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# Unique Features of Infective Endocarditis in Childhood

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ABBREVIATIONS. IE, infective endocarditis; CHD, congenital heart disease; 2D, 2-dimensional; IV, intravenous; NBTE, nonbacterial thrombotic endocarditis; MIC, minimum inhibitory concentration; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; 5-FC, 5-fluorocytosine.

## INTRODUCTION

Infective endocarditis (IE) is associated with substantial morbidity and mortality. Although it is relatively rare in children, its incidence may be increasing.<sup>1</sup> This paper focuses on the features that are particularly relevant to infants and children, including important issues for the primary care physician. The epidemiology of heart disease in children has changed over the past 3 to 4 decades. With the increased survival rate of children with congenital heart disease (CHD) and the overall decrease in rheumatic valvular heart disease in developed countries, CHD now constitutes the predominant underlying condition for IE in children over the age of 2 years in these countries. The complexities of management of neonatal and pediatric intensive care unit patients have increased the risks of catheter-related IE. In addition, postoperative IE is a long-term risk following correction of complex CHD. The proper use of the diagnostic microbiology laboratory is critical in the diagnosis and management of children with IE. Moreover, newer diagnostic guidelines have improved sensitivity for making the diagnosis of clinically definite IE. In addition, advances in non-invasive techniques such as two-dimensional (2D) echocardiography have enhanced our ability to diagnose IE. Newer antibiotics have become available that can be used in children with IE, and home intravenous (IV) therapy has become an acceptable approach for stable patients who are at low risk for embolization. Additionally, approaches to the prevention of endocarditis have been recently modified and are reviewed in this paper.

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## EPIDEMIOLOGY AND CLINICAL FINDINGS OF INFECTIVE ENDOCARDITIS IN CHILDREN

IE occurs less commonly in children than in adults and accounts for approximately 1 in 1280 pediatric admissions per year.<sup>2</sup> Although the reported hospitalization rates for IE vary considerably among published series, the frequency of endocarditis among children appears to have increased in recent years.<sup>3</sup> This is due in part to improved survival among children who are at risk for endocarditis, such as those with CHD and hospitalized newborn infants.

Before the 1970s, 30% to 50% of US children with IE had underlying rheumatic heart disease.<sup>3</sup> As the prevalence of rheumatic heart disease has declined in developed countries, it is now uncommon for patients with IE to have underlying rheumatic heart disease. At the same time, there has been an increase in cases of IE associated with CHD in children. Congenital heart defects such as ventricular septal defect, patent ductus arteriosus, aortic valve abnormalities, and tetralogy of Fallot are common underlying conditions. An increasing proportion of children with IE have had previous corrective or palliative surgery for CHD with or without implanted vascular grafts, patches, or prosthetic cardiac valves.<sup>1,3-6</sup>

IE in the absence of CHD is often associated with central indwelling venous catheters. In approximately 8% to 10% of pediatric cases,<sup>7</sup> IE develops without structural heart disease or other identifiable risk factors and usually involves infection of the aortic or mitral valve secondary to *Staphylococcus aureus* bacteremia.<sup>1,3,4</sup> Children with congenital or acquired immunodeficiencies but without identifiable risk factors for IE do not appear to be at increased risk for endocarditis compared with the general population. Factors commonly associated with IE in adults, such as IV drug abuse and degenerative heart disease, are not common predisposing factors in children.<sup>1,3-5</sup>

## ENDOCARDITIS IN CHILDREN WITH PREVIOUS CARDIAC SURGERY

Corrective surgery with no residual defect eliminates the attributable risk for endocarditis in children with ventricular and atrial septal defects or patent ductus arteriosus 6 months after surgery. Surgery itself may be an important risk factor for the development of IE. Approximately 50% of children with IE complicating CHD have had previous cardiac surgery, particularly palliative shunt procedures or

complex intracardiac repairs.<sup>4</sup> Morris et al<sup>6</sup> reviewed cumulative incidences of endocarditis for a number of congenital cardiac lesions. The highest annualized risk for IE was found in children who had repair or palliation of cyanotic CHD. The risk was highest among those patients who had undergone surgery for obstruction to pulmonary blood flow and those who had undergone prosthetic aortic valve replacement. The incidence of IE in the first postoperative month is low for most defects and increases with time after surgery. However, when prosthetic valves or conduits are used in surgical repairs and hemodynamic problems persist, the risk for IE is high even in the immediate (first 2 weeks) postoperative period.<sup>8</sup>

#### INFECTIVE ENDOCARDITIS IN NEWBORN INFANTS

When IE develops in newborn infants, it is associated with a very high mortality rate; the diagnosis is often made at postmortem examination.<sup>9–11</sup> However, with rapidly improving imaging technology and increasing clinical experience, the antemortem diagnosis of neonatal IE is being made with much greater facility than in the past, and the incidence of neonatal endocarditis may be increasing.<sup>9</sup> Most experts believe that the incidence has increased primarily because of the increasing use of invasive techniques to manage neonates with multiple complex medical problems.

#### PATHOGENESIS

Intact cardiac endothelium is a poor stimulator of blood coagulation and is weakly receptive to bacterial attachment. Damaged or denuded endothelium is a potent inducer of thrombogenesis and provides a nidus to which bacteria can adhere and eventually form an infected vegetation. In children with heart disease, the shear force associated with an abnormal high-velocity jet stream of blood can damage the endothelium. Thrombogenesis at such a site results in the deposition of sterile clumps of platelets, fibrin, and, occasionally, red blood cells, and the formation of nonbacterial thrombotic endocarditis (NBTE). NBTE can also be produced in children with indwelling IV catheters positioned in the right side of the heart. Such catheters may traumatize the endocardium or valvular endothelium, exposing the subendothelial collagen.<sup>1,12</sup> In animal models of IE, endocardial lesions can be produced by the insertion and removal of polyethylene catheters into the right atrium or across the tricuspid or aortic valves. If these animals are then inoculated intravenously with certain micro-organisms, IE develops as the NBTE lesions become colonized.<sup>13,14</sup> The pathogenesis of IE in children with indwelling IV catheters may be very similar to the animal models.

Bacteremia, even in the presence of NBTE, does not invariably produce IE, because bacteria must be able to survive in the bloodstream in sufficient numbers to adhere to the endocardium and propagate. After the bacteria adhere to the NBTE lesion, platelets and fibrin are deposited over the organisms,

leading to the enlargement of the vegetation. The organisms trapped within the vegetation are protected from phagocytic cells and other host defense mechanisms. They proliferate, reaching concentrations as high as  $10^7$  to  $10^{10}$  colonies forming units per gram of tissue. Once maximum bacterial density has been reached, most bacteria deep within the vegetation become metabolically inactive.<sup>15,16</sup>

In general, congenital cardiac lesions that involve high-velocity jets of blood flow and/or foreign material are associated with the highest risk for development of IE. Thus, in a recent series,<sup>4</sup> patients with complex cardiac anatomy who have undergone palliative shunt and conduit procedures were found to be the largest group at risk. Any lesion associated with turbulence of flow, with or without shunting, can be a substrate for IE. Aortic valve disease was a common lesion in a series of children who developed IE and had no history of surgery.<sup>17</sup> Additionally, the Second Natural History Study of Congenital Heart Disease<sup>18</sup> found that the risk of IE in children with ventricular septal defect was substantially increased by the presence of associated aortic regurgitation. Conversely, in secundum atrial septal defect, in which shunting is not associated with high-velocity jet flow, and in mild pulmonic stenosis, endocarditis is not likely to occur.<sup>19</sup>

Neonatal endocarditis frequently occurs on the right side of the heart and is associated with disruption of endocardium or valvular endothelial tissue produced by catheter-induced trauma. Neonates often experience transient episodes of bacteremia from trauma to the skin and mucous membranes, vigorous endotracheal suctioning, parenteral hyperalimentation, or placement of umbilical or peripheral venous catheters. The combination of endothelial damage and bacteremia is a critical one for the induction of IE.

Impressive gains in our understanding of endocarditis pathogenesis have occurred during the 1990s, largely due to the availability of newer molecular biological techniques. These techniques have allowed us to examine individual purported virulence factors of gram-positive cocci and to investigate important host-cell interactions with the micro-organisms. Several surface structures of staphylococci, streptococci, and enterococci have been identified as markers of virulence.<sup>20</sup>

In some cases, these factors have been purified and then used as immunogens in endocarditis experiments in animals and shown to induce protective antibody responses.<sup>21</sup> Considerable data support the notion that the interactions of gram-positive cocci with platelets and the organism's capacity to resist the antimicrobial host defense properties of platelets are pivotal in the production and persistence of endocardial infections.<sup>22</sup> Because of the advances in understanding of the pathogenesis of endocarditis, it is expected that novel interventional tools, including drugs, biological agents, and vaccines, may become useful in the future in the treatment and prevention of IE.

**TABLE 1.** Definitions of Terms Used in the Duke Criteria for the Diagnosis of IE

## Major criteria

- (1) Positive blood culture for IE
  - A. Typical micro-organism consistent with IE from 2 separate blood cultures as noted below:
    - (i) Viridans streptococci,\* *Streptococcus bovis*, or HACEK group *or*
    - (ii) Community-acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus *or*
  - B. Micro-organisms consistent with IE from persistently positive blood cultures defined as
    - (i)  $\geq 2$  Positive cultures of blood samples drawn  $>12$  h apart *or*
    - (ii) All of 3 or a majority of  $\geq 4$  separate cultures of blood (with first and last sample drawn  $\geq 1$  h apart)
- (2) Evidence of endocardial involvement
  - A. Positive echocardiogram for IE defined as
    - (i) Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, *or*
    - (ii) Abscess, *or*
    - (iii) New partial dehiscence of prosthetic valve *or*
  - B. New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

## Minor criteria

- (1) Predisposition: predisposing heart condition or IV drug use
- (2) Fever: temperature  $\geq 38.0^{\circ}\text{C}$
- (3) Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
- (4) Immunologic phenomena: glomerulonephritis, Osler nodes, Roth's spots, and rheumatoid factor
- (5) Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE
- (6) Echocardiographic findings: consistent with IE but do not meet a major criterion as noted above

HACEK indicates *Haemophilus* species, *Actinobacillus* (*Haemophilis*) *actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* species, and *Kingella kingae*; IE, infective endocarditis; IV, intravenous.

\* Includes nutritionally variant strains (*Abiotrophia* species).

Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis. From Durack et al.<sup>23</sup>

**DIAGNOSIS****Duke Criteria**

Recently proposed criteria (the Duke Criteria) to assist in the diagnosis of IE have been shown to be superior to previous criteria in adult populations<sup>23</sup> and are outlined in Tables 1 and 2. A small study from South America<sup>24</sup> and a larger US study<sup>7</sup> have recently verified that the Duke criteria are superior to previous criteria for the diagnosis of IE in children as well. The Duke criteria are weighted to favor *S. aureus* bacteremia as a major criterion of IE only if the infection is community-acquired in the absence of a primary focus. The Duke group has now recommended, on the basis of recent studies that used TEE to assess the presence of early endocarditis, that *S. aureus* bacteremia be a major criterion, regardless of whether the infection is nosocomially or community-acquired or whether a primary source of infection is present or absent.<sup>25</sup>

**CLINICAL FINDINGS IN CHILDREN**

The presentation generally is indolent, with prolonged low-grade fever and a variety of somatic complaints, including fatigue, weakness, arthralgias, myalgias, weight loss, rigors, and diaphoresis. Although these are nonspecific findings, the presence

of this cluster of symptom requires careful evaluation for IE in certain settings, such as in the patient with underlying heart disease.

As in adults, the clinical findings of IE in children relate to 4 underlying phenomena: bacteremia (or fungemia), valvulitis, immunologic responses, and emboli. Valvulitis may result in changing cardiac auscultatory findings or the development of congestive heart failure. Extracardiac manifestations of IE (eg, petechiae, hemorrhages, Roth's spots, Janeway lesions, Osler nodes, or splenomegaly) are considerably less common in children than in adults. Renal abnormalities (eg, glomerulonephritis, infarct) can result from an embolic or immune complex-mediated process. Emboli to the abdominal viscera, the brain, or the heart may produce symptoms associated with ischemia, hemorrhage, or both. Uncommonly, central nervous system mycotic aneurysms can occur; their rupture can be catastrophic.

On occasion, the presentation may be fulminant, with rapidly changing symptoms and high, spiking fevers. These children are acutely ill, and some require urgent intervention.

The cardiac examination in the child with IE is highly variable and depends on the type of heart disease present and the particular site of infection.

**TABLE 2.** Duke Clinical Criteria for Diagnosis of IE

Definite IE	
• Pathological criteria	—Micro-organisms: demonstrated by culture or histology in a vegetation, a vegetation that has embolized, or an intracardiac abscess, <i>or</i>
	—Pathological lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis
• Clinical criteria as defined in Table 1	2 major criteria, <i>or</i>
	1 major criterion and 3 minor criteria, <i>or</i>
	5 minor criteria
Possible IE	
	Findings consistent with IE that fall short of “definite” but not “rejected”
Rejected	
• Firm alternative diagnosis for manifestations of endocarditis, <i>or</i>	
• Resolution of manifestations of endocarditis with antibiotic therapy for $\leq 4$ d <i>or</i>	
• No pathological evidence of IE at surgery or autopsy, after antibiotic therapy for $\leq 4$ d	

IE indicates infective endocarditis.

From Durack et al.<sup>23</sup>

Valvular lesions that produce leaflet destruction result in regurgitant murmurs. In children with cyanotic CHD who have undergone systemic-pulmonary artery shunt procedures, however, the murmur may not change. Rather, declining systemic oxygen saturation may reflect graft infection with obstruction of flow. Patients with right-sided, catheter-related, intravascular infection may have few or no specific cardiovascular signs or may present with primarily pulmonary symptoms or signs related to septic pulmonary embolization.

### Clinical Findings in Newborn Infants

The clinical manifestations of IE in a neonate are variable and nonspecific and may be indistinguishable from septicemia or congestive heart failure from other causes.<sup>9–11</sup> Septic embolic phenomena are common, resulting in foci of infection outside the heart (eg, osteomyelitis, meningitis, pneumonia). Neonates with IE often have feeding difficulties, respiratory distress, and tachycardia. They may also have a new

or changing heart murmur and hypotension. Many neonates with IE also have neurologic signs and symptoms (seizures, hemiparesis, apnea). Although arthritis and arthralgia are common findings in older children with IE, arthritis is described infrequently in neonates. Osler nodes, Roth’s spots, Janeway lesions, and splinter hemorrhages have not been described in neonates.

## LABORATORY ASSESSMENT

### Microbiology

#### Blood Cultures

Blood cultures are indicated for all patients with fever of unexplained origin and a pathologic heart murmur, a history of heart disease, or previous endocarditis. Since bacteremia in patients with IE is usually continuous, it is not necessary to obtain the cultures at any particular phase of the fever cycle. It is important to obtain adequate volumes of blood from children, but it is ordinarily not possible to obtain the large volumes recommended for adults with suspected endocarditis. Lesser amounts, eg, 1 to 3 mL in infants and young children and 5 to 7 mL in older children, are optimal, depending on the blood culture detection system. Because it is rare for IE to be due to anaerobic bacteria, the emphasis is usually on inoculating blood into bottles designed for aerobic incubation. Usually 3 blood cultures are obtained by separate venipunctures on the first day, and if there is no growth by the second day of incubation, 2 more may be obtained (Table 1). There is usually no value in obtaining  $>5$  blood cultures over 2 days unless the patient received prior antibiotic therapy. In patients who are not acutely ill and whose blood cultures are still negative, antibiotics may be withheld for 48 hours or longer while additional blood cultures are obtained. Because therapy should not be delayed in patients with acute IE, 3 separate venipunctures for blood cultures can be performed over a short period (Table 1) and empiric antibiotic therapy started. Test request forms for the blood cultures should indicate that IE is suspected to ensure that the laboratory will incubate the cultures for at least 2 weeks. If fastidious or unusual organisms are suspected, the microbiology laboratory should be consulted.

#### Etiologic Agents Isolated From Blood Cultures

Most organisms that cause IE in children are gram-positive cocci (Table 3), including viridans group

**TABLE 3.** Principal Etiologic Bacterial Agents

Organism	Series		
	Johnson et al <sup>28</sup> N = 149	Martin et al <sup>5</sup> N = 76	Stockheim et al <sup>7</sup> N = 111
Viridans group streptococci	43%	38%	32%
<i>Staphylococcus aureus</i>	33%	32%	27%
Coagulase-negative staphylococci	2%	4%	12%
<i>Streptococcus pneumoniae</i>	3%	4%	7%
HACEK	n/a	5%	4%
<i>Enterococcus</i> species	n/a	7%	4%
Culture-negative	6%	7%	5%

( $\alpha$ -hemolytic) streptococci (eg, *Streptococcus sanguis*, *S. mitis* group, *S. mutans*, etc.), staphylococci, and enterococci. Enterococcal endocarditis occurs much less frequently in children than in adults.

Less commonly, other organisms such as the HACEK group (*Haemophilus parainfluenzae*, *H. aphrophilus*, *H. paraphrophilus*, *Actinobacillus* [*Haemophilus*] *actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* species, and *Kingella kingae*) are implicated. *A. actinomycetemcomitans* is an oral micro-organism that has been implicated in the etiology of localized juvenile periodontitis and occasionally may cause IE.<sup>26,27</sup>

Beyond the first year of life, the viridans group streptococci are the most commonly isolated organisms from patients with IE. *S. aureus* is the second most common cause of IE in children, but the most common cause of acute bacterial endocarditis. IE may be caused by viridans group streptococci that are dependent on L-cysteine or pyridoxal for growth, so-called "nutritionally variant streptococci" (*Abiotrophia* species). The laboratory must subculture positive blood culture bottles on special media to isolate these organisms. Viridans group streptococci, *Abiotrophia* species, or enterococci are associated with native valve endocarditis and endocarditis occurring >60 days after cardiac surgery. IE produced by these organisms is usually subacute in presentation.

IE associated with indwelling vascular catheters, prosthetic material, and prosthetic valves is frequently caused by *S. aureus* or coagulase-negative staphylococci. These infections are commonly implanted at the time of surgery and seen <60 days after cardiac surgery, but coagulase-negative staphylococci may be present as late as 1 year after surgery. Among newborn infants, *S. aureus*, coagulase-negative staphylococci, and *Candida* species are the most common causes of IE.<sup>7,9</sup> Less commonly, bacteria including the group B *Streptococcus* and *S. pneumoniae*, may also cause IE in this population. Although catheter-related bacteremias due to gram-negative bacilli occur in pediatric patients in intensive care units, IE is rarely caused by these organisms. The rarity of IE due to gram-negative bacilli to cardiac valves. Pediatric patients who inject drugs intravenously are at risk for IE, especially that due to *S. aureus*.

Fungal endocarditis is usually caused by *Candida* species, although *Aspergillus* species has been reported to cause endocarditis. In the past 2½ decades, with the introduction of central venous catheters in infants and children and the associated use of high glucose concentrations and hyperalimentation, *Candida* infections of the mural or valvular endocardium in infants have been widely recognized. Fungal endocarditis is also often associated with very large friable vegetations; emboli from these vegetations frequently produce serious complications.

#### Culture-Negative Endocarditis

A diagnosis of culture-negative endocarditis is made when a patient has clinical and/or echocardiographic evidence of IE but persistently negative blood cultures. The most common cause of culture-

negative IE is current or recent antibiotic therapy or infection due to a fastidious organism that grows poorly in vitro. At times, the diagnosis can be made only by removal of vegetations during surgery or at necropsy or by growth of organisms from an excised thrombus or embolus. In most centers in the US, the prevalence of culture-negative endocarditis may be approximately 5% to 7%, imposing a need to be thorough and precise in accepting a diagnosis of culture-negative endocarditis.<sup>5,7,28</sup> In patients with filamentous fungal IE, routine blood cultures are usually negative. Other relatively rare causes of IE with negative routine blood cultures include *Coxiella burnetii* (Q fever), *Brucella*, *Legionella*, *Bartonella* (*Rochalimaea*), and *Chlamydia*.<sup>29</sup> It is important to consult with the microbiology laboratory in all cases of culture-negative endocarditis to optimize the chance of identification of the causative micro-organism.

#### Other Microbiologic Tests

Testing for antibiotic susceptibility with determination of the minimum inhibitory concentration (MIC) of the antibiotic for the organism is critical in choosing the correct therapy for IE. Although not routinely recommended, the minimum bactericidal concentration of the antibiotic chosen for treatment may be helpful in selected circumstances, with infectious disease consultation.

#### Miscellaneous Laboratory Tests

A variety of other nonspecific laboratory findings may support the diagnosis of IE in children. The anemia of IE may be hemolytic or may represent the anemia of chronic disease. It should be noted that chronic low-grade hemolysis may also be due to a prosthetic valve in the absence of IE. Leukocytosis is not a consistent feature of IE, but immature forms may be present on peripheral blood smears. Hypergammaglobulinemia and elevated acute-phase reactants (eg, ESR and CRP) are present in a large proportion of patients. Hematuria may occur and may be accompanied by red blood cell casts, proteinuria, and renal insufficiency in patients who develop immune complex glomerulonephritis.

#### Echocardiography

Two-dimensional echocardiography has become the main modality for detecting endocardial infection. In fact, certain echocardiographic findings are included as major criteria<sup>23</sup> in the recent Duke criteria (Tables 1 and 2). Echocardiography can determine the site of infection and extent of valvular damage, and cardiac function can also be serially monitored. Baseline evaluation of ventricular performance and cardiac chamber dimension is important for comparison later in the course of the infection. Associated problems, such as pericardial effusion or myocardial abscess formation, can also be diagnosed. Color Doppler is a sensitive modality for detection of valvular insufficiency. The severity of valvular flow disturbances can be roughly estimated and may influence surgical and medical treatment decisions.

Typical echo-Doppler findings include vegetations, abscesses, new valvular insufficiency, and

other acute changes in intracardiac flow patterns. The hallmark echocardiographic finding—the vegetation—may not always be visible with transthoracic echocardiography (TTE), although it has long been recognized that echocardiography may visualize even small vegetations.<sup>30</sup> Conversely, some patients will remain “culture negative” but still manifest a vegetation on echocardiography. With a reported sensitivity of 81%,<sup>31</sup> TTE is more sensitive in the pediatric population than in the adult population for detection of vegetation. Of note, TTE is more likely to identify vegetations in children with normal anatomy or isolated valvular pathology than in those with complex cyanotic CHD, due to interference in the latter group by artificial grafts, conduits, and valves.<sup>4,32</sup> Although standard TTE is sufficient in most clinical circumstances, especially in younger infants or children, it may not be adequate when imaging is inhibited by poor ultrasound penetration. This can occur in the obese or very muscular adolescent, in post-cardiac surgery patients, or in the presence of compromised respiratory function or pulmonary hyperinflation. In these circumstances, transesophageal echocardiography (TEE) may be an important adjunct to TTE.

Data in adults have indicated superiority of TEE over TTE in identifying vegetations on both native and prosthetic valves.<sup>33,34</sup> Similar studies in children have not been published. TEE is useful for detecting complications of left ventricular outflow tract endocarditis, either valvular or subvalvular, and, in particular, development of aortic root abscess and involvement of sinus of Valsalva.<sup>35,36</sup> Because these lesions can be associated with dire consequences, TEE should be considered for all patients with aortic valvular endocarditis and changing aortic root dimensions as seen on a standard TTE study. TEE adds greatly to the diagnosis of paravalvular leakage and valve dehiscence due to prosthetic valve infection.

The prognostic significance of echocardiographic identification of vegetations is controversial. Certain echocardiographic features appear to be associated with complications (Table 4). These include large vegetation size (>1 cm), size that increases during therapy, and marked changes in Doppler evidence of worsening valvular or ventricular function.<sup>37</sup>

The limitations of echocardiography, including TEE, should be emphasized. The absence of vegetations on echocardiography does not in itself rule out IE. Conversely, an echogenic mass can represent a sterile thrombus, sterile prosthetic material, or normal anatomic variation rather than an infected vegetation.<sup>38</sup>

#### ANTIMICROBIAL TREATMENT

In general, the principles of treatment of pediatric endocarditis are similar to those for treatment of adult endocarditis.<sup>39</sup> In patients who are not acutely ill and whose blood cultures are still negative, antibiotics may be withheld for 48 hours or longer while additional blood cultures are obtained. A prolonged course of therapy (at least 2 weeks and often 4–8 weeks) is necessary for several reasons. Organisms are embedded within the fibrin-platelet matrix and

**TABLE 4.** Echocardiographic Features Suggesting Potential Need for Surgical Intervention‡

Vegetation
<ul style="list-style-type: none"> <li>• Persistent vegetation after systemic embolization:               <ul style="list-style-type: none"> <li>—Anterior mitral leaflet vegetation, particularly with size &gt;10 mm§</li> <li>—≥1 Embolic event during first 2 weeks of antimicrobial therapy§</li> <li>—≥2 Embolic events during or after antimicrobial therapy§</li> </ul> </li> <li>• Increase in vegetation size after 4 weeks of antimicrobial therapy*†</li> </ul>
Valvular dysfunction
<ul style="list-style-type: none"> <li>• Acute aortic or mitral insufficiency with signs of ventricular failure†</li> <li>• Heart failure unresponsive to medical therapy†</li> <li>• Valve perforation or rupture†</li> </ul>
Perivalvular extension
<ul style="list-style-type: none"> <li>• Valvular dehiscence, rupture, or fistula†</li> <li>• New heart block†</li> <li>• Large abscess or extension of abscess despite appropriate antimicrobial therapy†</li> </ul>

\* Surgery may be required because of risk of embolization.

† Surgery may be required because of heart failure or failure of medical therapy.

‡ See text for more complete discussion of indications for surgery based on vegetation characterizations.

§ Surgery may be required because of risk of recurrent embolization.

From Bayer et al.<sup>29</sup>

exist in very high concentrations with relatively low rates of bacterial metabolism and cell division, which results in decreased susceptibility to  $\beta$ -lactam and other cell wall-active antibiotics.<sup>15,16</sup>

Bactericidal, rather than bacteriostatic, antibiotics should be chosen whenever possible to decrease the possibility of treatment failures or relapses. In infants and children, IV antibiotics are preferred over intramuscular agents because of the patients' small muscle mass. Outpatient (home) treatment of endocarditis can be considered in selected patients after initial treatment in the hospital and confirmation that these patients are hemodynamically stable and afebrile, have negative blood cultures, and are not at high risk for complications. Additionally, patient and parent adherence to the medical plan is important. Frequent home monitoring by a home health nurse who assesses progress, adherence to drug therapy, absence of complications (see below), and evidence of drug toxicity is essential. The patient should also have prompt access to medical and surgical care and cardiac follow-up.

Bacteremia generally resolves within several days after appropriate therapy has begun; *S. aureus* bacteremia may persist for 3 to 5 days with  $\beta$ -lactam antistaphylococcal therapy and for 5 to 10 days with vancomycin therapy. Blood cultures should be repeated to assess the adequacy of treatment and to document the cessation of bacteremia. Additional blood cultures should be performed once or twice in the 8 weeks after completion of antibiotic treatment to ensure cure.<sup>40</sup>

Recommendations for antibiotic treatment of gram-positive IE in the adult population have been made by the American Heart Association.<sup>39</sup> Tables 5, 6, and 7 are modeled after these guidelines, with dosages adjusted for children.

**STREPTOCOCCAL IE ON NATIVE CARDIAC VALVES (NO PROSTHETIC MATERIAL) OR PROSTHETIC MATERIAL**

*Native Cardiac Valves*

Penicillin-susceptible streptococci are those with an MIC of  $\leq 0.1 \mu\text{g}$  of penicillin per mL. In patients with IE caused by penicillin-susceptible streptococci, and who are able to tolerate a  $\beta$ -lactam, 2 therapeutic regimens are associated with high cure rates (Table 5).

A 4-week regimen of IV aqueous crystalline penicillin G (or ampicillin if penicillin G is unavailable) achieves a high cure rate.<sup>41</sup> This approach is preferred for children with impairment of renal function or the eighth cranial nerve. In adult patients, 4 weeks of therapy with ceftriaxone given once daily is also recommended.<sup>29</sup> In adults, ceftriaxone therapy has a bacteriologic cure rate of 98%,<sup>42</sup> but there are no published data on the use of ceftriaxone in the treatment of IE in children. Although experience in children is limited, ceftriaxone may prove to be equally useful in pediatric IE.

A 2-week course of therapy with penicillin, ampicillin, or ceftriaxone combined with gentamicin has become increasingly popular and results in bacteriologic cure rates of up to 98% in adults.<sup>43</sup> This regimen is recommended for uncomplicated cases of native valve IE but not for patients who have had clinical symptoms of endocarditis for  $>3$  months or those who have an extracardiac focus of infection, an intracardiac abscess, or a mycotic aneurysm. It is also inappropriate for children at risk for adverse events caused by gentamicin therapy. In 1 study in adults,<sup>44</sup> single daily doses of gentamicin (3 mg/kg per day) combined with ceftriaxone (2 g/d for adults) for 2

weeks were as effective as 4 weeks of ceftriaxone alone. Although once-daily dosing of gentamicin has become an accepted practice for adult patients with infections other than endocarditis, there are few published studies about the use of this regimen for the treatment of streptococcal endocarditis in adults. Several studies have demonstrated the safety and efficacy of once-daily dosing of gentamicin in children with infections other than endocarditis. There is less clinical experience with this regimen in children than in adults. Additionally, there are no published studies about the use of single daily dosing of gentamicin for the treatment of infective endocarditis in children.

Occasionally, the infection may be due to streptococci that are relatively resistant to penicillin (MIC between  $>0.1 \mu\text{g/mL}$  and  $0.5 \mu\text{g/mL}$ ). In this situation, the recommended treatment is 4 weeks of penicillin, ampicillin, or ceftriaxone combined with gentamicin for the first 2 weeks. Patients with IE caused by nutritionally variant viridans streptococci (*Abiotrophia* species) or streptococci with an MIC of  $>0.5 \mu\text{g}$  of penicillin per milliliter should be treated with the antibiotics listed for enterococci. For children who are unable to tolerate  $\beta$ -lactam antibiotics, vancomycin should be used in combination with gentamicin (Table 6). Caution should be exercised because of the possibility of nephrotoxicity with this combination.

*Streptococcus pneumoniae* accounts for 3% to 5% of cases in children (Table 3). There has been a worldwide explosion of multi-drug resistance among clinical isolates of pneumococci during the 1990s. Because of this and the infrequency of the syndrome of pneumococcal IE, no optimal therapy has been es-

**TABLE 5.** Regimens for Therapy of Native Valve IE Caused By Viridans Group Streptococci, *Streptococcus bovis*, or Enterococci\*

Organism	Antimicrobial Agent	Dosage (per kg per 24 h)	Frequency of Administration	Duration (Weeks)
Penicillin susceptible streptococci (MIC $\leq 0.1 \mu\text{g/mL}$ )‡	Penicillin G† or ceftriaxone	200 000 U IV	q 4–6 h	4
	penicillin G† or ceftriaxone plus gentamicin	100 mg IV	q 24 h	4
		200 000 U IV	q 4–6 h	2
		100 mg IV	q 24 h	2
Streptococci relatively resistant to penicillin (MIC $>0.1$ – $0.5 \mu\text{g/mL}$ )	Penicillin G† or ceftriaxone plus gentamicin	3 mg IM or IV	q 8 h	2
		300 000 IV	q 4–6 h	4
		100 mg IV	q 24 h	4
		3 mg IM or IV	q 8 h§	2
Enterococci,¶ nutritionally variant viridans streptococci or high-level penicillin resistant streptococci (MIC $>0.5 \mu\text{g/mL}$ )	Penicillin G† plus gentamicin	300 000 U IV	q 4–6 h	4–6
		3 mg IM or IV	q 8 h¶¶	4–6

For treatment of patients with prosthetic cardiac valves or other prosthetic materials see text.

\* Dosages suggested are for patients with normal renal and hepatic function. Maximum dosages per 24 hours: penicillin 18 million units; ampicillin 12 g; ceftriaxone 4 g; gentamicin 240 mg. The 2-week regimens are not recommended for patients with symptoms of infection  $>3$  months in duration, those with extracardiac focus of infection, myocardial abscess, mycotic aneurysm, or infection with nutritionally variant viridans streptococci (*Abiotrophia* sp.).

† Ampicillin 300 mg/kg per 24 hours in 4–6 divided dosages may be used as alternative to penicillin.

‡ MIC—minimum inhibitory concentration of penicillin.

§ Studies in adults suggest gentamicin dosage may be administered in single daily dose. If gentamicin is administered in three equally divided doses per 24 hours, adjust dosage to achieve peak and trough concentrations in serum of approximately 3.0 and  $<1.0 \mu\text{g}$  of gentamicin per mL, respectively.

|| Studies in adults suggest that 4 weeks of therapy is sufficient for patients with enterococcal IE with symptoms of infection of  $<3$  months duration; 6 weeks of therapy is recommended for patients with symptoms of infection  $>3$  months duration.

¶¶ Adjust gentamicin dosage to achieve peak and trough concentrations in serum of approximately 3.0 and  $<1.0 \mu\text{g}$  of gentamicin per mL, respectively.

# For enterococci resistant to penicillins, vancomycin or aminoglycosides, treatment should be guided by consultation with specialist in infectious diseases (cephalosporins should not be used to treat enterococcal endocarditis regardless of in vitro susceptibility).



**TABLE 6.** Treatment Regimens for Therapy of IE Caused by Viridans Group Streptococci, *Streptococcus bovis*, or Enterococci in Patients Unable to Tolerate a Beta-lactam\*

Organism	Antimicrobial Agent	Dosage (per kg per 24 h)	Frequency of Administration	Duration (Weeks)
<i>Native valve (no prosthetic material)</i>				
Streptococci	Vancomycin	40 mg IV	q 6–12 h	4–6
Enterococci† or nutritionally variant viridans streptococci	Vancomycin plus gentamicin	40 mg IV 3 mg IM or IV	q 6–12 h q 8 h‡	6 6
<i>Prosthetic devices</i>				
Streptococci	Vancomycin plus gentamicin	40 mg IV 3 mg IM or IV	q 6–12 h q 8 h‡	6 2
Enterococci† or nutritionally variant viridans streptococci	Vancomycin plus gentamicin	40 mg IV 3 mg IM or IV	q 6–12 h q 8 h‡	6 6

\* Dosages suggested are for patients with normal renal function. Maximum daily dose per 24 hours of gentamicin is 240 mg.

† For enterococci resistant to vancomycin or aminoglycosides, treatment should be guided by consultation with specialist in infectious diseases.

‡ Dosage of gentamicin should be adjusted to achieve peak and trough concentration in serum of approximately 3.0 and <1.0 µg of gentamicin per mL, respectively.

established for this illness.<sup>45–47</sup> Penicillin with or without an aminoglycoside has been used for IE due to penicillin-susceptible strains. Consultation with an infectious disease specialist should be considered for IE due to *S. pneumoniae* that is not susceptible to penicillin.

#### *Prosthetic Cardiac Valves or Other Prosthetic Material*

Penicillin-susceptible strains should be treated for 6 weeks with penicillin, ampicillin, or ceftriaxone combined with gentamicin for the first 2 weeks of therapy. Infections caused by a strain with MIC >0.1 µg/mL of penicillin or by *Abiotrophia* sp. should be treated with a combination of penicillin, ampicillin, or ceftriaxone combined with gentamicin for 6 weeks. For patients unable to tolerate β-lactam therapy, a combination of vancomycin for 6 weeks together with gentamicin for the first 2 weeks of therapy is recommended. In such β-lactam intolerant patients with *Abiotrophia* infections, therapy should be a combination of vancomycin and gentamicin for 6 weeks.

#### **Enterococcal IE on Native Cardiac Valves or Prosthetic Material**

Enterococcal endocarditis is relatively uncommon in children. Treatment is difficult because of the relative resistance of enterococci to penicillin and ampicillin and their variable resistance to aminoglycosides and vancomycin.<sup>48,49</sup> The treatment regimen for native valve IE caused by susceptible strains requires a combination therapy of penicillin G or ampicillin (Table 5), together with gentamicin for 4–6 weeks.<sup>39,48</sup> The duration of therapy in patients with infections involving prosthetic material is a minimum of 6 weeks. This duration of therapy is based on the prevailing opinion of the authors who recognize that while other publications have listed 4 weeks as a treatment option, the virulence of the organism favors that 6 weeks of therapy is a better treatment option.<sup>39</sup> Patients with infections caused by susceptible strains of enterococci who are unable to tolerate β-lactam therapy should receive vancomycin combined with gentamicin for 6 weeks for native valve IE and for a minimum of 6 weeks for infection of prosthetic material.<sup>39</sup> In contrast to strep-

tococcal IE (see above), the aminoglycoside should be given for the entire course of therapy, and in patients with normal renal function, the aminoglycoside should be administered in two to three divided doses daily rather than in a single daily dose. Enterococci are resistant to ceftriaxone and other cephalosporins, and these drugs are not an option for treatment of enterococcal endocarditis. The emergence of high-level vancomycin, ampicillin, and aminoglycoside resistance in some enterococcal species has further complicated treatment choices. Infectious disease consultation is recommended for management of patients with enterococcal IE.

#### **Staphylococcal Endocarditis on Native Valves or Prosthetic Material**

##### *Native Valve IE*

Staphylococci are coagulase-positive (*S. aureus*) or coagulase-negative (*S. epidermidis* and various other species). The vast majority of staphylococci are highly resistant to penicillin G and ampicillin (Table 7) due to production of enzymes called β-lactamases.<sup>50</sup> Staphylococci that are susceptible to β-lactamase-resistant penicillins are termed methicillin susceptible. Therapy for methicillin-susceptible *S. aureus* endocarditis involving a native valve or other native cardiac tissue preferentially includes a semi-synthetic, β-lactamase-resistant penicillin (nafcillin or oxacillin) given intravenously for a minimum of 6 weeks. This duration of therapy is based on the prevailing opinion of the authors who recognize while other publications have stated 4 weeks as a treatment plan, the virulence of the organism favors 6 weeks of therapy as a better treatment option. The addition of gentamicin for the first 3 to 5 days is optional and may accelerate the killing of the staphylococci. In patients without a history of type 1 penicillin-allergic reactions, a first-generation cephalosporin, eg, cefazolin, is recommended as an alternative, with or without gentamicin for the first 3 to 5 days.<sup>39</sup> For patients unable to tolerate β-lactam antibiotics, vancomycin for a minimum of 6 weeks is recommended with or without gentamicin for the first 3 to 5 days of therapy.

Some staphylococcal strains may be methicillin-

**TABLE 7.** Treatment Regimens for Endocarditis Caused by Staphylococci\*

Organism	Antimicrobial Agent	Dosage (per kg per 24 h)	Frequency of Administration	Duration
<i>Native valve (no prosthetic materials)</i>				
Methicillin-susceptible	Nafcillin or oxacillin with or without gentamicin†	200 mg IV	q 4–6 h	6 wk
		3 mg IM or IV‡	q 8 h	3–5 d
β-lactam allergic	Cefazolin§ with or without gentamicin† or vancomycin	100 mg IV	q 6–8 h	6 wk
		3 mg IM or IV‡	q 8 h	3–5 d
Methicillin-resistant	Vancomycin	40 mg IV	q 6–12 h	6 wk
<i>Prosthetic device or other prosthetic materials</i>				
Methicillin-susceptible	Nafcillin or oxacillin or cefazolin§ plus rifampin   plus gentamicin‡	200 mg IV	q 4–6 h	≥6 wk
		100 mg IV	q 6–8 h	≥6 wk
		20 mg p.o.	q 8 h	≥6 wk
		3 mg IM or IV‡	q 8 h	2 wk
Methicillin-resistant	Vancomycin plus rifampin   plus gentamicin‡	40 mg IV	q 6–12 h	≥6 wk
		20 mg p.o.	q 8 h	≥6 wk
		3 mg IM or IV‡	q 8 h	2 wk

\* Dosages suggested are for patients with normal renal and hepatic function. Maximum daily doses per 24 hours: oxacillin or nafcillin 12 g; cefazolin 6 g; gentamicin 240 mg; rifampin 900 mg.

† Gentamicin therapy should be used only with gentamicin-susceptible strains.

‡ Dosage of gentamicin should be adjusted to achieve peak and trough concentrations in serum of approximately 3.0 and <1.0 μg of gentamicin per mL, respectively. Dosages suggested by rifampin are based upon results of studies conducted in adults.

§ Cefazolin or other first generation cephalosporin in equivalent dosages may be used in patients who do not have a history of immediate type hypersensitivity (urticaria, angioedema, anaphylaxis) to penicillin or ampicillin.

|| Dosages suggested by rifampin are based upon results of studies conducted in adults and should be used only with rifampin-susceptible strains.

resistant, and patients with IE caused by these organisms should not receive nafcillin, oxacillin, or a cephalosporin. Despite antibiotic susceptibility results indicating that methicillin-resistant coagulase-negative staphylococci are susceptible to cephalosporins, cross-resistance exists, and cephalosporins should not be used in these patients. Patients with methicillin-resistant staphylococcal endocarditis should be treated with vancomycin for a minimum of 6 weeks with or without gentamicin for the first 3 to 5 days of therapy.

#### Prosthetic Material IE

Staphylococcal endocarditis on a prosthetic cardiac valve or other cardiac prosthetic material is usually due to coagulase-negative staphylococci that are methicillin resistant, especially if the endocarditis develops within 1 year after cardiac surgery.<sup>51</sup> See details in Table 7 for treatment of methicillin-resistant and methicillin-susceptible staphylococcal endocarditis. Additional recommendations for the treatment of staphylococcal endocarditis on intracardiac prosthetic material are listed in the American Heart Association guidelines.<sup>39</sup>

The overall mortality associated with prosthetic valve endocarditis is relatively high but is highest for infections due to *S. aureus*.<sup>52</sup> Moreover, *S. aureus* as a cause of prosthetic valve infection has been shown to be an independent risk factor for death.<sup>53,54</sup> Results from 3 recently published investigations<sup>52,54,55</sup> of adult patients suggest that mortality rates due to *S. aureus* prosthetic valve endocarditis can be decreased with a combined medical-surgical approach to treatment as compared with medical therapy alone. None of the 3 studies, however, was conducted as a prospective, randomized comparative treatment trial. Nevertheless, on the basis of these studies, many authorities have concluded that replacement should

be performed in most, if not all, patients with prosthetic valve infection due to *S. aureus*. Patients with *S. aureus* prosthetic valve endocarditis should be cared for in a medical facility with cardiothoracic surgery capabilities and infectious diseases consultation.<sup>56</sup>

#### Gram-Negative IE

The gram-negative bacteria that most often cause IE in children are the HACEK group of fastidious coccobacilli. The recommended therapy for IE caused by the HACEK group is a 4-week course of ceftriaxone or another third-generation cephalosporin alone, or ampicillin plus gentamicin.<sup>39</sup>

Other gram-negative bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, or *Serratia marcescens* are rare causes of IE. Treatment must be individualized, guided by identification of the organism and antimicrobial susceptibility testing. Most infectious disease specialists use an extended-spectrum penicillin (eg, piperacillin) or a cephalosporin (eg, ceftazidime) together with an aminoglycoside.<sup>57</sup> A minimum of 6 weeks of therapy is recommended.

#### Fungal Endocarditis

With the exception of neonates with mural endocarditis and, occasionally, older children, medical therapy of fungal IE is usually unsuccessful. For most patients with fungal IE, surgery in conjunction with antifungal agents is required. Consultation with infectious disease, cardiology, and cardiac surgery services is recommended for these patients.

Amphotericin B remains the first-line antifungal agent for medical therapy, although it does not penetrate vegetations well. Although the imidazoles (eg, fluconazole) have no proven efficacy in human fungal IE, long-term suppressive therapy with these agents may be effective in patients (who are not able

to undergo curative surgery) with infections caused by susceptible organisms.

Some experts recommend the addition of 5-fluorocytosine (5-FC) to amphotericin B at a dosage of 100 to 150 mg/kg per day, divided every 6 hours, and given by mouth for *Candida* endocarditis caused by strains susceptible to 5-FC. The rationale is that the 2 drugs may act synergistically and potentiate fungal killing. The use of liposomal forms of amphotericin B may be considered in patients with moderate to severe renal impairment or those with unacceptable infusion-related toxicities.

### Prosthetic Valve and Other Prosthetic Material Endocarditis

Treatment for prosthetic valves infected with streptococci, staphylococci, or enterococci is discussed above.

Prosthetic valve endocarditis caused by diptheroids is best treated with penicillin and gentamicin, or with vancomycin together with gentamicin for penicillin-resistant organisms or in penicillin-allergic patients.<sup>51</sup> Duration of therapy should be 6 weeks.

Therapy of prosthetic valve endocarditis caused by gram-negative bacilli must be based on the results of in vitro susceptibility testing. Commonly, treatment includes a third-generation cephalosporin or a broad-spectrum penicillin with gentamicin for at least 6 to 8 weeks.

Often patients with staphylococcal or early-onset (within 60 days of surgery) prosthetic valve endocarditis should undergo replacement of the infected prosthetic material. The timing of surgical replacement of an infected prosthesis must be individualized. Experience with prosthetic valve endocarditis, derived mainly in adults, has shown that early surgical replacement of the infected valve in patients with staphylococcal infection may lower the high mortality rate.<sup>52</sup>

### Culture-Negative Endocarditis

Culture-negative endocarditis poses substantial problems in therapeutic decisions. The primary considerations for therapy are directed against staphylococci, streptococci, including *S. pneumoniae*, and the HACEK organisms. If blood cultures remain negative after careful evaluation and use of specialized laboratory techniques, patients with native or prosthetic valve IE should be treated with ceftriaxone and gentamicin.<sup>51,58</sup> If there is a high suspicion of staphylococcal IE, therapy should include the addition of a  $\beta$ -lactamase-resistant penicillin to ceftriaxone and gentamicin. For patients unable to tolerate  $\beta$ -lactam therapy, consultation with an infectious disease specialist is advised. Patients at risk of unusual cases of culture-negative IE, such as *C. burnetii*, *Brucella*, or *Bartonella*, should be managed in consultation with a specialist in infectious diseases. The activity in vitro of ceftriaxone against methicillin-susceptible *S. aureus* is less than that of anti-staphylococcal penicillins or first-generation cephalosporins. In addition, the antimicrobial activity in vivo of ceftriaxone is diminished by high protein binding (90%). Accordingly, if methicillin-sensitive staphy-

**TABLE 8.** Clinical Situations Constituting High Risk for Complications of IE

- Prosthetic cardiac valves
- Left-sided IE
- *Staphylococcus aureus* IE
- Fungal IE
- Previous IE
- Prolonged clinical symptoms ( $\geq 3$  mo)
- Cyanotic congenital heart disease
- Patients with systemic-to-pulmonary shunts
- Poor clinical response to antimicrobial therapy

IE indicates infective endocarditis.

From Bayer et al.<sup>29</sup>

lococcal IE is suspected, therapy should include a  $\beta$ -lactamase-resistant penicillin or vancomycin; if methicillin-resistant staphylococcal IE is suspected, vancomycin should be administered. Patients with culture-negative endocarditis should be treated for a minimum of 4–6 weeks in consultation with an infectious diseases specialist.

### COMPLICATIONS OF ENDOCARDITIS AND INDICATIONS FOR SURGERY

Factors in children with IE that predispose to the development of complications include type of organism, location and size of vegetation, important comorbid cardiac conditions, and occurrence of endocarditis in an otherwise normal heart, particularly in children under 2 years of age.<sup>4,5</sup> (Table 8)

The complications of IE comprise a broad spectrum (Table 9). Among the more frequent complications is congestive heart failure, which may occur acutely or insidiously. Acute congestive heart failure may be caused by abrupt structural changes, including perforation of a valve leaflet, rupture of infected mitral chordae or fistulous tracts, or, in patients with prosthetic valves, from development of perivalvular leaks or dehiscence. Progressive congestive heart failure is usually caused by worsening valvular regurgitation, often accompanied by ventricular dysfunction. Poor ventricular function is associated with increased surgical mortality.<sup>59,60</sup> Urgent surgery in patients with moderate to severe heart failure improves the likelihood of survival and preservation of cardiac function.<sup>61</sup>

Periannular extension of infection increases the risk of congestive heart failure.<sup>62,63</sup> The greatest risk for this complication exists in aortic valve endocarditis. Periannular infections may also advance to cause fistulous tracks into the pericardium as well as between cardiac chambers or vascular structures.

**TABLE 9.** Complications of IE

- Congestive heart failure
- Embolic events: eg, cerebral, pulmonary, renal, coronary
- Periannular extension of abscess
- Arrhythmia development, new heart block
- Prosthetic device dysfunction
  - Valvar dehiscence
  - Graft or shunt occlusion
- Persistent bacteremia or fungemia
- Metastatic infection
- Mycotic aneurysms
- Glomerulonephritis/renal failure

Such abscesses or fistulas usually do not respond to medical management alone and require surgical treatment. Clinical signs and symptoms of extension of infection beyond valve leaflets are nonspecific and include persistent bacteremia or fever, recurrent emboli, heart block, worsening congestive heart failure, or new pathologic murmurs in patients receiving appropriate antibiotics.<sup>64,65</sup> The development of new atrioventricular or bundle-branch block has a sensitivity for detection of perivalvular extension in adults of only 45% but a specificity of 88%.<sup>66</sup>

In children, a potentially life-threatening complication involves the development of endocarditis in a surgically created shunt or conduit. Because these prostheses are often Gortex or Dacron tubes, the likelihood of cure with antibiotics alone is decreased, and surgical intervention is often required.

Embolic complications may arise in any patient with IE but particularly in those with larger lesions. Even in the absence of prior embolization, vegetations >10 mm seem to have high predictive validity for embolic events.<sup>38</sup> The location of the primary vegetation may also be a factor. In adults, mitral lesions have been associated with higher rates of embolization than aortic vegetations (25% vs 10%, respectively), with the highest rate of embolization (37%) occurring when vegetations are attached to the anterior rather than the posterior mitral leaflet.<sup>67</sup> This may be related to the fact that the mitral valve (as compared with the aortic valve) undergoes 2 excursions per cardiac cycle. Staphylococcal and fungal infections carry a high risk of embolism regardless of vegetation size or its location. Although embolization can occur before diagnosis, during therapy, or even after therapy is completed, most embolic episodes occur within the first 2 to 4 weeks after therapy is instituted.<sup>68</sup> Although persistent vegetations are not predictive of adverse events,<sup>37</sup> an increase in vegetation size during the fourth to the eighth week of therapy is predictive of embolic events and abscess formation and may herald the need for valve replacement.<sup>29</sup>

Mycotic aneurysms are another complication of endocarditis and can occur in any systemic artery. Such aneurysms may result from septic embolization or, occasionally, from the spread of infection from contiguous tissue to the adjacent arterial wall. In most circumstances, development of an aneurysm as a complication of IE is an indication for surgery. Overall mortality among patients with intracranial mycotic aneurysms is high.<sup>29</sup> Management of mycotic aneurysms is discussed in greater detail in a recent paper by this committee.<sup>29</sup>

### Surgical Approaches

Cardiovascular surgery may be lifesaving in patients with IE, but decisions for surgical intervention must be individualized (Table 4). Common indications for surgery include progressive cardiac failure, valvular obstruction, perivalvular extension of infection, fungal endocarditis, persistent bacteremia despite appropriate antibiotic therapy, unstable prosthesis, ruptured sinus of Valsalva or ventricular septum, and significant embolic events,<sup>69-71</sup> espe-

cially when the aortic or mitral valve is involved. Management of progressive valvular damage and resulting heart failure with medical therapy alone is often unsuccessful. Surgery should not be delayed solely because a full course of antibiotic therapy has not been completed or because the patient is still bacteremic. A small number of patients with perianular extension of infection or myocardial abscess may be treated successfully without surgical intervention. These patients include those who do not have heart block, echocardiographic evidence of progression of abscess during therapy, valvular dehiscence, or insufficiency. Such patients should be monitored closely during therapy with serial echocardiography and it should be repeated at intervals of 2, 4, and 8 weeks after completion of antimicrobial therapy.<sup>29</sup>

### PREVENTION OF ENDOCARDITIS

Prevention of endocardial infection by the use of antimicrobial agents, although desirable, is not always possible. Many situations in which bacteremia may occur are not readily identifiable, and other bacteremias occur spontaneously (chewing of food, oral hygiene procedures) and cannot logically be prevented. Many cases of native valve endocarditis are caused by organisms that may originate in the oral cavity. All children at risk should be properly instructed to establish and maintain the best possible oral health to reduce these potential sources of bacteremia.

Certain patient populations at risk for endocarditis have been identified.<sup>72</sup> These individuals have a higher risk for developing endocarditis than does the general population. Antibiotic prophylaxis is therefore recommended when these individuals undergo procedures likely to cause bacteremia with organisms that cause endocarditis. The recommendations for prevention of endocarditis included here were previously issued by the American Heart Association.<sup>73</sup>

Prophylaxis is particularly important for children in whom endocarditis is associated with high morbidity and mortality. Cardiac conditions have been stratified into high-, moderate-, and negligible-risk categories (see Table 10). Prophylaxis is recommended for those in the high- and moderate-risk categories; these conditions are stratified primarily on the basis of the risk of endocarditis developing and its severity.<sup>73</sup> For example, individuals in the high-risk category are at much higher risk for developing a severe endocardial infection that is often associated with high morbidity and mortality. Individuals in the negligible-risk category have no greater risk for developing endocarditis than does the general population.

Antimicrobial prophylaxis in children with mitral valve prolapse is problematic. Individuals with prolapsing and regurgitant mitral valves are at increased risk for development of endocarditis and are placed in the moderate-risk category.<sup>72-74</sup> In two of the last three large clinical series of pediatric patients with endocarditis, prolapsed mitral valve has been the underlying cardiac diagnosis in large numbers of

**TABLE 10.** Cardiac Conditions*Endocarditis prophylaxis recommended:*

## High-risk category

- Prosthetic cardiac valves, including bioprosthetic and homograft valves
- Previous bacterial endocarditis
- Complex cyanotic congenital heart disease (eg, single-ventricle states, transposition of the great arteries, tetralogy of Fallot)
- Surgically constructed systemic-pulmonary shunts or conduits

## Moderate-risk category

- Most other congenital cardiac malformations (other than above and below)
- Acquired valvular dysfunction (eg, rheumatic heart disease)
- Hypertrophic cardiomyopathy
- Mitral valve prolapse with valvular regurgitation and/or thickened leaflets

*Endocarditis prophylaxis not recommended:*

## Negligible-risk category (no greater risk than the general population)

- Isolated secundum atrial septal defect
- Surgical repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus (without residua beyond 6 mo)
- Previous coronary artery bypass graft surgery
- Mitral valve prolapse without valvular regurgitation
- Physiological, functional, or innocent heart murmurs
- Previous Kawasaki disease without valvular dysfunction
- Previous rheumatic fever without valvular dysfunction
- Cardiac pacemakers (intravascular and epicardial) and implanted defibrillators and stents

From Dajani et al.<sup>73</sup>

patients.<sup>4,17</sup> Patients without regurgitation have not been demonstrated to be at higher risk than the general population and are listed in the negligible-risk category. Some pediatric cardiologists believe that a careful evaluation of valve morphology and function is needed in children who have isolated clinical findings (such as a nonejection systolic click), because this may be the only indication of an important mitral valve abnormality that requires prophylaxis.<sup>17</sup>

Specific antibiotic regimens for prophylaxis have been recommended by the American Heart Association and approved by the American Dental Association.<sup>73,75</sup> Further, health care providers should be mindful of circumstances in children that can impact compliance, especially when choosing oral forms of antibiotics. Chewable tablets and antibiotic suspensions may be indicated in children who have difficulty swallowing tablets.<sup>76</sup>

**SUMMARY**

The observed frequency of endocarditis in children during recent years necessitates that primary care physicians, as well as specialists, consider this diagnosis in children. Survivors of surgery for complex congenital heart disease who have implanted vascu-

lar grafts, patches, or prosthetic cardiac valves are at increased risk for IE. However, children with normal hearts may also develop IE. Unique aspects of IE in pediatric populations are discussed, and tailored approaches to diagnosis, laboratory evaluation, detection of complications, therapy, and prevention of IE are presented.

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