AHA Scientific Statement

Infective Endocarditis in Childhood: 2015 Update

A Scientific Statement From the American Heart Association

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In 2002, the American Heart Association (AHA) published "Unique Features of Infective Endocarditis in Childhood,"[1] which reviewed epidemiology, pathogenesis, diagnosis, clinical and laboratory findings, treatment, and prevention of infective endocarditis (IE) with particular attention to children. Since that time, other AHA reports have focused on new recommendations for treatment of IE in adults (in 2005[2]) and on major changes regarding prevention of IE (in 2007[3]). This document updates these issues and other concerns regarding IE, with specific attention to the disease as it affects infants and children. In particular, the impact of increased survival for children with congenital heart disease (CHD) on the epidemiology of IE is updated, and newer tools useful for diagnosis and treatment in the pediatric population are reviewed. This review emphasizes changing management perspectives and discussion of new agents that have utility for treatment of resistant organisms. In addition, proper use of the diagnostic microbiology laboratory remains critical to the diagnosis and management of children with IE, and newer diagnostic guidelines that have improved sensitivity and specificity for confirming the diagnosis of IE will be reviewed. Because of improved infrastructure available for home intravenous therapy, an update on outpatient management, an increasingly accepted approach for stable patients who are at low risk for complications, will also be discussed. Finally, since the publication of the last AHA document on pediatric IE, recommendations for prevention of IE have been modified substantially, and the most current recommendations are incorporated from the perspective of pediatric cardiovascular concerns.

Classification of Recommendations

In pediatrics, there are not likely to be any randomized controlled trials for treatment of IE, which posed a challenge for the writing group in compiling recommendations. Therefore, many of the indications are based on consensus. In cases of strong consensus that an intervention be considered as standard-of-care practice with scientific evidence, interventions were designated as Class I indications. Where the wording of treatments indicates a recommendation, the standard classification is used. Strength of the recommendation is according to the ACC/AHA classification system for recommendations (Table 1).

Epidemiology and Clinical Findings of IE in Children

In a previous report, IE occurred less often in children than in adults and accounted for approximately 1 in 1280 (0.78 per 1000) pediatric admissions per year from 1972 to 1982 at a referral insitution.[4] In a recent multicenter report,[5] the annual incidence rate in the United States was between approximately 0.05 and 0.12 cases per 1000 pediatric admissions from 2003 to 2010, without a significant trend. Although the reported hospitalization rates for IE vary considerably among published series, both the overall frequency of endocarditis among children and a shift toward those with previous cardiac surgery appear to have increased in recent years in some reports.[5–8] This may be related to improved survival among children who are at risk for endocarditis, such as those with CHD (with or without surgery) and hospitalized newborn infants.

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* COR III: No benefit — Procedure/Test: Not Helpful — Treatment: No Proven Benefit COR III: Harm — Procedure/Test: Excess Cost w/o Benefit or Harmful — Treatment: Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

Before the 1970s, 30% to 50% of US children with IE had underlying rheumatic heart disease.[9] Because the prevalence of rheumatic heart disease has declined in developed countries, including the United States, it has now become relatively unusual for patients with IE from the developed world to have underlying rheumatic heart disease. In the past 2 decades, CHD has become the predominant underlying condition for IE in children from the developed world >2 years of age. In fact, there has been an increase in cases of IE associated with CHD because most patients with CHD survive much longer than they did several decades ago. Early surgical correction of lesions that were major risk factors for IE in the past has also changed the substrate for this disease. Although congenital heart defects, such as aortic valve abnormalities, ventricular septal defect, and tetralogy of Fallot, are still common underlying conditions, an increasing proportion of children with IE have had previous corrective or palliative surgery for complex cyanotic CHD, with or without implanted vascular grafts, patches, or prosthetic cardiac valves.[10–14] Postoperative IE is a long-term risk after correction of complex CHD, especially in those with residual defects or in cases in which a surgical shunt is constructed or other prosthetic material is left in place.

Increasingly, IE develops in the absence of CHD. This circumstance is often associated with central indwelling venous catheters (central lines). The complexities of patient management in neonatal and pediatric intensive care units have

increased the risk of IE in children with structurally normal hearts. Currently, in approximately 8% to 10% of pediatric cases,[13] IE develops without structural heart disease or any other readily identifiable risk factors. In these situations, the infection usually involves the aortic or mitral valve secondary to *Staphylococcus aureus* bacteremia.[6,10–12] Recent initiatives developed to reduce central line bloodstream infections will likely improve the prognosis for all critically ill children, including those with cardiac conditions, and may impact IE development further in the diverse group of vulnerable patients with central lines. Interestingly, 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. Furthermore, factors often associated with IE in adults, such as intravenous drug abuse and degenerative heart disease, are not common predisposing factors in children.[7–11]

IE in Children With Previous Cardiac Surgery or After Placement of Transcatheter Devices

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. However, surgery itself, including such elements as central vascular catheters, intravenous alimentation, and days the patient resides in the intensive care unit, may be important risk factors 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. Morris et al[12] reviewed cumulative incidences of endocarditis for a number of congenital cardiac lesions in a follow-up series of Oregon residents. The highest annualized risk for IE was found in children who had had repair or palliation of cyanotic CHD. The greatest risk among those patients was for those who had either undergone surgery for obstruction to pulmonary blood flow or had prosthetic aortic valve replacement. In a follow-up of the series of Oregon residents, the highest incidence of IE in postoperative patients has been in the cohort with aortic valve stenosis, and this has increased over time, with a cumulative incidence of 13.3% at 25 years.[12] Endocarditis may manifest as a late complication, with presentation years after congenital heart surgical repair, and may be associated with a fulminant course or antibiotic failure.[14,15]

The incidence of IE in the first postoperative month is low for most defects and increases with time after surgery. An exception to this trend is that when prosthetic valves or conduits are used in surgical repairs and hemodynamic problems persist, the risk of IE is high even in the immediate postoperative period (first 2 weeks after surgery).[12] Two recently published studies showed a 25% incidence of previous cardiac surgery in patients with congenital heart disease who required surgery during active IE.[16,17]

Russell et al[18] reported 34 patients who met indications for surgical management of IE (of whom 37% had prior cardiac surgery) from a 21-year single-center review through 2011 at Children's Memorial Hospital, Chicago, IL. Five had operative mortality, and all deaths occurred in infants, with a mean age of 2.5 months. The infective organisms were identified in 86% of cases, with the most common being *S aureus* (n=8) and viridans streptococci (n=6). The Ross operation was performed successfully in 5 children with severe aortic valve disease. Ten of the 34 patients required reoperations at a later time.

The increasing prevalence of transcatheter placement of devices such as septal or vascular occluders and coils provides another potential risk factor for IE, particularly in the early postdeployment period before endothelialization has occurred.[3] Although a long-term study of transcatheter closure of atrial septal defects[19] showed no cases of IE, several case reports of endocarditis related to transcatheter device treatment of atrial and ventricular septal defects and patent ductus arteriosus do suggest that residual defects after device placement may be a factor in the risk for IE.[20–23]

IE in Newborn Infants

In a recent multicenter review, 7.3% of cases of pediatric IE (108 of 1480) were diagnosed in the first month of life.[24] Improved and widely available imaging technology, particularly echocardiography, and increased clinical awareness have greatly facilitated the diagnosis of IE in this patient group. The incidence of neonatal IE has increased in the past 2 decades in large measure because of the increasing use of invasive techniques to manage neonates with multiple complex medical problems, even those with structurally normal hearts. Central venous catheters designed to be in place for prolonged periods of time, such as peripherally inserted central catheters and tunneled central venous catheters, provide a portal of entry for surface bacterial despite the most meticulous management. As a result of the indwelling lines, infections frequently involve right-sided heart structures. It has been estimated that fewer than one-third of cases of neonatal endocarditis occur in the presence of congenital cardiac disease.[24–26] A recent review showed that 31% of infants who died of IE were premature.[24] The most common infecting organisms were *S aureus*, coagulase-negative staphylococcus strains, Gram-negative bacterial species, and *Candida* species.

The clinical manifestations of IE in the neonate are variable and nonspecific and may be indistinguishable from septicemia or from congestive heart failure associated with other causes.[27–29] In infants, septic emboli from IE are common, resulting in foci of infection outside the heart (eg, osteomyelitis, meningitis, or pneumonia). Neonates with IE often have feeding difficulties, respiratory distress, tachycardia, and hypotension. As with older children, neonates also may have a new or changing heart murmur. Many neonates with IE also have neurological signs and symptoms (eg, seizures, hemiparesis, or apnea). However, although arthritis and arthralgia are common findings in older children with IE, arthritis is rarely described in neonates. Osler nodes, Roth's spots, Janeway lesions, and splinter hemorrhages are also not mentioned in published cases of IE in neonates.

Pathogenesis

Early histopathologic studies in humans and decades-long investigations that have included an animal model of experimental endocarditis have confirmed 2 critical histopathologic

findings: (1) Damaged or denuded endothelium is necessary for initial pathogen colonization of a cardiac nidus; and (2) Gram-positive cocci, the predominant pathogens in both native and prosthetic value infections, express multiple adhesins that serve as virulence factors through their ability to enhance host cell/substrate attachments that are important in both the initiation and propagation of endocardial infection. (Adhesins are discussed further in a separate section.)

Denuded cardiac endothelium can occur when there is turbulence caused by abnormal cardiac structures, in particular stenotic or regurgitant valves, that results in high-velocity jets of blood. Once the endothelium is damaged, the host response includes platelet and fibrin deposition, leading to so-called nonbacterial thrombotic endocarditis (NBTE), at the wound site. NBTE serves as an excellent nidus for subsequent bacterial or fungal colonization in a patient with bacteremia or fungemia. The prevailing notion is that activities of daily living, such as chewing food, toothbrushing, and flossing, account for most bloodstream seeding of an NBTE site.

There are additional mechanisms involved in endocarditis pathogenesis. Right-sided endocarditis can occur when there are intravenous catheters, illicit intravenous drug use, or cardiovascular implantable electronic device leads that dwell in the right side of the heart. Damage to the endothelium occurs by 2 mechanisms. One involves direct damage produced by the foreign body "rubbing" directly against the endothelial surface. The other is via an indirect effect, such as when a foreign device interferes with normal tricuspid valve function and causes regurgitant jets of blood. Bacteremia may be caused by entry of organisms at the skin site of percutaneous catheters or leads, via the catheter lumen, or in contaminated infusate. Microorganisms carried by the bloodstream enter the right side of the heart, potentially causing IE on preexisting NBTE.

IE can also occur as a result of direct infection of an indwelling device. This occurs at the time of device placement into a cardiac locus (eg, valves, leads, other types of devices) and is an example of surgical site infection. These infections can occur despite the administration of antibiotic prophylaxis at the time of placement of cardiovascular devices such as heart valves, pacemaker leads, or left ventricular devices.

Adhesins

Virulence factors that are involved in bacterial adherence, so-called adhesins, have received the bulk of recent investigative attention. Advances in molecular biological techniques have been crucial in characterizing these cell surface structures, with attention specifically to staphylococcal, streptococcal, and enterococcal species, which account for the large majority of IE cases. These adhesins attach to either host cell structures or extracellular molecules that bind to host cells or to extracellular matrix.

The availability of an experimental animal model of endocarditis has been a pivotal aspect of these pathogenesis investigations. It has served as the ultimate evaluation of in vitro molecular techniques to obtain mutant and recombinant isolates that are developed to examine the effects of a single purported virulence factor expressed by a wild-type strain. Considering the fact that Gram-positive cocci typically express multiple adhesins, the ability to demonstrate the role of a single adhesin in infection pathogenesis is remarkable. For example, this approach demonstrated pilus involvement in attachment to collagen by *Streptococcus gallolyticus*. This was the first time that a virulence factor was demonstrated in an animal model of endocarditis.[30] Interestingly, strains that expressed pil1 did not adhere to either fibronectin or fibrinogen but did form biofilm in vitro. A nonpathological *Lactococcus lactis* strain that by recombinant techniques expressed Pil1 in vitro was examined with its parent strain that did not express Pil1 in a rat model of experimental endocarditis. The results suggested that Pil1 was important in vivo as a virulence factor; 82% of rats challenged with the Pil1+ strain developed experimental endocarditis, in contrast to the animals that received the Pil1− strain (36%, P=0.03).[30]

The "big 3" pathogens (viridans group streptococci [VGS], *S aureus*, and *Enterococcus* species) that account for the large majority of endocarditis cases have been the primary focus of pathogenesis studies.[31] Adhesins of *S aureus*, which have been referred to as MSCRAMMs (microbial surface components recognizing adhesive matrix molecules), are surface molecules involved in staphylococcal attachment to collagen, thrombospondin, laminin, fibrinogen, and fibronectin.[32] These interactions with host proteins not only may be important in the initial adherence of bacteria to a site of endothelial damage but also may be operative in bacterial persistence and engulfment by the host cell (endothelial cells, platelets). Similarly, there have been several bacterial surface structures identified in strains of VGS and *Enterococcus* species that appear critical in endocarditis pathogenesis.

Study of pathogenic mechanisms in IE is pivotal as we consider potential advances in infection treatment and prevention in the future. This knowledge serves as a foundation for the development of novel clinical tools that include therapeutics and vaccines. Indeed, identification of a virulence factor resulted in development of a vaccine that reduced the risk of endocarditis development in an animal model.[33]

Pathogenesis of IE on Prosthetic Material

Because perivalvular infection that involves the sewing ring is commonplace among patients with prosthetic valve endocarditis, particularly mechanical valves, the pathogenic mechanisms reviewed previously in this section apply to prosthetic valve endocarditis. In addition, biofilm formation can be operative in infection of prosthetic valves, similar to infection of a broad array of indwelling cardiovascular and noncardiovascular devices.[34]

A mature biofilm represents a unique and complex environment for organisms to attach to and thrive on a device surface. Both antimicrobial agents and immune cells have difficulty in penetrating biofilm, and because of metabolic changes of infecting organisms in biofilm, the ability of antimicrobial agents to kill biofilm-associated organisms is greatly reduced. Because of this, infection relapse at a prosthetic valve site is thought to be increased.

Oral/Dental Considerations

The oral mucosa and tooth surfaces of children who are beyond infancy are populated by a variety of pathogenic and

nonpathogenic bacteria, which are representative of hundreds of strains of aerobic and anaerobic species.[35,36] This oral flora, in both health and disease, is different from adults and less diverse, but it becomes more like that of adults as the child ages, including increases in the percentage of VGS (α-hemolytic streptococci), *Prevotella*, and *Actinomyces* species.[35–38] In health, the child's oral flora has a variety of VGS, *Neisseria* species, *Haemophilus* species, and *Staphylococcus* species. In older children, species responsible for periodontal diseases (eg, *Capnocytophaga*) can be found along with others known to cause IE (eg, *Aggregatibacter actinomycetemcomitans*).[39] This is particularly relevant with regard to the formation of plaque on the teeth of children at risk for IE.

Dental plaque biofilm formation begins soon after a tooth surface is cleaned, and in the absence of oral hygiene, this biofilm thickens and evolves to include a more pathogenic bacterial flora largely isolated from the immune system. In contrast to plaque in adults, plaque bacteria on the visible surfaces of the teeth (supragingival) in children are similar to those in the gingival crevice (subgingival space), where there are more Gram-negative and anaerobic species than other sites in the oral cavity.[35] The host response to plaque is gingival inflammation and enlargement (gingivitis). Gingivitis can result in an increased depth to this shallow gingival crevice between the tooth surface and the gingival crevicular mucosa that is more difficult to clean with a toothbrush and floss. In the absence of disease, the crevicular mucosa serves as a barrier to bacterial invasion. As in adults, however, the child's gingival crevice is most likely the source of virtually all transient bacteremia that occur from the mouth, whether from office-based dental procedures or routine activities of daily living such as toothbrushing. Gingival inflammation, however, may lead to thinning and ulceration, allowing dense colonies of bacteria and bacterial byproducts ready access to the increased gingival capillary circulation. Bacteremia may then result from minimal gingival manipulation. Children have a much lower prevalence and severity of gingivitis and periodontitis than adults, and data from bacteremia studies in adults may not be representative of children.

Bacteremia From Dental Procedures

Dental procedures are a frequent source of bacteremia, particularly from VGS.[40–48] Multiple clinical studies of children over the past 40 years focused on the impact of ≥1 of the following risks for development of bacteremia: class of prophylactic antibiotic drug[49]; nature and invasiveness of dental procedures[42,44–47,49–53]; indices of oral hygiene and disease[41,45,48,49,51,54,55]; timing of blood culture draws before, during, and after the dental procedure[45,48,56]; various methods of microbial analysis and identification[44,57]; and the impact of these variables on surrogate measures of risk for IE, such as the incidence, duration, nature, and magnitude of bacteremia.[44–48] Clearly, these surrogate measures are also influenced by multiple host factors.

These variable risks are associated with a wide range (0%–97%) in the incidence of bacteremia in children after various dental procedures and other manipulations of the gingiva, for example, tooth extractions (0%–96%)[41,44,45,48–50,53,57–60]; teeth cleaning and electric toothbrushing (0%–78%)[42,45,47,55,61–63]; restorations (16%–66%)[45,46,50]; dental injections (16%–97%)[52,64]; and other manipulations (13%–44%).[42,44,46,51–53] Of the more than 100 oral bacterial species recovered from blood cultures in children after dental procedures, the number and variety of species reflect the spectrum of oral flora in health and disease (Table 2). They also reflect the varied microbiological methodologies used in these studies (eg, culture-based rather than molecular), with the recognition that many bacterial species clearly enter the bloodstream but are not cultivable and therefore not recorded.[44,49,57] Of greatest importance is the subset of bacterial species reported in blood cultures after dental procedures that are known to cause IE.[66] Finally, the varied methodologies and results make it impossible to differentiate among procedures with regard to their risk for causing bacteremia. The collective published data from adult and pediatric studies suggest that the vast majority of dental office visits result in some degree of risk for bacteremia, and the emphasis has therefore changed from a focus on specific dental procedures to a focus on gingival manipulation of any kind.[3]

The role of duration of bacteremia as a risk factor for IE is uncertain. Older guidelines and some pediatric bacteremia studies reported positive blood cultures for only short periods (10–15 minutes) after tooth extraction(s),[56,67] but the vast majority of studies did not include blood draws beyond that time frame. A study of teenagers and adults demonstrated that blood cultures can remain positive for upwards of an hour after a dental procedure,[48] and a pediatric study reported that blood cultures can remain positive for >45 minutes.[46] The incidence of positive blood cultures drops sharply after the procedure such that the period of risk rarely exceeds 30 minutes.

A few studies report the magnitude of bacteremia in children after dental procedures,[43,44,47,49,56,57] often using cell lysis filtration or centrifugation rather than conventional broth-based methods. Cell lysis methods can be problematic, being time consuming, expensive, less sensitive for some oral bacterial species, and slower in detection, and having an increased risk of contamination. Results from different studies reflect the difficulty of determining magnitude, but the collective results suggest that the magnitude from dental procedures is low. Data from a large study of adults that used broth-based methods and molecular methodology for identification suggest that the magnitude of bacteremia resulting from toothbrushing and a dental extraction, opposite ends of the spectrum of gingival invasiveness, are both relatively low at $<10^4$ colony-forming units per milliliter of blood.[68]

The degree to which systemic antibiotic drugs reduce the incidence, duration, nature, or magnitude of bacteremia associated with dental procedures is controversial. Large, well-designed studies suggest that amoxicillin has a highly statistically significant impact on reducing the incidence and duration of bacteremia and changes the species identified after dental procedures in children.[45] It is not clear whether this antibiotic elimination of bacteria takes place in the gingival crevice or the bloodstream or whether it reduces the risk for IE.

Given the variability in outcomes from bacteremia studies and the mounting evidence that dental office procedures are at most a rare cause of IE, there has been a steady shift in the direction away from an emphasis on antibiotic prophylaxis and toward a focus on oral hygiene and diseases as far

Table 2. Bacteria Recovered From Blood After Dental Procedures* in Children

Abiotrophia[43]

Aggregatibacter actinomycetemcomitans[43]

Actinomyces[45,47,49,52,56,64]; *A georgiae*[46]; *A gerensceriae*[46]; *A israelii*[45,47]; *A iwolffii*[56]; *A lingnae*[46]; *A meyeri*[56]; *A meyeri/odontolyticus*[45]; *A naeslundii*[46,56]; *A neuii*[47]; *A odontolyticus*[45,46,48]; *A viscosus*[45,46,56]; *A urinae*[57]; *A viridans*[46]

Arthrobacter sp[47,56]

Bacillus[42]; *B licheniformis*[57]; *B megaterium*[57]; *B pumilus*[57]

Bacteroides[41,44,49,51,64,65]; *B capillosus*[40]; *B distasonis*[48]; *B fragilis*[48]

Bifidobacterium[45,48]

Brachybacterium spp[46]

Brevibacterium[50]

Capnocytophaga[49]

Cardiobacterium hominis[45]

Cellulomonas spp[47]

Corynebacterium[40–43,44–47,49,50,52,57,61,64]; *C hofmanii*[45,51]

Eikenella[45]

Enterobacter aerogenes[48]

Enterococcus faecalis[57]

Enterococcus gallinarum[48]

Eubacterium[45,61]; *E aerofaciens*[45,48]; *E lentum*[45]; *E ventriosum*[40]

Fusobacterium[49,61]; *F fusiforme*[45]; *F nucleatum*[45,48]; *F varium*[48]

Gemella[44,45,48,56,64]

Haemophilus[45,49]; *H parainfluenza*[40,42,44–46,48,50]

Lactobacillus[45,49,52,64]; *L acidophilus*[48]; *L brevis*[47]; *L casei*[56]; *L paracasei*[56]

Lactococcus cremoris[42,44]

Leuconostoc[53]

Listeria[42]; *L greyi*[47]

Micrococcus spp[40,42,45,50,52,56,57,64]

Micrococcus luteus[46]

Moraxella[42,44,45]; *M nonliquefaciens*[45]

Neisseria[41,42,44,45,51,52,57,64,65]; *N catarrhalis*[45]; *N cinerea*[47,48]; *N flava*[46]; *N lactamica*[48]; *N pharynges*[46]; *N polysaccharea*[53]; *N sicca/subflava*[48]

Pantoea agglomerans[46]

Pediococcus[50]

Peptostreptococcus[41,45,53,61]; *P asaccharolyticus*[45]; *P micros*[45,48,56]; *P prevotii*[45]

Prevotella[45]; *P acnes*[46]; *P corporis*[48]; *P melaninogenica*[45,50,61]

Propionibacterium[42,43,50,62]; *P acnes*[43,54]; *P jensenii*[38]

Rothia; *R dentocariosa*[44,54]; *R mucilaginosus*[44]

Saprophytic neisseria[43]

Staphylococcus; *S aureus*[42,44,52,53,57]; *S auricularis*[48]; *S capitis*[46–48,56,57]; *S cohnii*[46]; *S epidermidis*[40–42,44–48,51,53,56,57,61,64]; *S haemolyticus*[46–48]; *S hominis*[46,47,53,56]; *S pasteuri*[56]; *S saccharolyticus*[48]; *S saprophyticus*[46]; *S schleiferi*[46,48]; *S simulans*[47]; *S warneri*[46,47,56]

Stenotrophomonas maltophilia[56]

Streptococcus acidominimus[42,44,64]

Streptococcus capitis[51]

Streptococcus faecalis[40,57]

Streptococcus gordoni[56]

Streptococcus morbillorum[44,64]

Streptococcus peroris[46,56]

Streptococcus porcinus[57]

Streptococcus australis[46]

Viridans streptococci[40,41,51,60,61,65]

S anginosus group[42,43,45,49,53,64]; *S anginosus*[48,56]; *S constellatus*[45,46]; *S intermedius*[45,47,56,57]

S bovis group; *S bovis*[42,48,64]; *S gordonii*[46,52,57]

S mutans group; *S mutans*[42,44–46,48,51,53,54,56,57]; *S sobrinus*[47,56,64]

S mitis group; *S infantis*[44]; *S mitis*[42,44–48,51–53,56,57,64]; *S pneumoniae*[46,53]; *S oralis (S mitior, S sanguis II)*[40,44–47,49,52,57,64]

S sanguinis group; *S parasanguinis*[46,56]; *S sanguinis*[40,42,44–47,49,50,53,56,57,64]

S salivarius group[57]; *S salivarius*[45–48,52,53,56,57,64]; *S vestibularis*[47,52]

Veillonella[41,44,45,49,51,56,57,65]; *V alcalescens*[61]; *V dispar*[66]; *V parvula*[40,44,48]

*Dental procedures include dental extractions, restorations, dental hygiene (cleaning) procedures, toothbrushing, and other procedures.

more important risk factors for cases of IE that result from oral flora.[3,67,69]

Impact of Oral Disease and Hygiene Versus Dental Procedures on Bacteremia

AHA guidelines have long proposed that maintaining oral health may be important in the overall effort to prevent IE,[67,69] and there is increasing support from studies that report a frequent occurrence of bacteremia with toothbrushing (39%–46%).[42,55,68] It has also been suggested that chewing food may result in bacteremia, but there are no studies to confirm this in children.[70] Some studies reported no impact from oral hygiene or disease on bacteremia after dental procedures.[49,51,55] Other pediatric[41,44,54,60] and adult[66,68] studies of bacteremia after dental procedures support an association between various indices of oral hygiene and gingival and dental disease (caries) with the incidence of bacteremia from dental office-based procedures and from routine daily activities.

Virtually all dental office procedures have the potential to create a transient bacteremia. Because children are recommended to have dental cleaning procedures every 6 months, this suggests that office-based bacteremia may occur upwards of twice per year. Data from bacteremia studies strongly suggest that the incidence of bacteremia annually from toothbrushing and other daily activities far exceeds that of dental office procedures, perhaps by hundreds of times per year.[43,68] It is unknown whether frequency of bacteremia is more important than magnitude with regard to risk for IE, but current data support the importance of a focus on maintenance of good oral hygiene, prevention of gingival and dental disease, and access to routine dental care for children at risk for IE. Cases of IE from oral bacterial pathogens in children most likely result from exposure to relatively frequent, low-grade bacteremia from these activities of daily living.

Results of Clinical Studies of IE Prophylaxis for Dental Procedures

There has not been a prospective, randomized, placebo-controlled study of the efficacy of antibiotic prophylaxis to prevent IE in people whose risk is from dental procedures. The few published retrospective, epidemiological studies that relate to this question have had varied outcomes with respect to benefit from antibiotic prophylaxis. When an invasive procedure has occurred in close proximity to the onset of symptoms of IE, it cannot be determined that it caused IE, because there may have been episodes of bacteremia from natural causes in the same time frame.

In 2008, the National Institute for Health and Clinical Excellence (NICE) guidelines in the United Kingdom concluded that the use of antibiotic prophylaxis before any invasive procedures should cease, unless requested by the patient.[71] A subanalysis of data from a large, nationwide study in England[72] comparing the incidence and mortality from IE in 373 children <18 years old, both before and after the NICE guidelines, reported no change in the incidence of IE.[73] Although small in size, this subanalysis is the strongest study currently available concerning the efficacy of antibiotic prophylaxis for children, and it lends support to the position that antibiotic prophylaxis is ineffective and that it would be reasonable to shift the disproportionately large focus on antibiotic prophylaxis for dental procedures to oral hygiene and prevention of oral disease.

Recommendation

1. **It is reasonable to shift the disproportionately large focus on antibiotic prophylaxis to an emphasis on oral hygiene and prevention of oral disease *(Class IIa; Level of Evidence B)*.**

Diagnosis

Clinical Findings in Children and Adolescents

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 symptoms requires careful evaluation for IE in certain settings, such as in the patient with underlying heart disease. In contrast, 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. In these children, infection caused by *Streptococcus pneumoniae* or *S aureus* is likely.

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 are common (especially noted in the adult literature) and may produce symptoms associated with ischemia, hemorrhage, or both. In rare cases, central nervous system mycotic aneurysms can occur; their rupture can be catastrophic.

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. 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 asthma-like symptoms or signs related to septic pulmonary embolization

As described above, an increase in the population of children requiring a long-term central venous catheter (CVC) and of those with complex congenital heart defects and correspondingly complex surgical interventions requiring prosthetic materials has changed the epidemiology and microbiology of IE and impacted the diagnostic approach.

Duke Criteria

The modifications of the Duke criteria for diagnosis of IE[74–76] have been demonstrated to be helpful in diagnosing IE in children, although the number of patients in these studies has been small, and there have been questions of specificity (Tables 3 and 4).[9,77–79] The presence of a CVC may prolong a bacteremic state, thus requiring the removal of the CVC before criteria are met.[76] The incorporation into the modified Duke criteria of new molecular diagnostic methods on surgical specimens (eg, polymerase chain reaction [PCR]) has been proposed to help identify organisms in culture-negative IE.[80] Although the revised Duke criteria have been validated for the diagnosis of IE in children,[9] the emergence of *S aureus* as the most common pathogenesis has important implications. The Duke criteria identify *S aureus* bacteremia as a major criterion, regardless of whether the infection was nosocomial or community acquired or whether a primary source of infection was present or absent.[75] Another study[76] suggests that the presence of a CVC may skew the diagnosis of IE, because the attempt to salvage the catheter rather than remove it serves to prolong the bacteremic state and raises the question of whether *S aureus* bacteremia should be regarded as a major microbiological criteria only if cultures remain positive after removal of the CVC.

Laboratory Assessment

Microbiology: Blood Cultures

Blood cultures should be drawn for patients with fever of unexplained origin and a pathological heart murmur, a history of heart disease, or previous endocarditis. Because bacteremia in patients with IE usually is continuous and low grade, it does not matter whether cultures are obtained at any particular phase of the fever cycle. For children, it is ordinarily not practical to obtain the large volumes recommended for adults with suspected endocarditis. Lesser amounts (eg, 1–3 mL in infants and young children and 5–7 mL in older children) are optimal, depending on the blood culture detection system. Because IE is only rarely caused by anaerobic bacteria, emphasis is usually given to inoculating blood into bottles for aerobic incubation. It is reasonable to obtain 3 blood cultures by separate venipunctures on the first day, and if there is no growth by the second day of incubation, to obtain 2 or 3 more (Table 3). There is usually no value in obtaining >5 blood cultures over 2 days unless the patient has received antibiotic therapy within the past 2 weeks. In patients who are not acutely ill and whose blood cultures remain negative, withholding antibiotic drugs for 48 hours or longer while additional blood cultures are obtained may be considered, to determine the cause of IE.

In patients with acute IE who are severely ill and unstable, 3 separate venipunctures for blood cultures should be

Table 3. Definitions of Terms Used in Modified Duke Criteria for Diagnosis of IE

Major criteria
1. Positive blood culture for IE
   - A. Typical microorganism consistent with IE from ≥2 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. Microorganisms consistent with IE from persistently positive blood cultures, defined as:
     - (i) ≥2 Positive cultures of blood samples drawn >12 h apart
     - or
     - (ii) All of 3 or a majority of ≥4 blood cultures, irrespective of the timing
     - (iii) 1 Positive blood culture for *Coxiella burnetii* or antiphase-I immunoglobulin G antibody titer >1:800
2. Evidence of endocardial involvement
   - A. Positive echocardiogram (TEE recommended in prosthetic valves, rated at least possible IE by clinical criteria, or complicated IE; TTE as the first test in other patients) 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 ≥38.0°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

HACEK indicates *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; IE, infective endocarditis; IV, intravenous; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography.

*Includes nutritionally variant strains (*Abiotrophia* species). Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

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performed over a short period such as 1 to 2 hours (Table 3) and empirical antibiotic therapy initiated. Continuous-monitoring blood culture systems such as BACTEC (Becton, Dickinson and Co, Franklin Lakes, NJ) and newer molecular identification methods are more rapid and more sensitive than more conventional methods. If fastidious or unusual organisms are suspected, the director of the microbiology laboratory should be consulted for help in diagnosis. Culture of arterial blood is not useful because it does not increase yield.

Recommendations

1. **Blood cultures should be drawn for patients with fever of unexplained origin and a pathological heart murmur, a history of heart disease, or previous endocarditis *(Class I; Level of Evidence B)*.**
2. **It is reasonable to obtain 3 blood cultures by separate venipunctures on the first day, and if there is no growth by the second day of incubation, to obtain 2 or 3 more (Table 3) *(Class IIa; Level of Evidence B)*.**
3. **In patients who are not acutely ill and whose blood cultures remain negative, withholding antibiotic drugs for ≥48 hours while additional blood cultures are obtained may be considered to determine the cause of IE *(Class IIb; Level of Evidence C)*.**
4. **In patients with acute IE who are severely ill and unstable, 3 separate venipunctures for blood cultures should be performed over a short period such as 1 to 2 hours (Table 3) and empirical antibiotic therapy initiated *(Class I; Level of Evidence C)*.**
5. **If fastidious or unusual organisms are suspected, the director of the microbiology laboratory or a consultant in pediatric infectious diseases should be consulted for help in diagnosis and especially for guidance on molecular pathogen identification and when use of serological testing is likely to be beneficial *(Class I; Level of Evidence C)*.**
6. **Culture of arterial blood is not more useful than venipuncture because it does not increase yield over venous blood cultures, but it is acceptable if only arterial blood samples are able to be obtained *(Class III, No Benefit; Level of Evidence B)*.**

Pathogenic Agents Isolated From Blood Cultures

The very large majority of organisms that cause IE in children are Gram-positive cocci (Table 5), including VGS (eg, *Streptococcus sanguis*, *S mitis* group, *S mutans*), staphylococci (both *S aureus* and coagulase-negative staphylococci), β-hemolytic streptococci, and enterococci.[11,13,24,81] Enterococcal endocarditis is relatively less common in children than in adults. Less frequently, other organisms such as the HACEK group of organisms (HACEK indicates *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis, Eikenella corrodens*, and *Kingella* species) are implicated.

After the first year of life, VGS are generally the most frequently isolated organisms in patients with IE caused by underlying congenital heart disease. *S aureus* was the second most common cause of IE in children but is now the most common cause of IE in some series and is definitely the most common agent of acute (rapidly progressive) bacterial endocarditis. IE may be caused by organisms that are dependent on l-cysteine or pyridoxal for growth, previously referred to as the "nutritionally variant streptococci" (*Abiotrophia*

Table 4. Duke Clinical Criteria for Diagnosis of IE

Definite IE
Pathological criteria
Microorganisms: demonstrated by culture or histology in a vegetation, a vegetation that has embolized, or an intracardiac abscess
or
Pathological lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis
Clinical criteria as defined in Table 2
2 Major criteria
or
1 Major criterion and 3 minor criteria
or
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
or
Resolution of manifestations of endocarditis with antibiotic therapy for ≤4 d
or
No pathological evidence of IE at surgery or autopsy, after antibiotic therapy for ≤4 d

IE indicates infective endocarditis.

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and *Granulicatella* species). The laboratory must subculture positive blood culture bottles on special media supplemented with l-cysteine or pyridoxal phosphate to isolate these organisms. VGS, *Abiotrophia* or *Granulicatella species*, or enterococci are most associated with native valve endocarditis and endocarditis occurring >60 days after cardiac surgery. IE produced by these organisms usually is subacute in presentation.

IE associated with indwelling vascular catheters, prosthetic material, and prosthetic valves frequently is caused by *S aureus* or coagulase-negative staphylococci. These organisms often are implanted at the time of surgery, and infection manifests within 60 days after cardiac surgery, but coagulase-negative staphylococci infection may present as late as ≥1 years after surgery. Among newborn infants, *S aureus*, coagulase-negative staphylococci, and *Candida* species are the most common causes of IE.[9,13] Less frequently, group B *Streptococcus,* enteric Gram-negative rod species, and *S pneumoniae* cause IE in this population. Although catheter-related bacteremias caused by Gram-negative bacilli occur relatively frequently in pediatric patients in intensive care units, IE rarely is caused by these organisms. The rarity of IE caused by Gram-negative bacilli likely is attributable to poor adhesion of Gram-negative bacilli to cardiac valves. Pediatric patients who inject drugs intravenously are at risk for IE, especially caused by *S aureus.*

Fungal endocarditis in children usually is caused by *Candida* species, especially *C albicans*, although *Aspergillus* endocarditis also occurs. With the use of CVC in infants and children and infusions with high glucose concentrations and hyperalimentation, *Candida* infections of the mural or valvular endocardium in infants have occasionally been recognized. Fungal endocarditis is often associated with very large friable vegetations; emboli from these vegetations frequently produce serious complications.

Culture-Negative Endocarditis

A diagnosis of culture-negative endocarditis (CNE) is made when a patient has clinical or echocardiographic evidence of IE but persistently negative blood cultures. In most centers in the United States, the prevalence of CNE approximates 5% of IE cases in adults and children. However, in more recently published series, CNE was diagnosed in 8% to 36% of patients clinically diagnosed with endocarditis with persistently negative blood cultures.[79,84,85] The most common causes of CNE are current or recent antibiotic therapy or infection caused by a fastidious organism such as *Abiotrophia* and *Granulicatella* species or an HACEK organism that grows poorly in vitro. Diagnosis of fungal IE is limited by lower sensitivity of blood cultures for yeast and virtually no sensitivity for filamentous fungi. Right-sided endocarditis, in which organisms are filtered by the lungs, and marantic endocarditis (a noninfectious condition and a synonym for NBTE) are also more difficult to confirm by blood culture.

Other less common organisms such as *Bartonella* species, *Tropheryma whipplei, Coxiella burnetii* (Q fever), and *Brucella* species may cause CNE. *Legionella pneumophila* and *Mycoplasma* species occasionally cause CNE, but the role of *Chlamydia* (now *Chlamydophila*) species remains unclear.[86,87] Although there is less emphasis on requesting extended incubation of cultures than there was in the past, positive results may be missed unless blood cultures are held for extended (≥14 days) incubation and, in some cases, special culture methodologies that are not performed routinely are included. At times, the microbiological diagnosis can only be made by molecular confirmation of material removed at the time of surgery, including vegetations, thrombi, emboli, or valves.

Frequently, patients have recently received or are currently receiving antibiotic therapy. In those patients who have received <4 days of antibiotic drugs, cessation of treatment can be useful in providing a culture diagnosis after a few days. Consultation with an infectious diseases expert and with all care providers can be beneficial in making such a decision. Rates of cardiovascular surgery in the management of patients with IE have been increasing, and this may offer secondary benefits in providing material for diagnosis.

Members of the writing committee stressed the importance of consultation with the microbiology laboratory in all cases of CNE to optimize the chance of identification of the causative microorganism. Molecular techniques to identify 16S ribosomal RNA or DNA from tissue or PCR to detect DNA in blood specimens have identified agents of CNE on occasion[88]; however, molecular methods to diagnose CNE remain suboptimal when applied to detection in blood.[89] Commercial nucleic acid amplification tests (NAATs) do not currently target HACEK group organisms, *Mycoplasma* species, or zoonotic pathogens.[90] Serological methods are often used to diagnose *Bartonella* species*, T whipplei, C burnetii,*

Table 5. Principal Pathogenic Bacterial Agents

Organism	Series			
	Johnson et al[81] (n=149)	Martin et al[11] (n=76)	Stockheim et al[13] (n=111)	Day et al[24] (n=632)
Years reviewed	1933–1972	1958–1992	1978–1996	2000–2003
Viridans group streptococci	43	38	32	20
Staphylococcus aureus	33	32	27	57
Coagulase-negative staphylococci	2	4	12	14
Streptococcus pneumoniae	3	4	7	1
HACEK	N/A	5	4	N/A
Enterococcus species	N/A	7	4	N/A
Culture negative	6	7	5	N/A

Values indicate percentage of patients in the series.

HACEK indicates *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; and N/A, not applicable.

Brucella species, and *Mycoplasma* species.[89] Urinary antigen tests are available for *L pneumophila* serogroup 1. When one examines surgical materials (vegetations, valves, grafts) for potential bacterial or fungal pathogens, it is important to note that conventional culture techniques yield very high rates of false-positive results (13%–55%) compared with prior blood cultures or NAAT-based testing of surgical materials.[91,92] It is best that culture-based methods be supplemented by molecular methods or histological examination of tissues for greater specificity.[89] Histology of surgical materials contributes a major criterion to the Duke classification scheme and remains positive for months after antibiotic drugs are started.[93] NAAT-based testing of surgical materials is more sensitive than culture testing but may still yield false-positive results, and this is particularly obvious when multiple agents are identified.[94] NAAT-based testing of surgical materials may also detect organisms associated with previous episodes of IE that were treated up to 12 years before surgery and are unrelated to the current episode.[95,96] There is little loss of sensitivity by NAAT when surgical specimens are obtained within 5 days of initiation of antibiotic therapy; treatment for several weeks before surgery will increase the false-negative rate.[93,97] Investigational approaches to the pathogenesis of CNE include tissue-culture based growth for propagation of intracellular pathogens and autoimmunohistochemistry on surgical specimens.[89] In fact, it has been proposed that molecular techniques be added to the pathological criteria of the Duke classification scheme.[88]

(Treatment of CNE is discussed later, in "Antibiotic Treatment," where recommendations for empirical antibiotic treatment of patients diagnosed with CNE are contained in Table 8. Epidemiological clues that may help in narrowing empirical antibiotic coverage for patients diagnosed with CNE are contained in Table 9.)

Recommendations

1. **When pediatric patients have suspected endocarditis and have been treated with antibiotic drugs <4 days but have not had a prior blood culture, cessation of antibiotic drugs can be useful to clarify the pathogen's identity *(Class IIa; Level of Evidence C)* and may be considered if the patient is clinically stable *(Class IIb; Level of Evidence C)*. In such cases, consultation with the infectious disease specialist should be obtained.**
2. **Consultation with the director of the microbiology laboratory or an infectious diseases expert in all cases of CNE is recommended to optimize the chance of identification of the causative microorganism *(Class I; Level of Evidence C)*.**

Other Microbiological Tests

Testing for antimicrobial susceptibility with determination of the minimum inhibitory concentration (MIC) of the antibiotic for the organism is recommended in choosing the optimal therapy for IE. Although not routinely recommended, determination of the minimum bactericidal concentration of the antimicrobial agent chosen for treatment against the infecting organism may be considered in selected circumstances, such as with atypical organisms, organisms resistant to first-line antibiotic drugs, and unexplained failure to control bacteremia. Synergy studies, with a β-lactam agent and an aminoglycoside, although not always available and somewhat controversial, may be reasonable in determining optimal therapy of enterococcal or penicillin-nonsusceptible streptococcal IE. However, existence of an isolate resistant to a high level of aminoglycosides indicates a lack of potential for synergy.

Recommendations

1. **Testing for antimicrobial susceptibility with determination of the MIC of the antibiotic drug for the organism is recommended in choosing the optimal therapy for IE *(Class I; Level of Evidence B)*.**
2. **Although not routinely recommended, determination of the minimum bactericidal concentration of the antimicrobial agent chosen for treatment against the infecting organism may be considered in selected circumstances, such as with atypical organisms, organisms resistant to first-line antibiotic drugs, and unexplained failure to control bacteremia *(Class IIb; Level of Evidence C)*.**

3. **Synergy studies, with a β-lactam agent and an aminoglycoside, although not always available and somewhat controversial, may be reasonable in determining optimal therapy of enterococcal or penicillin-nonsusceptible streptococcal IE *(Class IIb; Level of Evidence C)*.**

Other Supportive 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. Chronic low-grade hemolysis also may be caused by 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. Acute IE is likely to manifest leukocytosis. Thrombocytopenia can occur, particularly in neonates with IE. Hypergammaglobulinemia and elevated acute-phase reactants (eg, erythrocyte sedimentation rate and C-reactive protein) are present in a large proportion of patients. Hematuria may occur and be accompanied by red blood cell casts, proteinuria, and renal insufficiency in patients who develop immune complex glomerulonephritis, but this is less common in children than adults. In patients with immune complexes, there may also be hypocomplementemia. Rheumatoid factor is present in a substantial proportion of IE patients whose duration of illness is >6 weeks. Other supportive and useful tests include the ECG, which can indicate the presence of complicating rhythm disorders such as ventricular ectopy and conduction disorders such as complete heart block. The presence of either of these findings, and in particular heart block, may signal a serious or even life-threatening IE complication.

Echocardiography

The standard diagnostic method for identifying the intracardiac manifestations of IE is 2-dimensional echocardiography although neither sensitivity nor specificity is 100%. Unlike the situation in adults, transthoracic echocardiography (TTE) is usually sufficient for children (especially if they weigh <60 kg) to fully understand cardiovascular findings in definite or presumptive IE. However, transesophageal echocardiography (TEE) is superior to TTE in diagnosing paravalvular leakage or dehiscence; left ventricular outflow tract complications, including root abscesses; involvement of the sinuses of Valsalva; and prosthetic valve endocarditis, even in children.[98] TEE is reasonable to consider for infants and children in whom TTE views may be limited. This includes those who have had chest wall disruptions from previous surgery or from trauma, who have had placement of intracardiac prosthetic material, or who have congenital or acquired anomalies of the thoracic cage. Although information in pediatric patients is not well developed, data from series in adult patients suggest that intracardiac echocardiography (ICE) may also be useful in selected circumstances such as potential pacemaker-lead infections and post–percutaneous prosthetic valve implantations. Patients with chronic lung disease of various pathogeneses may also have limited acoustic windows via TTE, which would make TEE the preferred approach. Narducci et al[99] recently reviewed their experience with the use of ICE in the diagnosis of IE involving implantable electronic devices (pacemakers and leads). Limited data confirm the utility of ICE as a diagnostic tool in such cases and perhaps its superiority as a diagnostic tool for this clinical circumstance. ICE added incremental value to TEE and other methodologies in selected situations,[101] particularly in patients with a probable diagnosis of IE based on the Duke criteria but in whom the TEE was negative.[100] To date, these data have not been replicated specifically in a pediatric series, although at least 1 case report has been published advocating ICE superiority in a pediatric case of pacemaker-related IE.[101] ICE has not been demonstrated thus far to be of additional value in the diagnosis of shunt-related IE in childhood. For this condition, definitive studies demonstrating enhanced accuracy for any particular modality are needed.

Echocardiography is particularly important for serial studies in a patient with known or suspected IE. Not only is objective documentation of progressive changes in cardiac function crucial, but identification of other important complications of IE by echocardiography can have direct bearing on decision making with regard to early surgical intervention, which can be critical for successful outcome.[102] The limited capacity of TTE to detect complications of IE in adults,[103] particularly in those with prosthetic valves, has been confirmed. Although TTE has been shown to effectively detect endocarditis in young children (up to 97% sensitivity), for those >10 years of age and weighing >60 kg, the TEE, as in adults, has been shown to be a more sensitive tool.[104]

Although there is limited experience with TTE for detecting aortic root abscesses, which can complicate native or prosthetic aortic valve IE in pediatric patients, it can be useful to perform TEE in patients who are at high risk for this complication.

Recommendations

1. **TEE is recommended for infants and children who had chest wall disruptions from previous surgery or from trauma or who have congenital anomalies involving the thoracic cage *(Class I; Level of Evidence B)*.**
2. **It can be useful to perform TEE in pediatric patients who are at high risk for aortic root abscesses, which can complicate native or prosthetic aortic valve IE *(Class IIa; Level of Evidence C)*.**

Antimicrobial Treatment

The principles of treatment of pediatric endocarditis are similar to those for treatment of adult endocarditis.[2] In patients who are not severely ill and whose blood cultures are still negative, or whose cultures may be positive for organisms that are frequently contaminants, it is reasonable to withhold antibiotic drugs for ≥48 hours while additional blood cultures are obtained. A prolonged course of therapy (at least 2 weeks and often 4–8 weeks; Table 6) has been the recommended practice for several reasons. Organisms are embedded within the fibrin-platelet matrix and exist in very high concentrations with relatively low rates of bacterial metabolism and cell division, which results in decreased susceptibility to β-lactam and other cell wall–active antibiotic drugs.[105,106]

Bactericidal rather than bacteriostatic antibiotic drugs should be chosen whenever possible. This recommendation is based on past reports of treatment failures and relapses when only bacteriostatic antibiotic drugs were given. In infants and children, one should use intravenous antibiotic drugs rather than intramuscular agents because of the patients' small muscle mass. Outpatient (home) intravenous treatment of endocarditis may 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 wellness, adherence to drug therapy, absence of complications (see Recommendations 4 and 5 for this section), and absence of drug toxicity are parts of the plan. Such a standard would reasonably include prompt (minutes to hours) access to medical and surgical care and cardiac follow-up should complications develop. All of the medications mentioned in the Tables in this publication are for the intravenous route of administration unless otherwise specified. An exception would be cases in which a drug is known to be 100% bioavailable when given orally, such as ciprofloxacin.

Bacteremia generally resolves within several days after appropriate therapy has begun. *S aureus* bacteremia, however, may persist for a longer time than streptococcal bacteremia, and it may be present for 3 to 5 days with β-lactam anti-staphylococcal therapy and for 5 to 10 days with vancomycin therapy. Additionally, IE caused by *S aureus* that is frequently associated with CVC and bacteremia may not be controlled until the catheter is removed. In a 2005 report, 12% of children with *S aureus* bacteremia were shown to have IE (using the modified Duke criteria[75]), and in 73% of those children with bacteremia, there was a central intravascular device and multiple positive blood cultures.[107] The repetition of blood cultures daily until they are sterile would allow assessment of the adequacy of treatment and document the cessation of bacteremia. Additional blood cultures performed after completion of antibiotic treatment may be considered, but this might result in isolation of a contaminant.[108]

Table 7 is modeled after guidelines that will be published by the AHA for treatment of IE in adults.[109] The dosages and, in some cases, the preferred antibiotic drugs are specific for children. Data on effectiveness of antibiotic drugs for IE in children generally come from reviews of experience. Because these are nonexperimental, there is a lack of useful information to compare different antibiotic regimens head-to-head; therefore, these and other recommendations in the literature are based on preferred practice in adults, qualitative interpretation of outcomes from pediatric reviews, and expert opinion from this committee.

Table 6. Length of Treatment of Infective Endocarditis*

Native valve highly susceptible streptococci	4 wk†
Native valve relatively resistant streptococci	4 wk
Prosthetic material, caused by viridans streptococci or *Streptococcus bovis*	6 wk
Native valve *Staphylococci*, susceptible to oxacillin	4–6 wk
Native valve *Staphylococci* resistant to oxacillin	6 wk
Prosthetic valve *Staphylococci*	At least 6 wk
Native or prosthetic valve enterococcus	4–6 wk
Native or prosthetic valve enterococcus treated with vancomycin	6 wk
Native or prosthetic valve HACEK endocarditis	4 wk
Native valve culture-negative endocarditis	4–6 wk
Prosthetic valve culture-negative endocarditis	6 wk
Enteric Gram-negative endocarditis	At least 6 wk

HACEK indicates *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species.

*These are approximate lengths of treatment for typical episodes of infective endocarditis. Patients with complicated episodes or recurrences may require additional treatment. Recommendations are the published consensus of expert reviewers.

†Two weeks may be adequate for some adult patients but is not recommended for children because of lack of effectiveness data.

Recommendations

1. **In patients who are not severely ill (do not have respiratory or hemodynamic compromise or change in mental status) and whose blood cultures remain negative or whose cultures may be positive for organisms that are frequently contaminants, it is reasonable to withhold antibiotic drugs for ≥48 hours while additional blood cultures are obtained *(Class IIa; Level of Evidence C)*.**
2. **A prolonged course of therapy (at least 4 weeks and often 6–8 weeks; Table 6) has been the recommended practice *(Class I; Level of Evidence B)*.**
3. **Bactericidal rather than bacteriostatic antibiotic drugs should be chosen whenever possible *(Class I; Level of Evidence A)*. This recommendation is based on past reports of treatment failures and relapses when only bacteriostatic antibiotic drugs were given.**
4. **In infants and children, one should use intravenous antibiotic drugs rather than intramuscular agents. The patients' small muscle mass is one reason *(Class I; Level of Evidence C)*. Outpatient (home) intravenous treatment of endocarditis may 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 (ie, not of young age and do not have a fungal pathogen) *(Class IIb; Level of Evidence C)*.**
5. **Patient and parent adherence to the medical plan is important. Frequent home monitoring by a home health nurse who assesses wellness, adherence to drug therapy, absence of complications, and absence of drug toxicity is part of the plan. It is reasonable that such a standard would include prompt (minutes to hours) access to medical and surgical care and cardiac follow-up should complications develop *(Class IIa; Level of Evidence C)*.**
6. **Additional blood cultures performed after completion of antibiotic treatment may be considered but might also result in isolation of a contaminant *(Class***

Table 7. Recommended Antibiotic Treatments for Pediatric Infective Endocarditis*

Organism/Condition	Recommended Antibiotic Drug/Daily Antibiotic Dose†	Alternative Antibiotic Drug Choice
Unknown agent (initial empirical therapy or culture-negative endocarditis, generally after at least 48 h of attempting to culture the causative organism except in severely ill children)		
Native valve (community acquired) or "late" prosthetic valve (>1 y after surgery) infection	Ampicillin/sulbactam plus gentamicin	Vancomycin (plus gentamicin)
	With or without vancomycin	
	For prosthetic valve endocarditis, add rifampin	
	Ampicillin-sulbactam 200–300 mg·kg^{-1}·d^{-1} IV divided every 4–6 h up to 12 g daily	Vancomycin 60 mg·kg^{-1}·d^{-1} IV divided every 6 h up to 2 g
	Gentamicin 3–6 mg·kg^{-1}·d^{-1} IV divided every 8 h. Adults: 3–5 mg·kg^{-1}·d^{-1}	Gentamicin 3–6 mg·kg^{-1}·d^{-1} IV divided every 8 h. Adults: 3–5 mg·kg^{-1}·d^{-1}
	Rifampin 15–20 mg·kg^{-1}·d^{-1} divided every 12 h up to 600 mg	
	Vancomycin 60 mg·kg^{-1}·d^{-1} IV every 6 h up to 2 g	
Nosocomial endocarditis associated with vascular cannulae or "early" prosthetic valve endocarditis (≤1 y after surgery)	Vancomycin plus gentamicin (± rifampin if prosthetic material present)	?
	Plus cefepime or ceftazidime†	
	Vancomycin 60 mg·kg^{-1}·d^{-1} IV divided every 6 h up to 2 g	
	Gentamicin 3–6 mg·kg^{-1}·d^{-1} IV divided every 8 h Adults: 3–5 mg·kg^{-1}·d^{-1}	
	Rifampin 20 mg·kg^{-1}·d^{-1} divided every 8 h up to 900 mg/d	
	Cefepime 100-150 mg·kg^{-1}·d^{-1} divided every 8–12 h up to 6 g/d	
	Ceftazidime 100–150 mg·kg^{-1}·d^{-1} IV divided every 8 h up to 2–4 g daily‡	
Streptococci		
Highly susceptible to penicillin G (MBC ≤0.1 μg/mL); includes most viridans streptococci, groups A, B, C, G nonenterococcal, group D streptococci (*S bovis*, *S equinus*)	Penicillin G or ceftriaxone	Vancomycin or first-generation cephalosporin or ceftriaxone
	Penicillin G 200 000–300 000 U·kg^{-1}·d^{-1} IV divided every 4 h up to 12–24 million U daily	Vancomycin 40 mg·kg^{-1}·d^{-1} IV divided every 8–12 h up to 2 g daily
	Ceftriaxone 100 mg·kg^{-1}·d^{-1} IV divided every 12 h or 80 mg·kg^{-1}·d^{-1} IV every 24 h up to 4 g daily (if over 2 g, divide BID)	Cefazolin 100 mg·kg^{-1}·d^{-1} IV divided every 8 h up to 12 g daily
		Ceftriaxone 100 mg·kg^{-1}·d^{-1} IV divided every 12 h or 80 mg·kg^{-1}·d^{-1} IV every 24 h up to 4 g daily
Relatively resistant to penicillin (MBC ≥0.2 μg/mL; includes enterococci and less-susceptible viridans streptococci)	Penicillin G (or ampicillin) plus gentamicin (for first 2 wk, or whole course for enterococci)	Vancomycin plus gentamicin for enterococci
	Penicillin G 200 000–300 000 U·kg^{-1}·d^{-1} IV divided every 4 h up to 12–24 million U daily	Ampicillin plus ceftriaxone (for aminoglycoside-resistant enterococci or aminoglycoside-intolerant patient)
	Ampicillin 200–300 mg·kg^{-1}·d^{-1} IV divided every 4–6 h up to 12 g daily	Ceftriaxone plus gentamicin (not for enterococcal endocarditis)
	Gentamicin 3–6 mg·kg^{-1}·d^{-1} IV divided every 8 h. Adults: 3–5 mg·kg^{-1}·d^{-1}	Vancomycin 40 mg·kg^{-1}·d^{-1} IV divided every 8–12 h up to 2 g daily
		Gentamicin 3–6 mg·kg^{-1}·d^{-1} IV divided every 8 h. Adults: 3–5 mg·kg^{-1}·d^{-1}
		Ceftriaxone 100 mg·kg^{-1}·d^{-1} IV divided every 12 h or 80 mg·kg^{-1}·d^{-1} IV every 24 h up to 4 g daily
		Ampicillin 200–300 mg·kg^{-1}·d^{-1} IV divided every 4–6 h up to 12 g daily
Staphylococci (*S aureus* or coagulase-negative staphylococci)		
Susceptible to ≤1 μg/mL penicillin G (rare)	Penicillin G	Oxacillin or nafcillin or first-generation cephalosporin or vancomycin
	Penicillin G 200 000–300 000 U·kg^{-1}·d^{-1} IV divided every 4 h up to 12–24 million U daily	Oxacillin or nafcillin 200 mg·kg^{-1}·d^{-1} IV divided every 4–6 h up to 12 g/d
		Cefazolin 100 mg·kg^{-1}·d^{-1} IV divided every 8 h up to 12 g daily
		Vancomycin 40 mg·kg^{-1}·d^{-1} IV divided every 8–12 h up to 2 g daily

(*Continued*)

Table 7. Continued

Organism/Condition	Recommended Antibiotic Drug/Daily Antibiotic Dose†	Alternative Antibiotic Drug Choice
Resistant to 0.1 μg/mL penicillin G	Penicillinase-resistant penicillin (oxacillin or nafcillin) ± gentamicin × 3–5 d	Vancomycin or a first-generation cephalosporin
	Oxacillin or nafcillin 200 mg·kg^{-1}·d^{-1} IV divided every 4–6 h up to 12 g/d	Cefazolin 100 mg·kg^{-1}·d^{-1} IV divided every 8 h up to 12 g daily
	Gentamicin 3–6 mg·kg^{-1}·d^{-1} IV divided every 8 h. Adults: 3–5 mg/kg	Vancomycin 40 mg·kg^{-1}·d^{-1} IV divided every 8–12 h up to 2 g daily for those highly allergic to β-lactam antibiotic drugs
Resistant to 4 μg/mL oxacillin (MRSA)	Vancomycin	Daptomycin for right-sided endocarditis, maybe for left-sided
	Vancomycin 40 mg·kg^{-1}·d^{-1} IV divided every 8–12 h up to 2 g daily	Daptomycin 6 mg/kg IV every 24 h; <6 y: 10 mg/kg
Vancomycin resistant or intolerant	Daptomycin	?
	Daptomycin 6 mg/kg IV every 24 h; <6 y: 10 mg/kg	
• For all staphylococci plus rifampin, plus gentamicin (for first 2 wk) if prosthetic material present		
Gram-negative enteric bacilli	Ceftazidime, cefepime, cefotaxime, or ceftriaxone plus gentamicin (or tobramycin or amikacin, depending on susceptibility)	A broad-spectrum penicillin plus gentamicin (or tobramycin or amikacin)
	Ceftazidime 100–150 mg·kg^{-1}·d^{-1} IV divided every 8 h up to 2–4 g daily‡	Piperacillin/tazobactam 240 mg·kg^{-1}·d^{-1} divided every 8 h up to 18 g daily
	Cefotaxime 200 mg·kg^{-1}·d^{-1} IV divided every 6 h up to 12 g daily	Gentamicin or tobramycin 3–6 mg·kg^{-1}·d^{-1} IV divided every 8 h. Adults: 3–5 mg·kg^{-1}·d^{-1}
	Ceftriaxone 100 mg·kg^{-1}·d^{-1} IV divided every 12 h or 80 mg·kg^{-1}·d^{-1} IV every 24 h up to 4 g daily	Amikacin 15 mg·kg^{-1}·d^{-1} IV divided every 8–12 h up to 15 mg·kg^{-1}·d^{-1}
	Gentamicin or tobramycin 3–6 mg·kg^{-1}·d^{-1} IV divided every 8 h. Adults: 3–5 mg·kg^{-1}·d^{-1}	
	Amikacin 15 mg·kg^{-1}·d^{-1} IV divided every 8–12 h up to 15 mg·kg^{-1}·d^{-1}	
HACEK group	Ceftriaxone or cefotaxime	Ampicillin (for susceptible organisms) plus aminoglycoside
	or	
	Ampicillin-sulbactam	Ampicillin 200–300 mg·kg^{-1}·d^{-1} IV divided every 4–6 h up to 12 g daily
	Cefotaxime 200 mg·kg^{-1}·d^{-1} IV divided every 6 h up to 12 g daily	Gentamicin or tobramycin 3–6 mg·kg^{-1}·d^{-1} IV divided every 8 h. Adults: 3–5 mg·kg^{-1}·d^{-1}
	Ceftriaxone 100 mg·kg^{-1}·d^{-1} IV divided every 12 h or 80 mg·kg^{-1}·d^{-1} IV every 24 h up to 4 g daily	
	Ampicillin-sulbactam 200–300 mg·kg^{-1}·d^{-1} IV divided every 4–6 h up to 12 g daily	Amikacin 15 mg·kg^{-1}·d^{-1} IV divided every 8–12 h up to 15 mg·kg^{-1}·d^{-1}
Fungi *Candida* spp, *Aspergillus* spp	Surgical resection plus amphotericin B with or without flucytosine	Amphotericin B followed by imidazole (eg, fluconazole, itraconazole, voriconazole) suppression if surgery cannot be performed§
	Amphotericin B 1 mg·kg^{-1}·d^{-1} IV administered over 3–4 h	
	Flucytosine 150 mg·kg^{-1}·d^{-1} orally divided every 6 h	Amphotericin B 1 mg·kg^{-1}·d^{-1} IV administered over 3–4 h
	Amphotericin liposomal/lipid-associated (3 formulations) 3–5 mg·kg^{-1}·d^{-1} in a single dose daily	Amphotericin liposomal/lipid-associated 3–5 mg·kg^{-1}·d^{-1} in a single dose daily

BID indicates twice per day; HACEK, *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; IV, intravenously; MBC, minimum bactericidal concentration; and MRSA, methicillin-resistant *Staphylococcus aureus* (includes resistance to oxacillin, nafcillin, and cephalosporins).

Treatment is generally for 4 to 6 weeks. See Table 8. Longer therapy may be required for recurrent endocarditis, prosthetic valve endocarditis, endocarditis attributable to uncommon species.

*As discussed in the text, these recommendations are based on consensus of experts and not experimental comparative studies (*Class IIa; Level of Evidence C*).

†Doses for neonates and infants not included. For cases of infective endocarditis in infants, consult infectious diseases and pediatric clinical pharmacists with special expertise in neonatal and infant clinical pharmacology.

‡Maximum daily dose or adult dose should not be exceeded on a per kilogram basis when treating children.

§Possibly lifelong suppression if no surgery or relapse after surgery.

IIb; Level of Evidence C).[108] **Some members of the writing group questioned whether there is value in taking blood cultures after completion of treatment unless there is evidence of return of symptoms.**

Streptococcal IE on Native Cardiac Valves (No Prosthetic Material) or Prosthetic Material

Native Cardiac Valves

This has been the most common form of IE in children for decades; some recent reports show staphylococcal IE overtaking streptococci as the most common organism.[24,110,111] Penicillin-susceptible streptococci are those with an MIC of ≤0.1 μg of penicillin per milliliter. In patients with IE caused by penicillin-susceptible streptococci who are able to tolerate a β-lactam antibiotic, 2 therapeutic regimens are associated with high cure rates (Table 7) and include penicillin G and ceftriaxone.

A 4-week regimen of intravenous aqueous crystalline penicillin G (or ampicillin if penicillin G is unavailable) achieves a high cure rate.[112] This approach avoids aminoglycoside-containing regimens for children with impairment of renal function, concurrently administered nephrotoxic drugs, or eighth cranial nerve impairment. In adult patients, 4 weeks of therapy with ceftriaxone given once daily also is a recommended approach.[2] In adults, a 4-week course of ceftriaxone therapy has a bacteriologic cure rate of 98%,[113] but only limited and retrospective data on the use of ceftriaxone in the treatment of IE in children have been published. The advantage of using ceftriaxone is that children initially treated for IE in the hospital can be transitioned to home intravenous therapy with an antibiotic that only requires a single infusion daily. Although home treatment for part of the antibiotic course appears to be becoming a more frequently used option, this decision is reasonable but requires careful selection of the appropriate candidate based on family accommodations and access to home healthcare providers.[10,11,24]

A 2-week course of therapy with penicillin, ampicillin, or ceftriaxone combined with an aminoglycoside has become increasingly popular and results in bacteriologic cure rates of up to 98% in adults.[114] This regimen is commonly used for uncomplicated cases of native valve IE but is not recommended 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 not recommended by this committee for children because of lack of data, and it should be used with caution in people at increased risk for adverse events caused by aminoglycoside therapy, such as those with renal impairment or those taking other nephrotoxic drugs. In 1 study in adults,[115] 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, few studies detailing the use of this regimen for the treatment of streptococcal endocarditis in adults have been published. Several studies have demonstrated the safety and efficacy of once-daily dosing of gentamicin in children with infections other than endocarditis; however, no studies describing outcomes after the use of single daily dosing of gentamicin for the treatment of IE in children have been published.

Occasionally, IE may be caused by streptococci that are relatively resistant to penicillin (MIC between 0.1 and 0.5 μg/mL). In this situation, concern about the efficacy of penicillin alone is avoided by use of a treatment regimen of 4 weeks of penicillin, ampicillin, or ceftriaxone combined with gentamicin for the first 2 weeks. Patients with IE caused by *Abiotrophia*, *Granulicatella* species, or streptococci with an MIC of >0.5 μg of penicillin per milliliter should be treated with the antibiotic regimen listed for enterococci. For children who are unable to tolerate β-lactam antibiotic drugs, vancomycin is an effective substitute, and current practice includes the addition of gentamicin for a 4-week course (Table 7). Caution should be exercised by obtaining blood levels of vancomycin and gentamicin, as well as serum creatinine levels, weekly because of the possibility of nephrotoxicity with this combination.

S pneumoniae accounts for 3% to 5% of cases in children (Table 5). Because of the potential for multidrug resistance and the infrequency of the syndrome of pneumococcal IE, no optimal therapy has been established for this illness.[116–118] A review of pneumococcal endocarditis published in 2004 reported on 11 cases of pneumococcal IE over a 10-year period at 8 children's hospitals, and 10 of the 11 survived to the time of discharge.[119] All isolates were susceptible to ceftriaxone, and 9 were susceptible to penicillin. One was resistant to penicillin, and 1 demonstrated an intermediate susceptibility to penicillin. Therapy consisted of cefotaxime or ceftriaxone for 5 patients, cefotaxime plus vancomycin for 2, penicillin for 2, and clindamycin for 1, and 1 patient received many different antibiotic drugs. One patient died during cardiac surgery and had received vancomycin and cefotaxime for a pneumococcal isolate intermediately susceptible to penicillin. Generally, for penicillin-susceptible strains, penicillin with or without an aminoglycoside has been used. It was the consensus of the writing group that consultation with an infectious disease specialist should be considered for all children with IE but especially for IE caused by *S pneumoniae* that is not susceptible to penicillin.

Recommendations

1. **A 4-week regimen of intravenous aqueous crystalline penicillin G (or ampicillin if penicillin G is unavailable) achieves a high cure rate in those with highly penicillin-susceptible streptococcal IE.**[112] **This approach avoids aminoglycoside-containing regimens for children with impairment of renal function, concurrently administered nephrotoxic drugs, or eighth cranial nerve impairment. In adult patients, 4 weeks of therapy with ceftriaxone given once daily also is a recommended approach**[113] ***(Class I; Level of Evidence B).***
2. **Although home treatment for part of the antibiotic course appears to be becoming a more frequently used option, this decision is reasonable but requires careful selection of the appropriate candidate based on family accommodations and access to home healthcare providers *(Class IIa; Level of Evidence B).***

3. **Patients with IE caused by *Abiotrophia*, *Granulicatella* species, or streptococci with an MIC of >0.5 μg of penicillin per milliliter should be treated with the antibiotic regimen listed for enterococci *(Class I; Level of Evidence C)*. For children who are unable to tolerate β-lactam antibiotic drugs, vancomycin is an effective substitute, and current practice includes the addition of gentamicin for a 4-week course.**
4. **Obtaining blood concentrations of vancomycin and gentamicin, as well as renal function tests, weekly because of the possibility of nephrotoxicity with multiple nephrotoxic antibiotic drugs may be considered *(Class IIb; Level of Evidence C)*.**

Prosthetic Cardiac Valves or Other Prosthetic Material

In cases in which endocarditis occurs in the setting of prosthetic material and is caused by a penicillin-susceptible streptococcal strain, therapy is continued for 6 weeks with penicillin, ampicillin, or ceftriaxone combined with gentamicin for the first 2 weeks of therapy. In the case of infections caused by a strain with an MIC >0.1 μg of penicillin per milliliter or by *Abiotrophia* or *Granulicatella* species, a combination of penicillin, ampicillin, or ceftriaxone combined with gentamicin for 6 weeks is recommended. For patients unable to tolerate β-lactam therapy, vancomycin for 6 weeks is combined with gentamicin for the first 2 weeks of therapy. In β-lactam–intolerant patients with *Abiotrophia* infections, therapy consists of a combination of vancomycin and gentamicin for 6 weeks.

Recommendation

1. **In cases in which endocarditis occurs in the setting of prosthetic material and is caused by a penicillin-susceptible streptococcal strain, therapy is continued for 6 weeks with penicillin, ampicillin, or ceftriaxone combined with gentamicin for the first 2 weeks of therapy. In the case of infections caused by a strain with an MIC >0.1 μg of penicillin per milliliter or by *Abiotrophia* or *Granulicatella* species, a combination of penicillin, ampicillin, or ceftriaxone combined with gentamicin for 6 weeks is recommended *(Class I; Level of Evidence C)*.**

Enterococcal IE on Native Cardiac Valves or Prosthetic Material

Enterococcal endocarditis is relatively rare in children. Treatment is difficult because of the relative resistance of enterococci to penicillin and ampicillin (which are not bactericidal for enterococci) and their variable resistance to aminoglycosides and vancomycin.[120,121] The treatment regimen for native valve IE caused by susceptible strains should be a combination therapy of penicillin G or ampicillin together with gentamicin for 4 to 6 weeks, with a longer duration of therapy in cases involving prosthetic material.[2,120,122] For patients with infections caused by susceptible strains of enterococci who are unable to tolerate β-lactam therapy, experts recommend vancomycin combined with gentamicin for 6 weeks for native valve IE and for a minimum of 6 weeks for infection of prosthetic material.[2,122] In contrast to therapy for streptococcal IE [“Streptococcal IE on Native Cardiac Valves (No Prosthetic Material) or Prosthetic Material”], the length of treatment with an aminoglycoside is for the entire course of therapy, and in patients with normal renal function, with the aminoglycoside divided into 2 to 3 doses daily rather than given in a single daily dose. The emergence of high-level vancomycin, ampicillin, and aminoglycoside resistance in some enterococcal species has further complicated treatment choices. The combination of ampicillin plus ceftriaxone was reported to be effective for aminoglycoside nonsusceptible *Enterococcus faecalis* strains first in a report from Spain and recently confirmed in a multi-institutional observational report.[123,124] Enterococci are resistant to ceftriaxone and other cephalosporins, and these drugs used alone are not an option for treatment of enterococcal endocarditis. Vancomycin-resistant enterococci may cause IE, but there are too few reports in the literature to determine the most effective treatment. The antibiotic drugs linezolid and daptomycin have activity against vancomycin-resistant enterococci in vitro, and successful treatment of adults with vancomycin-resistant enterococci IE has been reported. The consensus of the writing group is that management of patients with enterococcal IE should always involve infectious disease consultation as the standard of care.

Recommendations

1. **The treatment regimen for native valve IE caused by susceptible strains of enterococcus should be a combination therapy of penicillin G or ampicillin together with gentamicin for 4 to 6 weeks, with a longer duration of therapy in cases involving prosthetic material *(Class I; Level of Evidence A [in adults])*.**
2. **The consensus of the writing group is that management of patients with enterococcal IE should always involve infectious disease consultation as the standard of care *(Class I; Level of Evidence C)*.**

Staphylococcal Endocarditis on Native Valves or Prosthetic Material

Native Valve IE

Staphylococci may be coagulase positive (*S aureus*) or coagulase negative (*S epidermidis* and various other species) and appear to have overtaken streptococci as the most common cause of IE in children in recent years.[24,110,111] This may be attributable in part to the proliferation of intravascular catheters, as well as the nonspecificity of the Duke criteria in children causing false-positive diagnoses. Almost all staphylococci are highly resistant to penicillin G and ampicillin.[125] For those few that are susceptible to penicillin, penicillin or ampicillin will be effective, assuming a highly qualified laboratory has performed antibiotic susceptibility tests. Staphylococci that are susceptible to β-lactamase–resistant penicillins are termed methicillin susceptible or MSSA and may be *S aureus* or coagulase-negative strains such as *S lugdunensis*, which is typically susceptible and acts similarly to *S aureus*. In some centers, *S aureus* resistant to β-lactamase–resistant penicillins are termed MRSA, or ORSA or NRSA to indicate that oxacillin and nafcillin are the available penicillinase-resistant

penicillins and methicillin is no longer available. The usually accepted current standard of care for methicillin-susceptible *S aureus* endocarditis involving a native valve or other native cardiac tissue includes a semisynthetic, β-lactamase–resistant penicillin (nafcillin or oxacillin) given intravenously for a minimum of 4 to 6 weeks, assuming there has been an appropriate microbiological and clinical response to therapy. The addition of gentamicin for the first 3 to 5 days is an option and may accelerate the killing of the staphylococci, but this concept is based on extrapolation from experimental models. In patients without a history of type 1 penicillin allergic reactions, a first-generation cephalosporin, for example, cefazolin, is an alternative (for 4–6 weeks), with or without gentamicin for the first 3 to 5 days.[2,122] For patients unable to tolerate β-lactam antibiotic drugs, vancomycin for a minimum of 6 weeks, with or without gentamicin for the first 3 to 5 days of therapy, is an alternative.

Some staphylococcal strains may be methicillin 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 are not considered to be useful in these patients. Patients with methicillin-resistant staphylococcal endocarditis may be treated with vancomycin for a minimum of 6 weeks, with or without gentamicin for the first 3 to 5 days of therapy. It is the consensus of the writing group that patients with *S aureus* endocarditis should be cared for in a medical facility with cardiothoracic surgery capabilities and infectious diseases consultation. As with other IE cases, decisions about outpatient therapy may be individualized on the basis of clinical impression of symptomatic recovery, cardiovascular stability, assessment of the family's ability to follow prescribed treatment, and availability of infrastructure for outpatient monitoring.

Recommendations

1. **We recommend the current standard of care for methicillin-susceptible *S aureus* endocarditis involving a native valve or other native cardiac tissue, which includes a semisynthetic, β-lactamase–resistant penicillin (nafcillin or oxacillin) given intravenously for a minimum of 4 to 6 weeks, assuming there has been an appropriate microbiological and clinical response to therapy *(Class I; Level of Evidence A)*.**
2. **The addition of gentamicin for the first 3 to 5 days may be considered and may accelerate the killing of the staphylococci, but this concept is based on extrapolation from experimental models. Addition of gentamicin increases the likelihood of renal and otic toxicity *(Class IIb; Level of Evidence C)*.**
3. **Treatment of patients with methicillin-resistant staphylococcal endocarditis with vancomycin for a minimum of 6 weeks, with or without gentamicin for the first 3 to 5 days, is recommended except when the organism is not susceptible to vancomycin *(Class I; Level of Evidence B)*.**
4. **Patients with *S aureus* endocarditis should be cared for in a medical facility with cardiothoracic surgery capabilities and infectious diseases consultation *(Class I; Level of Evidence C)*.**
5. **As with other IE cases, decisions concerning outpatient therapy may be considered and may be individualized on the basis of clinical impression of symptomatic recovery, cardiovascular stability, assessment of the family's ability to follow prescribed treatment, and availability of infrastructure for outpatient monitoring *(Class IIb; Level of Evidence C)*.**

Prosthetic Material IE

Staphylococcal endocarditis on a prosthetic cardiac valve or other cardiac prosthetic material is usually caused by coagulase-negative staphylococci that are methicillin resistant, especially if the endocarditis develops within 1 year after cardiac surgery.[126] (See details in Table 7 for treatment of methicillin-resistant and methicillin-susceptible staphylococcal endocarditis based on consensus of the writing group and experience in the treatment of adult IE.) Additional recommendations for the treatment of staphylococcal endocarditis on intracardiac prosthetic material are listed in the AHA statement on "Infective Endocarditis: Diagnosis, Antimicrobial Therapy, and Management of Complications."[2] Eradication of infection involving prosthetic material is considered difficult at best, even when prolonged optimal antibiotic treatment is used. Despite occasional reports of successful medical treatment, which requires long-term use of multiple antimicrobial agents, in most circumstances removal of the infected material is required to achieve a satisfactory outcome.[127] The antibiotic rifampin is included as an addition to other antibiotic drugs in the treatment of staphylococcal IE, especially when there is prosthetic material. Most staphylococcal strains are susceptible to rifampin, and in experimental systems, it has good tissue penetration.

The overall mortality rate associated with prosthetic valve endocarditis is relatively high but is highest for infections caused by *S aureus*.[128] Although 1 study reporting cases from the 1970s showed that many cases of pediatric IE with patches or prostheses could be treated successfully with medical management alone, surgical management is generally necessary.[129]

Moreover, prosthetic valve infection caused by *S aureus* has been shown to be an independent risk factor for death.[130,131] Many authorities have concluded that valve replacement surgery is preferable in most if not all patients with prosthetic valve infection caused by *S aureus*. Decisions regarding transition to outpatient care in cases of prosthetic valve endocarditis should be individualized and should be made in consultation with pediatric infectious diseases consultants, taking into consideration the elements discussed at the end of "Staphylococcal Endocarditis on Native Valves or Prosthetic Material."

Recommendation

1. **Valve replacement surgery may be considered and is preferable in most if not all patients with prosthetic valve infection caused by *S aureus* *(Class IIb; Level of Evidence C)*.**

Gram-Negative IE (Including HACEK Species)

The Gram-negative bacteria that most often cause IE in children are the HACEK group of fastidious coccobacilli. The consensus of experts recommending 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.[2]

Other Gram-negative bacteria, such as *Escherichia coli*, *Pseudomonas aeruginosa*, or *Serratia marcescens*, are rare causes of IE. Few data are available to determine a single best antimicrobial agent, and thus, treatment is individualized according to the judgment of the expert consultant and guided by identification of the organism and antimicrobial susceptibility testing. Because these IE cases may be nosocomially acquired, the strains may have unpredictable antimicrobial susceptibilities and may be highly resistant to antimicrobial agents, having many different antibiotic resistance elements, including extended-spectrum β-lactamases. Most infectious disease specialists recommend an extended-spectrum penicillin (eg, piperacillin/tazobactam) or an extended-spectrum cephalosporin (eg, ceftazidime, ceftriaxone, or cefotaxime) together with an aminoglycoside[132] for a minimum of 6 weeks of therapy. There are few data on the use of quinolones for treatment of endocarditis in children, but such therapy has been successful in series of adults with IE. Limited data are available describing treatment of IE caused by Gram-negative pathogens with multidrug resistance (eg, extended-spectrum β-lactamase production).

Recommendations

1. **Therapy for IE caused by the HACEK group should be a 4-week course of ceftriaxone or another third-generation cephalosporin alone, or ampicillin plus gentamicin *(Class I; Level of Evidence C)*.**
2. **For IE caused by other Gram-negative species, we recommend an extended-spectrum penicillin (eg, piperacillin/tazobactam) or an extended-spectrum cephalosporin (eg, ceftazidime, ceftriaxone, or cefotaxime) together with an aminoglycoside,[132] with choice guided by antibiotic susceptibility of the isolate and input from an infectious diseases consultant for a minimum of 6 weeks of therapy *(Class I; Level of Evidence C)*.**

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. Early consultation with infectious disease, cardiology, and cardiac surgery services is recommended for these patients.

Amphotericin B has been the first-line antifungal agent for medical therapy, although it does not penetrate vegetations well. Although the imidazoles (eg, fluconazole) do not have proven efficacy in human fungal IE, long-term suppressive therapy with these agents has been recommended by experts for patients with infections caused by susceptible organisms who are not able to undergo curative surgery.[133,134]

The addition of 5-fluorocytosine (5-FC; 100–150 mg/kg per day, divided every 6 hours) to amphotericin B given by mouth for *Candida* endocarditis caused by strains susceptible to 5-FC may provide additional benefit. Monitoring blood levels of 5-FC will minimize toxicity associated with this agent. The rationale is that the 2 drugs may act synergistically and potentiate fungal killing. The use of liposomal forms of amphotericin B is an alternative for patients with moderate to severe renal impairment or those with unacceptable infusion-related toxicities. In some centers, fluconazole or liposomal forms of amphotericin have been used successfully for native valve fungal endocarditis.

Recommendations

1. **For most patients with fungal IE, surgery in conjunction with antifungal agents is required. Early consultation with infectious disease, cardiology, and cardiac surgery services is recommended for these patients *(Class I; Level of Evidence C)*.**
2. **The addition of 5-FC (100–150 mg/kg per day, divided every 6 hours) to amphotericin B given by mouth for *Candida* endocarditis caused by strains susceptible to 5-FC may be considered to provide additional benefit *(Class IIb; Level of Evidence C)*.**

Monitoring of Antibiotic Blood Levels (for Children Beyond the Neonatal Period)

When gentamicin is used for synergy, a reasonable dose is 3 to 6 mg/kg per day in children and is adjusted for a target peak blood concentration of 3 to 4 μg/mL and a trough of <1 μg/mL. A dose of up to 7.5 mg/kg per day may be required for treatment of Gram-negative rod isolates, with peak blood levels of 5 to 10 μg/mL and troughs of <1 to 1.5 μg/mL. The daily dose is divided into 3 doses and given every 8 hours. Currently, there is insufficient clinical experience for treatment of pediatric IE with single daily dosing. For vancomycin, a starting dose for children is 40 to 60 mg/kg per day, and only trough concentrations are used for monitoring. The target trough blood level is usually 10 to 15 μg/mL, although a higher blood level, 15 to 20 μg/mL, may be required to treat methicillin/oxacillin/nafcillin-resistant staphylococci with a vancomycin MIC of >1 μg/mL or when there is a lack of microbiological response. Children with renal failure require dosage adjustments, and in these cases, guidance from pharmacists, infectious diseases, or renal diseases consultants is recommended.

Recommendations

1. **When gentamicin is used for synergy, it is reasonable to give a dose of 3 to 6 mg/kg per day (divided as an every 8-hour regimen) in children, adjusted for a target peak blood concentration of 3 to 4 μg/mL and a trough of <1 μg/mL *(Class IIa; Level of Evidence B)*.**

2. **Currently, there is insufficient clinical experience for treatment of pediatric IE with single daily dosing (of gentamicin) *(Class III; Level of Evidence C)*.**
3. **Children with renal failure require dosage adjustments, and in these cases, guidance from pharmacists, infectious disease specialists, or renal diseases consultants is recommended *(Class I; Level of Evidence B)*.**

Culture-Negative Endocarditis

The causes of CNE are discussed in "Laboratory Assessment." All cases of CNE are considered management conundrums for at least 2 reasons. First, empirical therapy is necessary, and thus, the antimicrobial regimen selected for administration may not provide adequate coverage for the undefined pathogen. Second, empirical therapy could cause harm secondary to drug adverse events. A worst case scenario could develop in which the empirical regimen would result in clinical worsening and drug toxicity would develop because of an antimicrobial agent that would not have been used if the pathogen had been defined. For these reasons, and with the information that antibiotic treatment is the main cause of CNE, the writing committee deemed it reasonable to obtain the proper number of cultures before antibiotic drugs are started or to stop antibiotic drugs that were started fewer than 4 days earlier.

Empirical treatment regimens are devised only after important epidemiological factors are considered, including the pivotal issue as to whether or not there has been recent antimicrobial exposure before obtaining blood cultures. Other key factors that are included in such a decision are the following: what specific antimicrobial agent was given (if there was prior antimicrobial exposure); determination of the route of acquisition of microbes; whether the infection was community acquired, nosocomial, or non-nosocomial health care associated; what environmental exposures there had been (including injection drug use; Table 9); type of valve infected (whether native or prosthetic) and, if prosthetic, how long it had been implanted; and the clinical course of infection, whether acute, subacute, or chronic.

Specific empirical regimens that are considered for use in patients with CNE are listed in Table 8. Because of the major limitations related to administration of therapy that is not specifically pathogen directed, it was the consensus of the writing group that infectious diseases consultation should be obtained in each case of CNE. An infectious diseases consultant will review any adverse events related to prior receipt of any drug, types of adverse events, whether there is residual organ damage related to these events or that caused by underlying medical or surgical conditions, and the potential for clinically important drug interactions with agents other than antimicrobial agents.

Recognition of the common causes of IE in specific clinical presentations is pivotal (Table 9). For example, in cases of native valve infection acquired in the community with a subacute clinical course, VGS, HACEK organisms, or, less likely, *Enterococcus* species should be considered. For an acute course of infection in the same setting, *S aureus*, *S pneumoniae*, and β-hemolytic streptococci are more likely pathogens.

Recommendations

1. **For CNE, it is reasonable to obtain the proper number of cultures before antibiotic drugs are begun or to stop antibiotic drugs that were started fewer than 4 days earlier *(Class IIa; Level of Evidence C)*.**
2. **Infectious diseases consultation should be obtained in each case of CNE *(Class I; Level of Evidence C)*.**

Complications and Surgical Issues

In the current era, outpatient antibiotic therapy after initial diagnosis and stabilization is increasingly used. This makes it extremely important to define the patient population that is at higher risk for complications. Several factors predispose children with IE to potentially life-threatening complications that may require early surgery. Risk factors are listed in Table 10. Other considerations that increase concern and the need for surveillance for complications include the size and location of the vegetation, acute onset of atrioventricular block, type of organism, occurrence of IE in an otherwise normal heart, and occurrence in children <2 years of age.[10,11] The complications of IE can be classified into cardiac and extracardiac sequelae.

Cardiac complications include congestive heart failure, new or progressive valvular dysfunction that is usually seen as increased regurgitation, periannular extension of infection, sinus of Valsalva rupture, myocardial dysfunction, obstruction of conduits or shunts, prosthetic valve dysfunction including dehiscence, pericardial effusion, and less commonly, septic emboli to the coronary arteries.

Congestive heart failure is caused by various combinations of the above factors and is one of the more frequent complications that carries a guarded prognosis. Progressive congestive heart failure usually is caused by worsening valvular regurgitation, often accompanied by ventricular dysfunction. Poor ventricular function is associated with an increased surgical mortality rate.[135,136] Urgent surgery in patients with moderate to severe heart failure improves the likelihood of survival and preservation of cardiac function.[137] In general, for patients with IE, the degree of illness is not considered a limitation to surgical intervention because the alternative, to delay or defer surgery, can have dire consequences.

Periannular extension of infection also increases the risk of congestive heart failure.[138,139] The greatest risk for this complication exists in aortic valve endocarditis. Periannular infections also cause fistulous tracks into the pericardium, as well as between cardiac chambers or vascular structures. Such abscesses or fistulae usually do not respond to medical management alone and require surgical treatment. Sinus of Valsalva aneurysms may occur with rupture into any of the cardiac chambers.[140] 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 pathological murmurs in patients receiving appropriate antibiotic drugs.[141,142]

Surgically created shunts or intracardiac conduits are a potential source for complications of IE. Because these connections

Table 8. Empirical Therapy in Culture-Negative Endocarditis*

Regimen	Dosage and Route	Duration, wk	Strength of Recommendation (Class/LOE)	Comments
Native valve				
Ampicillin-sulbactam†	12 g/d IV in 4 equally divided doses	4–6	IIb/C	Consensus of experts is that patients with culture-negative endocarditis should be managed with consultation with an infectious diseases specialist
plus				
gentamicin sulfate‡	3 mg·kg^{-1}·d^{-1} IV/IM in 3 equally divided doses	4–6		
Vancomycin§	40 mg·kg^{-1}·d^{-1} IV in 2 equally divided doses	4–6	IIb/C	Vancomycin is recommended only for patients who are unable to tolerate penicillins
plus				
gentamicin sulfate	3 mg·kg^{-1}·d^{-1} IV/IM in 3 equally divided doses	4–6		
plus				
ciprofloxacin	1500 mg/d PO or 800 mg/d IV in 2 equally divided doses	4–6		
	Pediatric dosage: Ampicillin-sulbactam 300 mg·kg^{-1}·d^{-1} IV in 4–6 equally divided doses; gentamicin 3 mg·kg^{-1}·d^{-1} IV/IM in 3 equally divided doses; vancomycin 40 mg·kg^{-1}·d^{-1} in 2 or 3 equally divided doses; ciprofloxacin 20–30 mg·kg^{-1}·d^{-1} IV/PO in 2 equally divided doses			
Prosthetic valve (early, ≤1 y)				
Vancomycin	40 mg·kg^{-1}·d^{-1} IV in 2 equally divided doses	6	IIb/C	
plus				
gentamicin sulfate	3 mg·kg^{-1}·d^{-1} IV/IM in 3 equally divided doses	2		
plus				
cefepime	6 g/d IV in 3 equally divided doses	6		
plus				
rifampin	900 mg/d PO/IV in 3 equally divided doses	6		
	Pediatric dosage: Vancomycin 40 mg·kg^{-1}·d^{-1} IV in 2 or 3 equally divided doses; gentamicin 3 mg·kg^{-1}·d^{-1} IV/IM in 3 equally divided doses; cefepime 150 mg·kg^{-1}·d^{-1} IV in 3 equally divided doses; rifampin 20 mg·kg^{-1}·d^{-1} PO/IV in 3 equally divided doses			
Prosthetic valve (late, >1 y)		6	IIb/C	Same regimens as listed above for native valve endocarditis
Suspected *Bartonella,* culture negative				
Ceftriaxone sodium	2 g/d IV/IM in 1 dose	6	IIa/B	Patients with *Bartonella* endocarditis should be treated in consultation with an infectious diseases specialist
plus				
gentamicin sulfate	3 mg·kg^{-1}·d^{-1} IV/IM in 3 equally divided doses	2		
with or without				
doxycycline	200 mg/d IV/PO in 2 equally divided doses	6		

(*Continued*)

Table 8. Continued

Regimen	Dosage and Route	Duration, wk	Strength of Recommendation (Class/LOE)	Comments
Documented *Bartonella,* initially culture negative, determined to be positive by nonculture tests				
Doxycycline	200 mg/d IV or PO in 2 equally divided doses	6	IIa/B	If gentamicin cannot be given, then replace it with rifampin 600 mg/d PO/IV in 2 equally divided doses
plus				
gentamicin sulfate	3 mg·kg^{-1}·d^{-1} IV/IM in 3 equally divided doses Pediatric dosage: Ceftriaxone 100 mg·kg^{-1}·d^{-1} IV/IM once daily; gentamicin 3 mg·kg^{-1}·d^{-1} IV/IM in 3 equally divided doses; doxycycline 2–4 mg·kg^{-1}·d^{-1} IV/PO in 2 equally divided doses; rifampin 20 mg·kg^{-1}·d^{-1} PO/IV in 2 equally divided doses	2		

As discussed in the text, these recommendations are based on consensus of experts and not experimental comparative studies (*Class IIa; Level of Evidence C*).
Note: Pediatric dosage should not exceed that of a normal adult.
IM indicates intramuscular; IV, intravenous; LOE, level of evidence; and PO, oral.
*Dosages recommended are for patients with normal renal function.
†If ampicillin-sulbactam is unavailable, vancomycin is the suggested alternative (see Table 7 for empirical treatment of native valve infective endocarditis).
‡See text and Table 7 for appropriate dosing of gentamicin.
§See Table 7 for appropriate dosing of vancomycin.

involve various prosthetic materials, including Gore-Tex, Dacron, or homografts, bacteriologic cure is often impossible without surgical intervention. Septic vegetations at these sites may lead to dehiscence, obstruction, or distal emboli.[15,143]

Extracardiac complications are the result of sepsis, immune complex–mediated vasculitis, and, most importantly, embolic phenomena from septic vegetations. Embolic complications may involve the cerebral, pulmonary, renal, splenic, coronary, or peripheral arteries, depending on the original locus of infection. Neurological sequelae include stroke, brain abscess, hemorrhage, seizures, diffuse vasculitis, or meningitis, and these events may occur in up to 30% of cases.[144] The incidence of stroke has been reported to be 6% in pediatric populations[145] and 11% in those of all ages with CHD.[146] Mycotic aneurysms may occur in any systemic artery or the pulmonary arteries but are particularly dangerous in the cerebral circulation; surgical therapy may be used because of the risk of rupture. Numerous studies in adults[102,147] have shown increased risk for embolization with vegetations >10 mm, which indicates a role for early surgical intervention in those with such large vegetations. Recently, this finding was supported in a pediatric study.[148] The location of the vegetation may also be a factor, with mitral valve anterior leaflet lesions having a higher rate of embolization than aortic valve vegetations (25% versus 10%, respectively).[149] Particular organisms, namely, staphylococci, pneumococci, and fungi, also carry a high risk of embolism. Most emboli occur early in the course of the illness, but an increase in the size of the vegetation while a patient is receiving effective treatment may be predictive of emboli.[150] The kidney and spleen may be involved during IE, with infarcts or abscesses related to emboli. The kidney may also be affected by glomerulonephritis secondary to immune complex depositions.

Although mortality from IE has clearly improved in the current era, the mortality rate remains 5% to 10% for patients (including children) with this condition,[24,146,151] with the risk of death clearly related to the presence of underlying heart disease, as shown in a review of a large pediatric inpatient database.[24] In that study, the overall mortality was only 5%, but it was 48% in patients with tetralogy of Fallot and pulmonary atresia and 8% in patients who had prosthetic valves.

Recommendations

1. **In general, for patients with IE, we recommend that the degree of illness not be considered a limitation to surgical intervention, because the alternative, to delay or defer surgery, can have dire consequences *(Class I; Level of Evidence B)*.**
2. **Mycotic aneurysms may occur in any systemic artery or the pulmonary arteries but are particularly dangerous in the cerebral circulation; surgical therapy may be considered because of the risk of rupture *(Class IIb; Level of Evidence B)*.**

Indications for Surgery

Cardiovascular surgery is often urgently necessary and may be lifesaving in patients with IE, but decisions regarding surgical intervention are best made when individualized. Recommendations for surgical management of pediatric IE are mostly an extension of recommendations of experts for management of adult IE. The most common reasons for surgical management of IE are congestive heart failure, progressive valve dysfunction, and embolic phenomena. Prediction of an individual patient's risk for embolization

Table 9. Epidemiological Clues in Pathogenic Diagnosis of Culture-Negative Endocarditis

Epidemiological Feature	Common Microorganism(s)
Injection drug use	*Staphylococcus aureus*, including community-acquired methicillin/oxacillin/nafcillin-resistant *S aureus*
	Coagulase-negative staphylococci
	β-Hemolytic streptococci
	Fungi
	Aerobic Gram-negative bacilli, including *Pseudomonas aeruginosa*
	Polymicrobial
Indwelling cardiovascular medical devices	*S aureus*
	Coagulase-negative staphylococci
	Fungi
	Aerobic Gram-negative bacilli
	Corynebacterium spp
Genitourinary disorders, infection, and manipulation, including pregnancy, delivery, and abortion	*Enterococcus* species
	Group B streptococci (*Streptococcus agalactiae*)
	Listeria monocytogenes
	Aerobic Gram-negative bacilli
	Neisseria gonorrhoeae
Chronic skin disorders, including recurrent infections	*S aureus*
	β-Hemolytic streptococci
Poor dental health, dental procedures	Viridans group streptococci
	"Nutritionally variant streptococci"
	Abiotrophia defectiva
	Granulicatella species
	Gemella species
	HACEK organisms
Alcoholism, cirrhosis	*Bartonella* species
	Aeromonas species
	Listeria species
	Streptococcus pneumoniae
	β-Hemolytic streptococci
Burn patients	*S aureus*
	Aerobic Gram-negative bacilli, including *P aeruginosa*
	Fungi
Diabetes mellitus	*S aureus*
	β-Hemolytic streptococci
	S pneumoniae
Early (≤1 y) prosthetic valve placement	Coagulase-negative staphylococci
	S aureus
	Aerobic Gram-negative bacilli
	Fungi
	Corynebacterium species
	Legionella species
Late (>1 y) prosthetic valve placement	Coagulase-negative staphylococci
	S aureus
	Viridans group streptococci
	Enterococcus species
	Fungi
	Corynebacterium species
Dog-cat exposure	*Bartonella* species
	Pasteurella species
	Capnocytophaga species
Contact with contaminated milk or infected farm animals	*Brucella* species
	Coxiella burnetii
	Erysipelothrix species
Homelessness, body lice	*Bartonella* species
AIDS	*Salmonella* species
	S pneumoniae
	S aureus
Pneumonia, meningitis	*S pneumoniae*
Solid-organ transplant	*S aureus*
	Aspergillus fumigatus
	Enterococcus species
	Candida species
Gastrointestinal lesions	*Streptococcus bovis*
	Enterococcus species
	Clostridium septicum

HACEK indicates *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species.

remains difficult, with conflicting data published regarding the specific value of echocardiographic determination of vegetation size or specific location as predictors.[152,153] Nevertheless, left-sided heart lesions, specifically those involving the mitral valve anterior leaflet, particularly if associated with *S aureus*, appear to be at highest risk for embolization.[154,155] However, at this time, there are no pediatric evidence-based data to indicate that prophylactic surgery to prevent a primary embolic event is definitively indicated given the immediate and long-term risks of valve replacement in childhood.

Other important issues for which early surgery is used include perivalvular extension of infection, fungal endocarditis, persistent bacteremia despite appropriate antibiotic therapy, unstable prosthesis, ruptured sinus of Valsalva, or ventricular septal and mycotic aneurysms.[156–158] The indications for surgical intervention tabulated in Table 11 should be considered recommendations of experts.[17] Although the clinical circumstances seem dire, even difficult aortic root complications can be treated successfully with aortic homografts or Ross procedure autografts.[159,160] Depending on the degree of valve or great vessel root damage, valve-sparing operations are often possible.[110,152,161] In some

Table 10. 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 (>3 mo)
Cyanotic congenital heart disease
Patients with systemic-to-pulmonary shunts
Poor clinical response to antimicrobial therapy

IE indicates infective endocarditis.
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circumstances, cardiological evaluation may suggest a need for early surgical therapy, performed even before sterilization of blood. In a recent 15-year review of children treated for IE at the Texas Heart Institute in Houston, TX, early surgery was performed in 61% of patients, with most of these surgeries occurring within 7 days and half within 3 days of diagnosis.[16] Several other studies have also shown that early surgery can be performed with low morbidity and mortality in childhood and improves the overall outcome from IE.[152,156,161] Recent observational studies in adults have suggested that when adjusted for both selection and survivor biases, surgery in patients with left-sided IE, even when not considered urgent, may produce better outcomes and lower mortality than medical therapy alone.[162,163] Although these data have not been replicated in specific pediatric-focused studies, the information does provide a reasonable framework for similar consideration in pediatric IE. Similarly, in prosthetic valve endocarditis, data from series in adults indicate that even aside from obvious indications for early surgery such as symptomatic heart failure, valve dehiscence, and great vessel root abscess formation, among others, surgery may benefit patients with relapsing prosthetic valve endocarditis even if valvar function remains intact after prolonged medical therapy.

Recommendations

1. **Prophylactic surgery to prevent a primary embolic event is not recommended given the lack of proven benefit and long-term risks of valve replacement in childhood *(Class III; Level of Evidence C)*.**
2. **Surgery may be considered for patients with relapsing prosthetic valve endocarditis even if valvar function remains intact after prolonged medical therapy *(Class IIb; Level of Evidence B)*.**

Prevention of Endocarditis

For >5 decades, scientific organizations and public healthcare policy groups around the world have advocated for the administration of antibiotic drugs for prophylaxis against IE. This recommendation, however, was never firmly grounded on well-designed, appropriately powered randomized clinical trials, and thus, scientific challenges to the concept emerged. These challenges were abetted by epidemiological facts that became apparent as well. Only ≈20% of endocarditis cases have actually been related to a preceding invasive procedure for which antibiotic drugs would have been recommended, and only 50% of cases of IE occur in people with an existing cardiac condition for which antibiotic prophylaxis would have been prescribed. Thus, even the core epidemiology of IE was at variance with the existing, traditional guidelines. Moreover, increasing concern developed in recent years that the dispensing of millions of doses of antibiotic drugs for a weakly supported rationale contributes to the development of antibiotic resistance. These issues were the impetus for extensive topical reviews performed by the AHA, the European Society of Cardiology, the British Society for Antimicrobial Chemotherapy, and other leading groups that all concluded that sharply limiting the use of antibiotic drugs for prophylaxis against IE was appropriate and timely.

The 2007 AHA guideline on "Prevention of Infective Endocarditis"[3] has become a widespread standard and is similar to the European Society of Cardiology statement. The British guidelines (NICE) carried the revisions furthest, with recommendations to eliminate prophylactic antibiotic drugs altogether for all patients under any circumstances. In summary, the AHA and the European Society of Cardiology statements limit the use of prophylactic antibiotic drugs to patients in whom the risk for IE is highest (eg, patients with a history of previous IE), and equally important but somewhat more controversial, recommend antibiotic drugs be considered for those patients with the greatest risk for morbidity or mortality from IE (eg, heart transplant patients with a valvulopathy in the implanted heart).

Since the publications of these recommendations, at least 1 study has documented the lack of any demonstrable increase in IE as a cause of hospitalization for children,[72] and another has carefully documented the absence of any impact on the rate of IE case development in the United Kingdom, where the NICE guidelines have been in place and where antibiotic dispensing for IE prophylaxis is monitored carefully.[73]

Children who are at risk for IE and their families and care providers can benefit from education about the importance of good oral health and the techniques useful for its maintenance. Additionally, children with cyanosis may have specific periodontal concerns, which makes optimum oral hygiene particularly important for them.[3] The AHA recommends that for those in the highest-risk groups, there may still be a role for prophylactic antibiotic drugs. Families of children and young adults, in particular, are counseled that their risk for IE might actually increase as they become subject to cardiovascular therapies for their CHD, although those conditions might not have required IE prophylaxis before treatment. In this regard, valve replacement and septal defect occlusion with prosthetic devices are relevant examples. In the last review of IE prophylaxis, the conditions the

AHA recommended as highest risk for adverse outcomes from IE and for which prophylaxis before high-risk dental procedures is reasonable included cardiac valve repair with a prosthetic valve or prosthetic material; previous IE; certain CHD (unrepaired cyanotic CHD, repaired CHD with prosthetic material or device during the first 6 months after the procedure, repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device); and recipients of cardiac transplants who develop cardiac valvulopathy.[3]

Finally, as growing numbers of children successfully transition to adult-based healthcare circumstances, carrying their complex cardiovascular histories with them, the issues surrounding IE prevention will continually be reiterated as part of their healthcare maintenance program.

Recommendation

1. **Children with cyanosis may have specific periodontal concerns, which makes optimum oral hygiene particularly important for them. The AHA recommends that for those in the highest-risk groups, prophylactic antibiotic drugs before certain dental procedures may be considered[3] *(Class IIb; Level of Evidence C)*.**

Table 11. Echocardiographic Features Suggesting Potential Need for Surgical Intervention*

Vegetation
Persistent vegetation after systemic embolization
Anterior mitral leaflet vegetation, particularly with size >10 mm†
≥1 Embolic event during first 2 wk of antimicrobial therapy†
≥2 Embolic events during or after antimicrobial therapy†
Increase in vegetation size after 4 wk of antimicrobial therapy‡§
Valvular dysfunction
Acute aortic or mitral insufficiency with signs of ventricular failure§
Heart failure unresponsive to medical therapy§
Valve perforation or rupture§
Perivalvular extension
Valvular dehiscence, rupture, or fistula§
New heart block§
Large abscess or extension of abscess despite appropriate antimicrobial therapy§

*See text for more complete discussion or indications for surgery based on vegetation characterizations.
†Surgery may be required because of risk of recurrent embolization.
‡Surgery may be required because of risk of embolization.
§Surgery may be required because of heart failure or failure of medical therapy.
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Disclosures

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*Modest.
†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
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