures are obtained before broad-spectrum antibiotics are initiated. Staphylococcus aureus grows from the blood in fewer than 12 hours. Despite blood cultures obtained on subsequent days being sterile, his condition worsens. He is taken to the operating room, and the conduit is replaced. His recovery is uneventful.

Definitions

Endarteritis:	Infection of the lining of blood vessels (eg, in a patient who has postoperative coarctation of the aorta)
Endocarditis:	Inflammation of the valvular or mural endocardium, whether from an infection or from a noninfectious inflammatory process
Infective endocarditis:	Endocarditis caused by microorganisms (bacteria or fungi) involving either the heart or the great vessels (ie, endarteritis); the pathology also may include abscess formation
Mycotic aneurysm:	A term applied to fungal or bacterial infection within the wall of a vessel
Mycotic endocarditis:	Endocarditis caused by fungus

Overview

Few problems in pediatrics cause as much consternation as heart murmurs or positive blood cultures; their nexus raises concern for infective endocarditis (IE). This review provides the pediatrician with an evidence-based and practical framework for the evaluation and management of the febrile child who has a murmur.

Epidemiology

The epidemiology of endocarditis has changed in the modern era. Although it remains a rare diagnosis, the rate of IE may be increasing, and it is a frequent concern among pediatricians. The prevalence of rheumatic heart disease has decreased, and a population of patients who survive beyond infancy with severe congenital cardiac malformations has

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emerged. Importantly, 90% of IE cases occur in individuals who have heart disease, usually congenital. In fact, IE may be the presenting sign of a bicuspid aortic valve. The increased use of invasive procedures in neonatal and pediatric intensive care units, however, has placed individuals whose hearts are structurally normal at risk.

Although most cases of IE are not procedure-related, certain procedures, such as dental extraction, rigid bronchoscopy, and tonsillectomy/adenoidectomy, are believed to increase the risk for IE in susceptible individuals, as do atopic dermatitis, acne, and poor dental hygiene. The American Heart Association considers a number of procedures to be low risk for IE, including restorative dentistry (when bleeding of the gums does not occur), local anesthetic injection in the mouth, tympanostomy tube insertion, endotracheal intubation, gastrointestinal endoscopy, urethral catheterization in uninfected tissue, cardiac catheterization, and circumcision. (A complete list is available at <http://circ.ahajournals.org/cgi/content/full/96/1/358>.)

Pathogenesis

Bacteremia is relatively common; IE is not. IE tends to occur when bacteremia that has a *causative organism* is present in the setting of damaged cardiac or vascular endothelium. Bacteremia occurs in the postoperative setting; in immunocompromised patients; and in non-hospital settings such as after tooth-brushing, tattooing, body piercing, and intravenous street-drug use.

Gram-positive cocci are the most likely pathogens, although gram-negative rods and fungi can cause IE. Gram-positive cocci have a predilection for subendocardial connective tissue, especially fibronectin, that is exposed when endocardium is disrupted. Virulence factors and a unique “cytokine milieu,” however, can cause other bacterial species to adhere to intact endocardium.

Congenital heart disease (postsurgical or unrepaired) is a major risk factor for IE. For individuals undergoing evaluation for IE who do not have previously known heart disease, bicuspid aortic valve is the most common newly discovered cardiac malformation. Jets of blood spurting through a regurgitant mitral valve, a patent ductus arteriosus, or a ventricular septal defect can damage the endothelium and deposit bacteria at the site of injury. For unknown reasons, disrupted endocardium usually occurs at the low-pressure side of the jet (except in aortic stenosis, in which the vegetations occur on the ventricular side of the leaflets).

Foreign materials such as homograft tissue and Gore-Tex[®] also can serve as infectious loci in postoperative patients. Central lines that protrude into the right atrium

or cross the tricuspid valve annulus can damage endocardial tissue.

The current theory of pathogenesis is that exposed fibronectin at the site of injury induces the clotting cascade and fibrin deposition. The blood stream delivers microbes into the clot, where they thrive in a relatively avascular environment. The original nidus of infection grows into a vegetation that encases the bacteria inside an organized, often calcified, mass. Vegetations that occur on valve leaflets can be very destructive, causing valve regurgitation and heart failure. Pieces of bacteria-containing vegetation may embolize to the lungs, brain, kidney, or extremities. Bacteria can infiltrate deeper tissues of the heart or arteries, causing abscesses.

Noncardiac manifestations of IE, originally believed to be due to vegetative emboli, now are recognized as immunologic phenomena. Circulating immune complexes, rheumatoid factor, and other evidence of inflammation persist even after the blood is sterilized, and their disappearance can serve as a marker of successful therapy.

In one prospective study of patients who had congenital heart disease, *Streptococcus viridans* and *S aureus* both were found in 23% of the total of culture-positive IE cases, followed by beta-hemolytic streptococci (9%) and *Staphylococcus epidermidis* (9%). Gram-negative organisms cause IE less commonly, probably due to their inability to bind fibronectin. The gram-negative rods that cause IE are the so-called “HACEK” organisms (*Haemophilus* sp, *Actinobacillus* [*Haemophilus*] *actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* sp, and *Kingella kingae*). Fungi also can cause infective endocarditis. The most common fungus is *Candida*, followed by *Aspergillus*.

Clinical Findings

The diagnosis of IE should be considered in any child who has unexplained fever and is known to have heart disease. IE, outside of the immediate postoperative period, usually presents as an indolent disease, so-called “subacute bacterial endocarditis.” Fulminant IE, as presented in Case 2, has been called acute bacterial endocarditis. These terms are employed less commonly as physicians have sought to describe the specific cause of the infection rather than a general syndrome. Besides fever, common symptoms include myalgia, arthralgia, headache, and generalized malaise. A history of anorexia and weight loss is common. The classic signs, such as Roth spots, Janeway lesions, and Osler nodes, are very rare in children (Table 1). Splinter hemorrhages also are rare and nonspecific. Almost all patients who have IE have a murmur, although it may be an innocent murmur caused

Table 1. Presenting Signs in 73 Children Who Had 76 Episodes of Infective Endocarditis

Sign	Number (%)
Fever	75 (99)
Petechiae	16 (21)
Changing murmur	16 (21)
Dental caries	11 (14)
Hepatosplenomegaly	11 (14)
Congestive heart failure	7 (9)
Splenomegaly	5 (7)
Splinter hemorrhages	4 (5)
Retinal hemorrhages (Roth spots)	4 (5)
Osler nodes	3 (4)
Arthritis	2 (3)

From Martin JM, Neches WH, Wald ER. Infective endocarditis: 35 years of experience at a children's hospital. *Clin Infect Dis.* 1997;24:669–675. Used with permission from the University of Chicago Press.

by turbulent flow through a left ventricular outflow tract during the high-output state associated with a severe systemic illness. (See Table 1 for an estimated frequency of presenting signs.)

Diagnosis

The definitive diagnosis of IE is elusive and often requires input from pediatricians, infectious disease specialists, laboratory microbiologists, and cardiologists. A variety of worrisome factors affects the clinician's attempts to make this diagnosis: heightened concern for missing or not treating a condition that has a potentially fatal outcome, the potential need for weeks or months of intravenous therapy, the uncertainty in diagnosing culture-negative endocarditis, and the high prevalence of innocent murmurs in children during illness.

Duke Criteria

The lack of a consistent, evidence-based method to establish the diagnosis of IE prompted the creation of the Duke Criteria (Tables 2 and 3). This system employs a combination of clinical, microbiologic, and echocardiographic criteria to determine the likelihood of IE similar to the use of the Jones Criteria in the diagnosis of rheumatic fever. The utility of the Duke criteria in diagnosing IE in pediatric patients has been established. Effective blood culturing technique is key to the successful diagnosis of IE using the Duke Criteria (Table 4).

Table 2. Modified Duke Criteria for the Diagnosis of Infective Endocarditis (IE)

Definite IE

- Pathologic evidence of intracardiac or embolized vegetation or intracardiac abscess OR
- Clinical criteria: two major, or one major and three minor, or five minor criteria (see Table 3)

Possible

- One major and one minor or three minor criteria

Rejected

- Firm alternate diagnosis
- "IE syndrome" resolved within 4 days of antibiotic therapy
- No pathologic evidence of IE at surgery or autopsy within 4 days of antibiotic therapy
- Case does not meet "possible IE" criteria

Modified from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke Criteria for the diagnosis of infective endocarditis. *Clin Infect Dis.* 2000;30:633–638. Used with permission from the University of Chicago Press.

Echocardiography

The echocardiographic findings that constitute IE in the Duke scheme are: 1) vegetation on a valve or supporting structure (Figure), 2) abscess, or 3) new partial dehiscence of a prosthetic valve. Because these findings are relatively rare in children, the diagnosis often must be considered in the absence of echocardiographic evidence. Indeed, when the overall suspicion for IE is low, echocardiography is of little value.

Transesophageal echocardiography (TEE) is of proven utility in adults, in whom acoustic penetration often is limited by a thick chest wall or by the air-filled lungs. Such problems are less common in children, in whom TEE should be reserved for those who have poor echo windows, in whom prosthetic valves cause "shadowing," and in whom the transthoracic echocardiography (TTE) view appears normal despite a high index of suspicion for IE.

Culture-negative IE

Retrospective studies suggest that blood cultures may be persistently negative in approximately 5% of cases of IE. In such a situation, numerous blood cultures, prolonged culture periods, studies of surgically isolated vegetations or emboli, and serologic investigations (antibody titers and polymerase chain reaction tests) fail to identify the

Table 3. Modified Duke Criteria: The Clinical Criteria

Major Criteria

- Positive blood culture*
- Positive echocardiogram (vegetation, paravalvular abscess, or valve dehiscence after surgery)
- New valvular regurgitation (by auscultation, not echocardiogram)

Minor Criteria

- Predisposing heart condition (including prior IE)
- Injection drug use
- Fever (temperature $\geq 100.4^{\circ}\text{F}$ [38°C])
- Major arterial emboli
- Septic pulmonary infarcts
- Mycotic aneurysm
- Intracranial hemorrhage
- Conjunctival hemorrhage
- Janeway lesions (painless hemorrhagic lesions on palms and soles)
- Glomerulonephritis
- Osler nodes (painful lesions at fingertips)
- Roth spots (retinal hemorrhages)
- Positive rheumatoid factor
- Single positive blood culture
- Serologic evidence of active infection with an "organism consistent with IE"

Note: Splinter hemorrhages and erythrocyte sedimentation rate are not criteria. Also, there are no "minor" echo criteria, ie, valvular regurgitation alone is not a criterion.

*A positive blood culture is a major criterion when 1) there is growth on two occasions of a microorganism "typical for" IE (eg, *Streptococcus viridans*, *Staphylococcus aureus*, or enterococcus), OR 2) there are "persistently positive" blood cultures (two positive cultures from samples 12 h apart or three positive cultures drawn 1 h apart) of a microorganism "consistent with IE," such as *S epidermidis*, OR 3) *Coxiella burnetii* (Q fever) grows from a single blood culture or there is serologic evidence of *C burnetii* (IgG titer $>1:800$).

From Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke Criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30:633–638. Used with permission from the University of Chicago Press.

offending organism. Potential reasons for false-negative blood cultures are many:

- The causative organism is difficult to culture (fungi, anaerobes, or HACEK organisms)
- An insufficient volume of blood was inoculated into the culture medium

- The patient received antibiotics before blood cultures were drawn
- The lungs "filtered out" bacteria originating from right-sided cardiac lesions
- Sequestration of the organism within a vegetation prevented its access to the blood stream

Table 4. Blood Cultures in Patients in Whom Infective Endocarditis (IE) is Suspected

- Likelihood of culturing the offending organism is related directly to the volume of blood obtained (1 to 3 mL in infants; 5 to 7 mL in older children)
- Not necessary to time blood sampling with fever because bacteremia in IE usually is continuous
- If child not ill, draw three aerobic cultures over the first day and hold antibiotics; if cultures are sterile after 24 hours, draw two cultures and hold for 2 weeks
- If child ill, draw three cultures, with 1 hour separating first and last, before administering antibiotics

Modified from Ferrieri P, Gewitz MH, Gerber MA, et al. Unique features of infective endocarditis in childhood. *Pediatrics*. 2002;109:931–943.

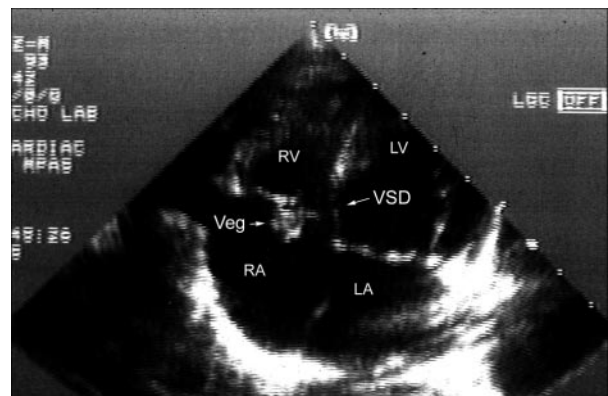


Figure. Two-dimensional cardiac ultrasonography image of a large vegetation (Veg) adhering to the tricuspid valve. This 6-year-old female was known to have a hemodynamically insignificant ventricular septal defect (VSD). She presented with typical signs and symptoms of IE. Her IE was treated uneventfully, and 6 months later she had surgical closure of the VSD. LV=left ventricle, RV=right ventricle, RA=right atrium, LA=left atrium

The diagnosis of culture-negative endocarditis depends on a high degree of suspicion and indirect evidence. Therefore, a patient who has congenital heart disease and suggestive symptoms should be studied aggressively. Cardiac magnetic resonance imaging, radiolabeled white blood cell scans, or other types of nuclear imaging may be helpful.

Management

The Duke Criteria were designed to standardize diagnosis, but they provide little guidance for management. Although antibiotics are recommended for individuals who have “definite” IE, the need for treating “possible” or even “rejected” IE is not excluded in that scheme. The diagnosis and treatment of IE must be determined case by case. Management depends on assessing the reliability of the blood cultures, searching for underlying heart disease, and occasionally on determining, rather arbitrarily by consensus, the presence or absence of IE.

Antibiotics

If the patient who presumably has IE is ill and the pediatrician feels that antibiotics should be started before blood culture results are available, empiric treatment should be directed at the most common offenders: streptococci and staphylococci. A standard regimen is penicillin or ampicillin (or vancomycin, if allergic to penicillin) plus gentamicin. If an organism is isolated from the blood, susceptibilities should be determined. Emerging resistance patterns or elusive bacteria often complicate antibiotic choice, and help from infectious disease specialists is needed, especially for enterococcal infections. Therapy must be intravenous to attain persistently high bactericidal concentrations in relatively avascular valve leaflets and to penetrate infected thrombi. The usual course of therapy is 4 to 6 weeks, but infection of prosthetic valves and tissue may require longer treatment. New, as yet unvalidated, therapies include cyclosporine, linezolid, and teicoplanin (similar to vancomycin). There are intriguing reports of the successful use of recombinant tissue plasminogen activator to lyse intracardiac vegetations in severely ill infants. The investigators offered the hope of avoiding surgery in persistently symptomatic neonates.

Surgery

Indications for surgery during the acute phase of IE are continued bacteremia after 2 weeks of appropriate therapy, fungal vegetations, abscess formation, worsening heart failure (due to valvular regurgitation caused by

ruptured leaflets or chordae), or systemic emboli. Patients eventually may require surgical intervention for chronic valvular stenosis or regurgitation caused by previous IE. IE related to a hemodynamically trivial ventricular septal defect warrants surgical repair following successful treatment of the infection (Figure).

Discussion of Case Reports

In Case 1, a boy has a new murmur and bacteremia. In this setting, the Duke Criteria help assess the likelihood of IE. The murmur represents a major criterion if it signifies valve disease. It may, however, be an innocent flow murmur brought about by a fever-caused hyperdynamic state. Fever and a single positive blood culture both are minor criteria. These findings, however, may be sufficient to establish the diagnosis of “possible” IE by the Duke criteria if the murmur is, in fact, significant. Consultation with a pediatric cardiologist is warranted to help determine if the murmur represents structural heart disease. TTE should be obtained if findings on the physical examination suggest valvular disease. Continued antibiotic therapy for the septic joint and possible osteomyelitis is warranted. If the murmur is found to be innocent, the pediatrician, cardiologist, and infectious disease specialist need to reassess the patient if the fever persists or if any other signs or symptoms of IE develop.

In Case 2, the presentation of a patient who has congenital heart disease, has a fever, and appears ill suggests fulminant IE, which is in contrast to the usual indolent presentation. Patients at high risk for IE include those who have tetralogy of Fallot or other complex cyanotic congenital heart diseases, prosthetic cardiac valves (including bioprosthetic and homograft valves), and flow jets through narrowed areas. Unsterile body piercing is dangerous for anyone; in the setting of congenital heart disease, however, it is potentially lethal. Ear piercing, often performed with suspect sterile technique in shopping malls, should be avoided in at-risk individuals. In this case, TTE quickly demonstrated the vegetation, verifying the diagnosis under the Duke Criteria, and appropriate treatment was initiated. The decision to proceed to surgery is always difficult and usually requires considerable effort by the nonsurgical caregivers to convince the surgeons to take an acutely ill and obviously infected patient to the operating room. In this child, continued deterioration despite appropriate medical therapy warranted a surgical approach. Evidence is substantial that in specific circumstances, surgical intervention in acute IE can be lifesaving.

Prophylaxis

The rationale behind antibiotic prophylaxis for IE is that certain medical or dental procedures can cause bacteremia and lead to endocarditis in patients who have heart disease and that antibiotics administered at the time of the procedure can prevent the disease. The guidelines published by the American Heart Association (AHA) for prophylaxis serve as the basis for treatment decisions by caregivers. It should be recognized, however, that direct evidence to support these recommendations is limited. According to the AHA, procedures that are likely to produce bacteremia involving IE-causing pathogens in susceptible patients should be targeted for antibiotic prophylaxis. Surgery that involves any mucosal surface or infected tissue is considered a risk. An important exception is heart surgery itself, in which antibiotic prophylaxis typically is given. The antibiotic regimen for prophylaxis depends on the procedure. Incision of oral, respiratory, or esophageal mucosa requires an antibiotic that is effective against *viridans* streptococci, making amoxicillin the first choice. Incision of intestinal or genitourinary mucosa requires a regimen effective against enterococcus; thus, intravenous ampicillin and gentamicin are used. The AHA's specific recommendations have been published by Dajani and associates (see Suggested Reading).

Prognosis

The course of IE can be complicated by embolization to virtually any organ, depending on whether the disease involves the right or left side of the heart. Other problems include abscess formation, heart failure, heart block, and mycotic aneurysms. In one relatively recent study of pediatric IE, 13 of 73 patients died. Complications included valvular insufficiency (18%), surgical interventions (15%), pulmonary embolus (10%), arrhythmia (8%), stroke (8%), congestive heart failure (7%), seizures

(4%), renal abscess (3%), and osteomyelitis (1%). Patients who have the highest risk for complications include those who have prosthetic valves, left-sided IE, *S aureus* or fungal IE, prior episodes of IE, duration of symptoms greater than 3 months, cyanotic heart disease, systemic artery-to-pulmonary artery shunts, and poor clinical response to antibiotics.

Conclusion

IE is an often considered, yet rare, diagnosis in children. The Duke criteria help guide the diagnosis and initial evaluation, but a high index of suspicion in persistently febrile patients is necessary. Pediatric cardiologists, infectious disease specialists, and cardiothoracic surgeons can aid in management.

Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

1. A 1-year-old male who has unrepaired tetralogy of Fallot comes to your clinic for a health supervision visit. His mother has heard that he should take antibiotics if he ever has to have surgery. According to the American Heart Association, which of the following procedures is considered to increase his risk of infective endocarditis the *most*?
 - A. Circumcision.
 - B. Endoscopy.
 - C. Routine dental cleaning.
 - D. Tonsillectomy and adenoidectomy.
 - E. Tympanostomy tube placement.
2. Which of the following organisms *most* commonly causes infective endocarditis in children?
 - A. *Aspergillus* sp.
 - B. *Haemophilus influenzae*.
 - C. *Staphylococcus epidermidis*.
 - D. *Streptococcus pneumoniae*.
 - E. *Streptococcus viridans*.
3. Which of the following presenting signs is associated *most* frequently with infective endocarditis in children?
 - A. Dental caries.
 - B. Fever.
 - C. Hepatosplenomegaly.
 - D. Janeway lesions.
 - E. Retinal hemorrhages.
4. A 2-year-old boy is brought to the emergency department because of several days of fever and malaise. He appears ill and has a heart rate of 130 beats/min and normal blood pressure. Physical examination findings are unremarkable except for a III/VI systolic murmur and mild splenomegaly. His mother denies the presence of a murmur at previous examinations. You suspect infective endocarditis. Which of the following diagnostic methods should you order at this time to confirm your diagnosis?
 - A. A single 5-mL blood culture drawn at the time of fever.
 - B. Cardiac magnetic resonance imaging.
 - C. Polymerase chain reaction testing for *Streptococcus viridans*.
 - D. Three 5-mL blood cultures drawn 1 hour apart.
 - E. Transesophageal echocardiography.

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