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REVIEW ARTICLE

Antibiotic Therapy for Infective Endocarditis in Childhood

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Infective endocarditis is relatively uncommon in childhood, but its epidemiology has changed in the past three to four decades and its incidence has been increasing in recent years. With the improved survival rates of children with congenital heart diseases and the overall decreased frequency of rheumatic valvular heart disease in developed countries, congenital cardiac abnormalities now represent the predominant underlying condition for infective endocarditis in children over the age of two years in Western Europe and Northern America. Moreover, the complex management of neonatal and pediatric intensive care unit patients has increased the risk of catheter-related endocarditis. More specifically, the surgical correction of congenital heart alterations is associated with the risk of postoperative infections. Endocarditis in children may be difficult to diagnosis and manage. Emerging resistant bacteria, such as methicillin- or vancomycin-resistant staphylococci and vancomycin-resistant enterococci, are becoming a new challenge for conventional antibiotic therapy. Newer antimicrobial compounds recently introduced in clinical practice, such as streptogramins and oxazolidinones, may be effective alternatives in children with endocarditis sustained by Gram-positive cocci resistant to glycopeptides. Home intravenous therapy has become an acceptable approach for stable patients who are at low risk for embolic complications. However, further clinical studies are needed in order to assess efficacy and safety of these antimicrobial agents in children. This review should help outline the most appropriate antimicrobial treatments for infective endocarditis in children.

KEYWORDS antibiotic, childhood, enterococci, infective endocarditis, pediatrics, staphylococci, streptococci

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INTRODUCTION

Infective endocarditis (IE) is a serious but highly treatable microbial infection of the endocardial surface of the heart. In the pre-antibiotic era, this infectious disease was invariably fatal, but it is associated with substantial morbidity and mortality still today. IE is relatively rare in children, occurring with a significantly lower incidence in pediatric patients than in adult ones. It was estimated that IE was responsible for 1 in 500 to 1 in

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ABBREVIATIONS CHD, congenital heart disease; CoNS, coagulase-negative staphylococci; HACEK, *Haemophilus* spp., *Actinobacillus* spp., *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*; IDSA, Infectious Disease Society of America; IE, infective endocarditis; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus;* PBP, PICU, pediatric intensive care unit; Q-D, quinupristin-dalfopristin; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; UK, United Kingdom; US, United States

1000 pediatric hospitalizations in the United States (US) in the thirty-year period from 1960 to 1990,[1] and Van Hare et al. have reported an incidence of approximately 1 in 1280 pediatric admissions per year.[2] Although the observed hospitalization rates for IE in childhood are generally lower than in adults, they vary considerably among published studies. Moreover, the incidence of IE among children appears to have increased in recent years, simultaneous to the epidemiological changes in pediatric heart diseases that have occurred over the past three to four decades.

The increased survival rate of children with congenital heart disease (CHD) and the overall decrease in the frequency of rheumatic valvular heart disease in developed countries have profoundly changed the epidemiological features of IE among children. CHD now represents the most frequent underlying predisposing factor for endocardial infections in children over the age of two years in western countries, and postoperative IE is a long-term risk following corrective or palliative surgery for CHD.[3]

Moreover, the complex management of neonatal and pediatric intensive care unit (PICU) patients with indwelling venous catheters, the more frequent use of invasive diagnostic and therapeutic procedures, and the congenital or acquired suppression of the immune system (such as human immunodeficiency virus infection or immunosuppressive therapy) represent new predisposing conditions for IE.[1,2,4] Particularly, IE in the absence of CHD is often associated with central indwelling venous catheters, and the presence of these intravenous devices increases the risk for thrombotic complications by causing vascular obstruction and low blood flow in addition to direct endothelial lesion.[5]

Despite the advance in non-invasive diagnostic techniques and the introduction in clinical practice of new potent antibiotics available for children, the most appropriate clinical management of pediatric IE is debated, owing to the lack of prospective clinical studies in pediatric patients. Moreover, during the last two decades, increasing levels of drug resistance have been reported, mostly among staphylococci, viridans streptococci, enterococci, and Gram-negative bacilli. Because of such resistance, the optimal antimicrobial therapy for IE is often problematic.

This review will focus on the most appropriate therapeutic options for IE in childhood, with great attention devoted to the most recent and effective antimicrobial compounds and to antibiotic prophylaxis in children with higher risk for developing endocarditis. The quality of evidence and the strength of recommendations used in the development of these practice guidelines for clinical management of pediatric IE are specified in conformity with the Infectious Disease Society of America (IDSA) evidence-grading system (Table 1).[6]

EPIDEMIOLOGY AND PATHOGENESIS

The improved survival among children who are at risk for endocarditis, such as those with CHD and hospitalized newborn infants, has led to the increased frequency of IE observed in childhood in recent years.[3] Until the 1970s, rheumatic heart disease was the most common risk factor for endocarditis in children, and 30% to 50% of US pediatric patients with IE had underlying rheumatic valvular abnormalities. As the prevalence of rheumatic heart disease has declined in developed countries, these valvular alterations became an unusual risk factor for endocarditis in children.[7-9]

At the same time, the incidence of IE associated with CHD has gradually increased, and congenital heart abnormalities are considered today the prevalent risk factors for pediatric IE.[7,10,11] The most common congenital heart alterations associated with endocarditis include ventricular septal defects, patent ductus arteriosus, aortic valve abnormalities, and tetralogy of Fallot. Moreover, an elevated proportion of children with IE have undergone previous corrective or palliative surgery for CHD, especially implantations of prosthetic cardiac valves, patches, or vascular grafts. In fact, surgery may increase the risk of endocarditis in the first two postoperative months. Viewed in another way, prolonged life resulting from the surgery may also increase the risk, thereby lengthening the period over which pediatric patients are candidates to develop this infective complication.[11-13]

Approximately 50%–70% of children with endocarditis complicating CHD have had previous cardiac surgery, such as complex intracardiac repairs or palliative shunt procedures.

Table 1. System for ranking recommendations in clinical guidelines approved by the Infectious Disease Society of America (IDSA)[6]

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
1	Evidence from one or more properly randomized, controlled trials
2	Evidence from one or more well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies; from multiple time-series; or from dramatic results from uncontrolled experiments
3	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

The highest risk for IE was found in patients who had undergone surgery for obstruction to pulmonary blood flow, prosthetic aortic valve replacement, and repair or palliation of cyanotic CHD. In a cohort of 3,860 children with CHD, the cumulative incidence of IE at 25 years after the heart surgery was 13.3% for valvular aortic stenosis, 3.5% for the aortic coarctation, 2.8% for primum atrial septal defect, 2.7% for isolated ventricular septal defect, and 1.3% for tetralogy of Fallot.[12]

The incidence of endocarditis is usually low in the first postoperative month for most defects and increases with time after surgery. Nevertheless, in children with persistent hemodynamic alterations or after surgical repairs with prosthetic valves or conduits, the risk for IE is elevated even in the first two postoperative weeks.[3,7,12,14] On the other hand, successful repair of uncomplicated ventricular or atrial septal defects and closure of a patent ductus arteriosus with no residual defects seem to eliminate the attributable risk for endocarditis in children with these congenital abnormalities six months after surgery.[9,13]

In the absence of CHD, pediatric endocarditis is often associated with indwelling venous catheters. The presence of venous catheters may cause direct endothelial damage and increase the risk for thrombolytic complications by causing vascular obstruction and reduced blood flow.[4-7] Children with congenital or acquired immunodeficiency, but without identifiable risk factors for IE, do not appear to be associated with an increased risk for endocarditis compared with the general population.[3] IE occurs without structural heart defects or other identifiable predisposing conditions in approximately 8% to 10% of pediatric cases. These cases generally involve the aortic or mitral valve in association with a *Staphylococcus aureus* bacteremia.[3,7]

Pathogenetic mechanisms of IE have been only partially understood. Damaged endothelium usually induces thrombogenesis and becomes a nidus to which bacteria can adhere and eventually form an infected vegetation. In children with CHD or other valve abnormalities, the shear force associated with an abnormally high-velocity jet stream of blood, such as that caused by indwelling venous catheters, can damage the endothelium. Intravenous catheters positioned in the right side of the heart may traumatize the endocardium or valvular endothelium, exposing the subendothelial collagen. Thrombogenesis induced by the en-

dothelium lesions results in the deposition of sterile clumps of platelets, fibrin, and red blood cells, leading to the occurrence of non-bacterial thrombotic endocarditis.[14,15]

When there is a bacteremia and bacteria are able to survive in the bloodstream in sufficient number, they adhere to the initial non-bacterial thrombotic lesions and propagate. At the same time, platelets and fibrin are deposited over the organisms, leading to the enlargement of the vegetation. The bacteria proliferate, and once maximum bacterial density has been reached, most bacteria deep within the vegetation become metabolically inactive and are protected from phagocytic cells, other host defense mechanisms, and antibacterial drugs.[16,17] The highest risk for IE development was found among patients with CHD that involved high-velocity jets of blood flow and/or foreign material. Examples include children with complex cardiac anatomy who have undergone palliative shunt and conduit procedures. However, with or without shunting, endocarditis occurs more frequently in patients with cardiac lesions associated with turbulence of flow.

Aortic valve abnormalities were the most common lesions in a series of children who developed IE and had no history of surgery,[12] and the risk of endocarditis in patients with ventricular septal defect is generally increased by the presence of associated aortic regurgitation. On the contrary, IE is an uncommon event in secundum atrial septal defects, in which shunting is not associated with high-velocity jet flow. IE is also uncommon in mild pulmonary stenosis.[18]

IE in newborn infants frequently involves the right side of the heart, an area susceptible to catheter-induced trauma which may disrupt the endocardium or valvular endothelial tissue. Moreover, neonates often experience transient episodes of bacteremia from trauma to the skin and mucous membranes, placement of umbilical or peripheral venous catheters, parenteral hyperalimentation, or vigorous endotracheal suctioning. The association of transient bacteremia and endothelial lesions may lead to the occurrence of neonatal IE.[19,20]

Finally, the availability of newer molecular biological techniques during the 1990s has significantly improved our understanding of endocarditis pathogenesis. Several surface structures of staphylococci, streptococci, and enterococci have been identified as markers of virulence, and considerable data support the hypothesis that the interactions of Gram-positive cocci with platelets and the organism's capacity to resist the antimicrobial host defense properties of platelets are pivotal in the occurrence and persistence of IE.[21]

Table 2. Principal bacterial agents of IE in children[6,22,23]

Pathogens	Prevalence in pediatric series (%)
Viridans group streptococci	32–43
Staphylococcus aureus	27–33
Coagulase-negative staphylococci	2–12
Streptococcus pneumoniae	3–7
Enterococci	4–7
HACEK bacteria	4–5
Culture-negative endocarditis	5–7

HACEK, Haemophilus parainfluenzae, H. aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae.

The most common microorganisms responsible for IE in childhood are listed in Table 2. Principal etiologic bacterial agents are the Gram-positive cocci, including viridans group streptococci (such as *Streptococcus mitis*, *S. sanguis*, *S. mutans*, and *S. milleri* group), staphylococci (such as *S. aureus* and coagulase-negative staphylococci), and enterococci. However, enterococcal endocarditis is diagnosed much more rarely in children than in adults.[6,22,23] Less common causative agents are represented by *Streptococcus pneumoniae* and HACEK group bacteria (including *Haemophilus parainfluenzae, H. aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens*, and *Kingella kingae*).[24]

IE among newborn infants is commonly caused by *S. aureus*, coagulase-negative staphylococci, and *Candida* species, followed by group B streptococci and *Streptococcus pneumoniae*. The most frequent etiological agents of IE in the first year of life are viridans group streptococci, followed by *S. aureus* (which is the most common cause of acute bacterial endocarditis). IE associated with prosthetic valves, prosthetic material, and indwelling venous catheters is

more frequently sustained by *S. aureus* or coagulase-negative staphylococci. Staphylococcal infections are usually implanted at the same time of surgery and lead to early prosthetic valve endocarditis (occurring < 60 days after cardiac surgery). However, coagulase-negative staphylococci may cause valvular infections as late as one year after surgery. On the other hand, viridans group streptococci and enterococci are usually associated with native valve endocarditis and intermediate or late prosthetic valve endocarditis (occurring > 60 days after cardiac surgery).[3,25]

Finally, gram-negative bacilli are a very uncommon cause of endocarditis in infants, even though catheter-related bacteremia due to these organisms occurs frequently in pediatric patients in intensive care units. Bacteremia caused by Gram-negative bacilli leads rarely to IE probably because of their poor adhesion to the heart valve endothelium.[3,25,26] Owing to the introduction of central venous catheters in infants and children in the last 25 years, and the frequent use of high glucose concentrations and hyperalimentation, fungal endocarditis has been widely recognized in pediatric patients in recent years. *Candida* species are the most common fungal agents of IE in childhood, although *Aspergillus* species have been also reported to cause endocarditis.[12,18]

Culture-negative endocarditis is diagnosed when a patients has clinical and/or echocardiographic evidence of IE but persistently negative blood cultures. Negative blood cultures may be caused by recent antibiotic therapy or infection due to a fastidious organism that grows poorly *in vitro*. Microorganisms that can be responsible for culture-negative endocarditis include filamentous fungi, *Coxiella burnetii, Legionella, Brucella, Bartonella*, and *Chlamydia*, and clinicians must consult with microbiologists to optimize the chance of identification of these etiologic agents.[23,27]

CLINICAL FINDINGS AND DIAGNOSIS

As in adults, the clinical features of IE in children are related to one or more of four underlying phenomena: bacteremia, valvular abnormalities, immunological response, and vascular manifestations. Valvular lesions may result in changing cardiac auscultatory findings or the development of hemodynamic complications such as congestive heart failure. Immunological phenomena (e.g., glomerulonephritis or Osler nodes) and extracardiac vascular manifestations (e.g., petechiae, hemorrhages, Roth's spots, Janeway lesions, splenomegaly, and systemic emboli) are considerably less frequent in children than in adults. Similarly, central nervous system mycotic aneurysms occur very rarely, but their rupture can be lethal. The clinical presentation of IE in children is usually indolent, with persistent low-grade fever, fatigue, weakness, arthralgias, myalgias, rigors, weight loss, and diaphoresis. Sometimes, the presentation may be acute, with high, septic fever and rapidly changing symptoms.

Cardiac examination may disclose regurgitant murmurs in children with valvular lesions that produce leaflet destruction. However, in patients who have cyanotic CHD and who have undergone systemic-pulmonary artery shunt procedures, the murmur may not change, but in these patients reduced systemic oxygen saturation may reflect graft infection and obstruction of flow. Furthermore, children with IE associated with right-sided catheters may have no specific cardiovascular signs or may present with primarily pulmonary manifestations related to a septic embolization to the lungs.[3,12,28]

The clinical findings of IE in neonates are usually non-specific and variable and may be similar to those of septicemia or congestive heart failure from other causes. Newborn infants with endocarditis often present with feeding difficulties, respiratory distress, tachycardia, new or changing heart murmur, and arterial hypotension.

Septic embolization is also common in newborns and may lead to focal, secondary infections outside the heart, such as pneumonia, meningitis, osteomyelitis, and abdominal abscess. Neurologic signs and symptoms have been also described in many neonates, including seizures, hemiparesis, lethargy, and apnea. Arthritis and arthralgia are uncommon clinical findings in neonatal endocarditis.[25,29]

Laboratory tests may reveal a wide range of non-specific hematological or biochemical alterations in children with IE. Blood tests frequently show the presence of normocromic

Table 3. Modified Duke criteria for diagnosis of IE[32]

Major criteria	**Microbiological** typical microorganism isolated from two separate blood cultures (viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*, or community-acquired enterococcal bacteremia without a primary focus), or microorganism consistent with IE isolated from persistently positive blood cultures, or single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer to *C. burnetii* > 1:800
	Endocardial involvement new valvular regurgitation (increase or change in pre-existing murmur is not sufficient), or positive echocardiography (oscillating intracardiac mass or vegetation, abscess, or new partial dehiscence of prosthetic valve)
Minor criteria	predisposition to IE, which includes certain cardiac conditions and injection-drug abuse fever ≥ 38°C vascular phenomena (major arterial emboli, septic pulmonary infarct, mycotic aneurism, intracranial hemorrhage, conjunctival haemorrhage, Janeway's lesions) immunologic phenomena (rheumatoid factor, glomerulonephritis, Osler's nodes, or Roth spots) microbiologic findings (positive blood cultures that do not meet the major criteria; serologic evidence of active infection) echocardiography consistent with IE but not meeting the major criteria
Diagnosis	**Definite IE** pathology or bacteriology of vegetations, major emboli, or intracardiac abscess specimen, or two major criteria, or one major criterion and three minor criteria, or five minor criteria
	Possible IE one major criterion and one minor criterion, or three minor criteria

and normocytic anemia, leukocytosis with immature forms on peripheral blood smears, hypergammaglobulinemia, elevated erythrocyte sedimentation rate and C-reactive protein levels, and abnormal urinalysis (including hematuria and proteinuria).[12,18]

Several sets of diagnostic criteria have been proposed in order to standardize the endocarditis diagnosis, such as the von Reyn's criteria[30] in 1981 and the Duke criteria suggested by Durack and colleagues[31] in 1994 at Duke University. These criteria include the presence of concomitant predisposing factors to developing endocarditis, clinical manifestations, blood-culture isolates, echocardiographic alterations, and serological tests, and they were modified by Li and colleagues[32] in the year 2000 (Table 3).

When pathologically confirmed cases were considered to be the gold standard for assessing the Duke criteria, their collective sensitivity in several studies was greater than 80%,[32-34] and their very high specificity (about 99%) has been similarly confirmed in other reports.[35,36] Two studies involving pediatric cases have verified that the Duke criteria are superior to previous criteria for diagnosis of IE in children as well, and according to Li et al., diagnoses of IE may

be either "definite" or "possible". Other cases must be "rejected". Two-dimensional echocardiography has become the main modality for disclosing endocardial involvement in patients with IE, and echocardiographic features are included in the modified diagnostic Duke criteria. In fact, echocardiography may show the site of infection, the extent of valvular damage, the cardiac function abnormalities, and eventual concomitant complications such as myocardial abscess formation, new partial dehiscence of prosthetic valve, or pericardial effusion. Echo-color-Doppler is a sensitive modality for detection of valvular insufficiency, changes in intracardiac flow patterns, and typical findings of endocardial infections (e.g., oscillating intracardiac mass or vegetation).

Transthoracic echocardiography (TTE) is more precise in the pediatric population than in adults for detection of vegetation, with a reported sensitivity of 81%.[37-39] Particularly, TTE's sensitivity discloses more vegetations in children with normal thoracic anatomy or isolated valvular abnormalities than in those with complex cyanotic CHD because of interference in the latter group by artificial grafts, conduits, and valves. Moreover, TTE may not be adequate when there is a poor ultrasound penetration, such as in obese or very muscular adolescents, in post-cardiac surgery patients, or in children with compromised respiratory function or pulmonary hyperinflation. In these cases, transesophageal echocardiography (TEE) is considered more sensitive than TTE.[39,40]

Currently, there are no studies in children showing the superiority of TEE over TTE in identifying vegetations on both native and prosthetic valves. TEE is thought to be useful for disclosing complications of left ventricular outflow tract endocarditis (either valvular or subvalvular), the development of aortic root abscesses, and involvement of the sinus of Valsalva. Most authors recommend TEE for all patients with aortic valve endocarditis and changing aortic root dimension as seen as a standard TTE, and for children with prosthetic valve infection, because transesophageal evaluation adds greatly to the diagnosis of paravalvular leakage and valve dehiscence.[40,41] However, echocardiography (including TEE) is characterized by some limitations that should be underlined. The absence of vegetations on echocardiographic evaluation is not enough to exclude diagnosis of IE, while an echogenic intracardiac mass may represent sterile prosthetic material or a sterile thrombus rather than an infected vegetation.[40-42]

ANTIMICROBIAL THERAPY

In general, treatment of IE depends on a multidisciplinary approach involving at least specialists in infectious diseases, cardiology, and cardiovascular surgery. The principles of treatment of pediatric endocarditis are similar to those for treatment of IE in adults, but pediatricians and pediatric pharmacists need to contribute also.

Antimicrobial therapy with prolonged (at least 2 weeks, and often 4-8 weeks) parenteral administration of a bactericidal antibiotic or combination of antimicrobial agents is currently recommended for children with IE. Because bacteria are embedded within the fibrin-platelet matrix, with very high concentrations and relatively low rates of bacterial metabolism and cell division, they demonstrate reduced susceptibility to beta-lactam and other cell wall-active antibiotics. Moreover, in infants and children, intravenous antibiotic therapy is usually preferred over intramuscular treatment because of the patients' small muscle mass. In patients who are not acutely ill and whose blood cultures are still negative, antimicrobial treatment may be withheld for 48 hours or longer while additional blood cultures are obtained.[16,17,43]

Antibiotic treatment should be started in the hospital, but it could be completed on an outpatient basis on the following conditions: fever has disappeared, follow-up blood cultures are negative, the patient is hemodynamically stable, the patient is not at high risk for complications, and there are no indications for cardiac surgery. However, the patient should also have prompt access to medical and surgical care and cardiac follow-up.[44,45]

Penicillin G has always been the most helpful antimicrobial drug for treatment of IE, and most streptococci are sensitive still today. However, isoxazolyl penicillins, cephalosporins, or glycopeptides must be employed for staphylococcal and enterococcal infections due to increasing resistance rates during the last

50 years. Aminoglycosides have a well-defined place in the treatment of IE because they have a good distribution into the vegetations and, combined with penicillin, have a proven synergistic action against most viridans streptococci and enterococci.[44-46] For staphylococci, combinations of drugs with activity against the cell wall plus aminoglycosides or possibly rifampicin exert bactericidal synergy against both coagulase-positive and coagulase-negative strains, even though the mechanisms of such synergy are poorly defined.

The mechanism of bactericidal synergy has been delineated only for enterococci. These pathogens are relatively resistant to penicillin G and ampicillin (with mean minimal inhibitory concentration or MIC of 2 μg/mL), with each agent yielding a bacteriostatic effect. In association with aminoglycosides, penicillin G and ampicillin facilitate the intracellular uptake of gentamicin or streptomycin, causing the subsequent bactericidal effect against the enterococci, while there is a poor intracellular uptake of the aminoglycosides in the absence of β–lactam agents.[47] The identification of synergistic antibiotic combinations with rapid bactericidal effect should potentially reduce morbidity and mortality associated with sepsis syndrome, ongoing valvular damage, periannular extension, and metastatic abscess formation in subjects with IE.

Empirical treatment is often needed initially, and a combination of penicillin G and an aminoglycoside is usually recommended. In acute cases, a first- or second-generation cephalosporin in combination with an aminoglycoside may be employed in order to cover both *S. aureus* and β–haemolytic streptococci or pneumococci. If nosocomial IE is diagnosed, vancomycin should be used to cover enterococci and coagulase-negative staphylococci (CoNS).[47,48]

In vitro antimicrobial susceptibility testing is necessary to define the optimal therapy for streptococcal, staphylococcal, and enterococcal endocarditis, as well as infections sustained by Gram-negative bacilli. Determination of the MIC of penicillin is required to choose the most appropriate therapy for streptococcal infections. In addition, susceptibility of staphylococci should be determined for methicillin, vancomycin, rifampicin, and gentamicin. Similarly, susceptibility testing of enterococci from patients with IE should include determination of the MICs of penicillin, vancomycin, gentamicin, and streptomycin in addition to the evaluation of the most effective synergistic bactericidal combination of a cell wall-active antibiotic plus an aminoglycoside.[46-48]

The most appropriate antibiotic treatments for causes of IE are more extensively discussed in following sections and summarized in Tables 4, 5, 6, and 7.

In the absence of clinical clues to a specific cause, therapy for culture-negative native-valve endocarditis should include penicillin, ampicillin, ceftriaxone, or vancomycin, often in association with an aminoglycoside. On the other hand, treatment for culture-negative prosthetic-valve endocarditis occurring within 12 months after valve replacement usually includes at least vancomycin and gentamicin. However, for culture-negative prosthetic-valve endocarditis beginning 12 months or more after valve surgery, ceftriaxone or cefotaxime could be added to cover for so-called HACEK bacteria (including *Haemophilus* spp., *Actinobacillus* spp., *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*). If fever caused by IE persists after empirical therapy, valve replacement surgery for debridement should be considered in order to obtain material for microbiological and pathological studies.[44-47]

Anticoagulant therapy for native-valve endocarditis is restricted to patients with a clear indication separated from IE, because it has not been shown to prevent embolization and may increase the risk of intracerebral hemorrhage. In patients with prosthetic-valve infections that require maintenance anticoagulant therapy, anticoagulation may be cautiously continued during treatment for IE but should be temporarily interrupted in the presence of central nervous system embolization with hemorrhage.[49]

Staphylococcus aureus

Staphylococcus aureus is the most common cause of IE in much of the developed world. The increase in incidence of *S. aureus* endocarditis is primarily a consequence of healthcare contact such as surgical wounds, intravascular catheters, prosthetic devices.[50] *S. aureus* accounts for 25%–40% of native-valve endocarditis, 30%–39% of prosthetic-valve endocarditis in the first 12 months after surgery, and

Table 4. Recommended antibiotic treatment for pediatric endocarditis sustained by *Staphylococcus aureus* and coagulase-negative staphylococci*[3,50]

Microorganisms	Regimens for native-valve endocarditis	S.R.	Regimens for prosthetic-valve endocarditis	S.R.
Methicillin-susceptible *Staphylococcus aureus* and coagulase-negative staphylococci	**Nafcillin or oxacillin** (200 mg/kg IV daily in 4-6 equally divided doses) for 6 wk ***plus*** **gentamicin**[*†] (3 mg/kg IV/IM daily in 3 equally divided doses) for 3-5 d	A1	**Nafcillin or oxacillin** (200 mg/kg IV daily in 4-6 equally divided doses) ***plus*** **rifampin**[‡] (20 mg/kg IV/PO daily in 3 equally divided doses) for at least 6 wk ***plus*** **gentamicin**[*†] (3 mg/kg IV/IM daily in 3 equally divided doses) for 2 wk	A2
Methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci	**Vancomycin**[*§] (40 mg/kg IV daily in 2-3 equally divided doses) for 6 wk	A2	**Vancomycin** (40 mg/kg IV daily in 2-3 equally divided doses) ***plus*** **rifampin**[‡] (20 mg/kg IV/PO daily in 3 equally divided doses) for at least 6 wk ***plus*** **gentamicin**[*†] (3 mg/kg IV/IM daily in 3 equally divided doses) for 2 wk	A2

IV, intravenous; IM, intramuscular; PO, oral; S.R., strength of recommendation (see Table 1)

** Recommended dosages are for patients with normal renal and hepatic function. Pediatric dose should not exceed that of a normal adult.*

† Gentamicin therapy should be used only with gentamicin-susceptible strains. Dosage of gentamicin should be adjusted to achieve peak and trough concentrations in serum of approximately 3-4 and <1 µg/mL, respectively, when 3 divided doses are used. Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of IE exist.

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

§ Vancomycin dosage should be adjusted to obtain peak (1 hr after infusion completed) serum concentration of 30-45 µg/mL and a trough concentration range of 10-15 µg/mL.

15%–20% of prosthetic-valve endocarditis after the first post-operative 12 months. It is associated with considerable morbidity and mortality (ranging from 25% to 82%), and multivariate models demonstrate that prosthetic-valve infections and cardiovascular complications are the only independent predictors of increased mortality.[51,52]

Rapid sterilization of vegetations could result in less valve damage and reduced risk of metastatic complications. Although studies from the 1960s demonstrated the *in vitro* efficacy of penicillin G against *S. aureus*, the emergence of penicillinase-producing strains have made semisynthetic penicillinase-resistant penicillins, such as methicillin, nafcillin, and oxacillin, the treatment of choice. The combination of nafcillin and gentamicin has been evaluated extensively *in vitro* and *in vivo*, and a close correlation has been observed between *in vitro* synergy and enhanced *in vivo* outcomes in experimental IE documented by most authors.[50-52] In fact, *in vitro* and *in vivo* studies have demonstrated that a β–lactam antibiotic plus an aminoglycoside are more rapidly bactericidal for staphylococci than a β–lactam agent alone.[50]

Recommended antimicrobial regimens for staphylococcal endocarditis in children are listed in Table 4. The combination of agents that have activity against the cell wall plus aminoglycosides exerts bactericidal synergy against both coagulase-positive and coagulase-negative strains, but the mechanisms of such synergy are undefined still today. For instance, the benefit of the combination therapy with a β–lactam agent and an aminoglycoside has not been definitively established by human clinical trials regarding *S. aureus* IE. A more rapid clearance of native-valve endocarditis-related bacteremia has been reported by some authors in the combination therapy group (nafcillin and gentamicin) versus the nafcillin-alone group, but it was associated with a higher rate of nephrotoxicity and did not lead to a significant reduction in mortality.[53,54]

These findings have led to the suggestion that the aminoglycoside may be discontinued after 3-7 days of therapy for left-sided native-valve endocarditis in the hope that more rapid

control of bacteremia would be accompanied by a lesser incidence of metastatic infections and accelerated sterilization of heart valves. This abbreviated therapy would also avoid the toxic effects associated with a long course of aminoglycoside therapy.[52-54] Prosthetic-valve IE due to *S. aureus* is the most common form of IE occurring after the first 12 months following valvular replacement and is associated with a high mortality, ranging from 28% to 82% in different studies. A recent report shows a reduction in mortality for surgically treated patients, suggesting that all subjects might benefit from medical-surgical treatment.[55]

As therapy for *S. aureus* prosthetic-valve endocarditis, most authors suggest penicillinase-resistant penicillin or vancomycin for 4-6 weeks combined with an aminoglycoside for the initial 2 weeks.[56,57] The addition of oral rifampin is favored by some authors due to its unique role in sterilizing foreign bodies infected with *S. aureus*. In fact, it is thought that rifampin effectiveness is caused by its excellent tissue penetration and ability to enter living phagocytes and kill intracellular bacteria, as well as its ability to kill stationary phase microorganisms.[58,59] However, the possibility of the development of resistance to rifampin during vancomycin-plus-rifampin or a triple-agent treatment has been observed both in experimental animal models and clinical infections and should be carefully evaluated.[59,60]

In patients with *S. aureus* IE, combination regimens are recommended still today in both United Kingdom (UK) and US guidelines. The UK guidelines make similar recommendations for the choice of therapy in both native-valve and prosthetic-valve staphylococcal endocarditis. A 4-6-week treatment with nafcillin or oxacillin is suggested, and the association with gentamicin is recommended for the initial 7 days of therapy, with rifampin being proposed for difficult cases.[54] On the contrary, the US guidelines make a distinction between native- and prosthetic-valve infections. For native-valve endocarditis, gentamicin is suggested for the first 3-5 days of treatment, while for prosthetic-valve infection, initial triple-agent therapy with vancomycin or a β-lactamase-resistant penicillin, rifampin, and gentamicin is recommended.[50,61]

A course of therapy may be difficult to determine for staphylococcal endocarditis in patients truly unable to tolerate a β-lactam. A first-generation cephalosporin, such as cefazolin (100 mg/kg IV daily in 3 equally divided doses), is recommended in patients with non-anaphylactoid penicillin allergies such as a simple skin rash.On the other hand, vancomycin therapy is recommended for *S. aureus* endocarditis in children with anaphylactoid β-lactam allergies. However, glycopeptides may be less effective than β-lactam agents in infections sustained by methicillin-susceptible staphylococci because of their limited bactericidal activity and poor penetration into vegetations.[50]

The choice of antimicrobial therapy for staphylococcal IE might be problematic when blood cultures yield the isolation of methicillin-resistant *S. aureus* (MRSA), as demonstrated by the *in vitro* susceptibility testing. All methicillin-resistant staphylococci carry a low-affinity PBP called PBP2A, which confers cross-resistance to most β-lactam agents. MRSA represents a major cause of nosocomial infection, and glycopeptides remain the standard therapy for the treatment of IE due to such strains. However, the emergence of MRSA strains with reduced susceptibilities to glycopeptides emphasizes the need for new therapeutic approaches that may include vancomycin associated with other antibiotics or new antimicrobial compounds. High vancomycin resistance emerged 15 years ago in enterococci and can be transferred experimentally to *S. aureus*. A few highly vancomycin-resistant *S. aureus* organisms have been isolated in clinics, and their vancomycin-resistance genes were also acquired from enterococci.[62,63]

Quinupristin-dalfopristin (Q-D) is an injectable combination of a type A (dalfopristin) and a type B (quinupristin) streptogramin, which exerts a synergistic effect and is active *in vitro* against MRSA. Unfortunately, most strains of MRSA are cross resistant to macrolide, lincosamide, and streptogramin B (MLS_B)-type antibiotics by methylation of the ribosomal target, and the expression of MLS_B resistance is more frequently constitutive than inducible in MRSA. When it is constitutive, strains are resistant to quinupristin but remain susceptible to Q-D, although the bacterial activity of streptogramins is reduced both *in vitro* and *in vivo*.[64,65] Therefore, in order to increase bacteri-

cidal activity and to prevent the emergence of resistance *in vivo,* Q-D plus another antibiotic might be required for the treatment of severe infection due to quinupristin-resistant strains . Recent reports have demonstrated that combination of Q-D and vancomycin or gentamicin is more active than monotherapy *in vitro* and in experimental rabbit endocarditis due to MRSA with or without the constitutive MLS_B resistance phenotype in terms of the bactericidal activity and the rate of sterilization.[66-68]

Oxazolidinones are a new class of antimicrobials which inhibit the bacterial protein synthesis by binding to the 50S ribosomal subunit and preventing formation of a functional initiation complex in bacterial translation systems. Linezolid is an oxazolidinone indicated in infections sustained by gram-positive microorganisms, and its use in treating staphylococcal infections has been well documented. In fact, this compound has been the subject of few clinical reports of resistance and may provide a needed alternative to glycopeptide therapy in serious multidrug-resistant staphylococcal infections.[69-71]

Recent studies have shown that in rabbits with experimental aortic-valve endocarditis sustained by MRSA linezolid oral therapy to significantly reduced bacterial vegetation densities and was clinically effective. The use of linezolid in cases of serious staphylococcal infections with resistance to vancomycin or other antimicrobials may be a valid approach in humans and may reduce the hospital costs associated with long-term intravenous catheter dosing because of both its intravenous and oral formulation.[70,71]

Among the more active fluoroquinolones against Gram-positive cocci, levofloxacin and garenoxacin were evaluated in the treatment of experimental endocarditis due to *S. aureus*. Levofloxacin was found to be highly effective as a single agent for experimental aortic-valve endocarditis in rabbits infected with methicillin-susceptible or methicillin-resistant strains of *S. aureus*, and resistance to levofloxacin was very uncommon *in vitro* and not observed *in vivo*.[72]

In a recent report, garenoxacin showed a high efficacy in treatment of experimental endocarditis due to *S. aureus*, and sterilized 70% of the vegetations infected with ciprofloxacin-resistant MRSA isolates, while therapy with levofloxacin failed against these organisms. On that account, levofloxacin and garenoxacin may be considered a potential alternative for the treatment of IE sustained by *S. aureus*.[73]

Coagulase-negative staphylococci

CoNS have long been regarded as harmless skin commensals and dismissed as culture contaminants, but their important role as pathogens has been increasingly recognized in recent years. The rising use of prosthetic devices, intravascular catheters, and other invasive technologies in patients who are sicker, immunosuppressed, and at the extremes of life has brought CoNS to the forefront of nosocomial pathogens, resulting in remarkable morbidity and higher medical costs.[74]

While CoNS are one of the common causes of prosthetic valve endocarditis, the role of CoNS as pathogens on native valves is well documented as well. Native-valve endocarditis due to CoNS accounts for 4%–8% of all native-valve infections, generally involves children with documented underlying valvular abnormalities (particularly mitral valve prolapse), and is characterized by a generally indolent clinical course. Despite its usually subacute clinical presentation, it may often lead to serious complications (such as systemic embolization, congestive heart failure, anular abscesses, and disruption of valve leaflets), with a great mortality (up to 36%) and frequent need of operative valve replacement.

Native-valve endocarditis is usually community-acquired in origin, and *Staphylococcus epidermidis* is the most common causal species, even though other bacterial species may be implicated such as *Staphylococcus warneri* and *Staphylococcus lugdunensis*. Particularly, *S. lugdunensis* tends to cause a substantially more virulent form of IE, with a higher rate of perivalvular extension of infection and metastatic embolisms. This organism is usually susceptible *in vitro* to most antibiotics, but most authors recommend that this form of endocarditis be treated with standard regimens based on the *in vitro* susceptibility testing and with a careful monitoring for the development of periannular extension or extracardiac spread of infection.[75-77]

CoNS are the most common cause of prosthetic-valve endocarditis during the first 12

months after surgery, accounting for 40%–50% of all prosthetic-valve infections, with *S. epidermidis* predominating over all other pathogens. CoNS infections tend to have early onset (within 60 days postoperatively), an indolent clinical course, and frequent complications (including dehiscence of the valve, obstruction, or myocardial abscess). Perhaps because of the extra-vascular location of valve-ring abscesses, blood cultures may be negative, with valve dysfunction and fever being the only apparent symptoms. Antibiotic treatment alone is often inadequate, and additional surgical intervention is needed in the majority of cases.[74,77]

CoNS have become increasingly resistant to multiple antibiotics over the years, the most recent threat being the emergence of strains with moderate levels of vancomycin resistance. Antistaphylococcal penicillins (such as methicillin and oxacillin) are the first-line agents for the treatment of susceptible staphylococcal infections. These agents prove potent and rapidly bactericidal, and they have shown effectiveness against difficult-to-eradicate infections such as IE. First- and second-generation cephalosporins, such as cefazolin and cefuroxime, usually show a very high activity against methicillin-sensitive staphylococci, but more than 80% of clinical strains are presently resistant to methicillin and cephalosporins as a whole. These resistant organisms are particularly prominent among patients with healthcare-associated staphylococcal endocarditis. Caution must be exercised in interpreting the results of *in vitro* susceptibility testing because some systems fail to detect oxacillin resistance, particularly among CoNS. Oxacillin-resistant strains also are clinically resistant to cephalosporins and carbapenems and should be treated with glycopeptides.[50,74]

Glycopeptides are not as rapidly bactericidal as methicillin, but they have emerged as the mainstay therapy for methicillin-resistant staphylococcal infections in the last three decades. However, the widespread distribution of vancomycin resistance among enterococci and reduced vancomycin susceptibility among *S. aureus* and CoNS, in addition to the detection of vancomycin-resistant *Staphylococcus haemolyticus*, emphasize the importance of a more selective and appropriate use of these antimicrobial agents.[78]

A variety of other antibiotics may test active against CoNS, but their effectiveness is very variable and must be confirmed by *in vitro* susceptibility testing. Rifampin demonstrates highly active against staphylococci, but the rapid development of induced resistance during treatment limits its usefulness. Thus, this last drug should be employed only in association with other antistaphylococcal agents.[74,77,78]

Aminoglycosides have a bactericidal effect against susceptible CoNS strains, and may be synergistic with methicillin, vancomycin, and rifampicin *in vitro*.[79] In a retrospective clinical study, the enhanced efficacy of combination antibiotic regimens in prosthetic-valve endocarditis due to *S. epidermidis* was evaluated, and the addition of rifampicin and/or an aminoglycoside to vancomycin therapy improved the cure rates to 90%, compared with a cure rate of 50% for vancomycin monotherapy.[80] Therefore, the US guidelines for native-valve endocarditis due to CoNS recommend treatment with nafcillin or vancomycin (depending on the susceptibility testing) for 4-6 weeks with or without addition of gentamicin for the first 3-5 days of therapy. In patients with prosthetic-valve endocarditis, triple-drug therapy with either nafcillin or vancomycin and rifampicin administered for a minimum of 6 weeks, together with gentamicin for the initial 2 weeks of treatment, is recommended. If the organism is resistant to gentamicin, then an aminoglycoside to which it is susceptible should be substituted for gentamicin. If there is a resistance to all available aminoglycosides, the aminoglycosides should be omitted.[50,65]

Alternative therapy with trimethoprim-sulfamethoxazole, doxycycline, minocycline, or newer antimicrobial compounds (such as Q-D and linezolid) has the potential to treat IE due to CoNS, but published experimental data are limited. Such alternative therapies should be further evaluated in larger clinical trials.[50,81,82]

Streptococci

Viridans group streptococci (or α-haemolytic streptococci) are common etiologic agents responsible for community-acquired endocarditis. The taxonomy of viridans group streptococci is evolving, and the species most commonly associated with IE include *S. sanguis, S. mitis, S. salivarius, S. mutans, Gemella morbillorum*,

and members of the *S. milleri* or *S. intermedius* group (*S. intermedius, S. anginosus,* and *S. constellatus*). In contrast to other α-haemolytic streptococci, the *S. milleri* group tends to form abscesses and cause hematogenously disseminated infections. As a consequence, the duration of antimicrobial therapy for IE sustained by these organisms may need to be longer than that for endocarditis caused by other α-haemolytic streptococci. Moreover, although the *S. intermedius* group usually shows a full sensitivity to penicillin, some strains may exhibit variable penicillin resistance. At the same time, *S. pneumoniae* accounts for 3% to 5% of cases in children, and multi-drug resistance among clinical isolates of this microorganism during the 1990s has progressively increased.

In a recent retrospective study, patients with endocarditis due to β-haemolytic streptococci tended to have more underlying medical conditions and fewer previous heart disorders than those with infection sustained by viridans streptococci. Multivariate analyses showed that a longer median time of IE evolution before diagnosis and identification of the presumed portal of entry were independently associated with viridans streptococci endocarditis, while extracardiac complications were more frequent in the β-haemolytic streptococci group. In both variants of IE just noted, about 60% of patients underwent surgical valve replacement, mortality ranged from 14% to 27%, and the only significant risk factor for death was older age.[83]

IE caused by β-haemolytic streptococci is infrequently seen, but the incidence of endocardial infection due to *Streptococcus agalactiae* has increased during recent years in elderly patients, non-pregnant women, and patients with chronic immunosuppressive disease such as alcoholism, diabetes mellitus, liver cirrhosis, malignancies, and HIV infection. Although *S. agalactiae* is usually highly susceptible to penicillin, cardiac surgery is often necessary for treatment because of the rapid valvular destruction and the high incidence of systemic embolisms. The large size of vegetations and their friability may explain the frequent occurrence of systemic embolization, and the lack of *S. agalactiae* fibrinolysin production in the vegetations might also account for the pathogenesis of this complication. *S. agalactiae* endocarditis usually involves native valves and is associated with an overall mortality ranging from 10%–20% in patients with right-sided infection, to 30%–40% in those with left-sided endocarditis. Prosthetic-valve disease is rarely reported, but it is associated with the highest mortality rate (80%–90%).[84,85]

S. agalactiae and other β-haemolytic streptococci are usually sensitive to penicillin, but penicillin-tolerant *S. agalactiae* isolates have been increasingly described in subjects with serious infections that have been associated with therapeutic failures. Streptococci are becoming increasingly resistant to penicillin and other β-lactam antibiotics because of a reduced β-lactam affinity of their membrane-bound PBPs.[86] Therefore, it is important to recognize penicillin tolerance by *in vitro* susceptibility testing because it could be associated with treatment failure. The combination of a β-lactam agent with an aminoglycoside shows *in vitro* and *in vivo* synergistic activity against penicillin-susceptible and –resistant *S. agalactiae* strains.[87]

A 4-week regimen of intravenous penicillin G achieves a high cure rate in native-valve streptococcal endocarditis, and this approach is preferred for children with impairment of renal or eighth cranial nerve function. In adults, four weeks of therapy with ceftriaxone given once daily is also recommended, but there are no published data on the efficacy and safety of ceftriaxone in the treatment of pediatric IE. Although experience in childhood is limited, ceftriaxone may prove to be equally useful in children with endocarditis.[3]

Two weeks of therapy with penicillin, ampicillin or ceftriaxone combined with gentamicin has become increasingly popular, and this regimen is recommended for uncomplicated cases of native-valve endocarditis but not for patients who have had clinical symptoms of endocarditis for more than three months. It is also inappropriate for children who have an extracardiac focus of infection, an intracardiac abscess, a mycotic aneurysm, or previous adverse events caused by gentamicin therapy.[88,89]

Several studies have demonstrated the safety and efficacy of once daily dosing of gentamicin in children with infections other than endocarditis. There is less clinical experience with this regimen in children than in adults. Particularly,

there are no published studies about the use of a single daily dosing of gentamicin for the treatment of infective endocarditis in children.[3]

For children who are unable to tolerate β-lactam antibiotics, vancomycin should be used in combination with gentamicin, but caution should be exercised because of the possible nephrotoxicity associated with this combination. Similarly, very few cases of penicillin-resistant viridans streptococcal endocarditis have been reported in the international literature. *In vitro* studies and experimental animal models have demonstrated that a combination of penicillin and streptomycin is significantly more effective than penicillin alone, in decreasing concentrations of bacteria in cardiac valve vegetations caused by penicillin-resistant strains of viridans streptococci. The combinations of vancomycin or teicoplanin and gentamicin, and of imipenem and gentamicin also tested effective. Present consensus guidelines suggest that penicillin-resistant viridans streptococcal IE should be treated in the same manner as enterococcal endocarditis, with the association of penicillin G or ampicillin and gentamicin for 4-6 weeks.[50,90]

Prosthetic-valve streptococcal endocarditis caused by penicillin-susceptible strains should be treated with a 6-week course of penicillin, ampicillin, or ceftriaxone therapy combined with gentamicin for the first two weeks, while infections caused by penicillin-resistant streptococci should be treated with a combination of penicillin, ampicillin or ceftriaxone associated with gentamicin for six weeks.

Vancomycin or newer antibiotics (e.g., Q-D and linezolid) active against drug-resistant, gram-positive bacteria may be effective when used alone or in combination with other drugs. In particular, the effectiveness of streptogramins against viridans streptococci is somewhat dependent on the species, being least active against *Streptococcus bovis* and most active against *Streptococcus gordonii* and *S. mitis*.[82] Recommended antimicrobial regimens for streptococcal endocarditis in children are reported in Table 5.

Enterococci

Enterococcal endocarditis is relatively rare in children, and its treatment is often difficult because of the frequent resistance of enterococci to penicillin and ampicillin and their variable resistance to aminoglycosides and glycopeptides. In comparison with streptococci, enterococci are inherently more resistant to β–lactam agents and are typically more tolerant to the bactericidal activity of these and other antimicrobial compounds that act at the level of the cell wall synthesis. Streptococci are usually killed by penicillin, ampicillin, or vancomycin alone, whereas enterococci are inhibited but not killed. Killing of susceptible strains of enterococci calls upon the synergistic effect of penicillin, ampicillin, or vancomycin in association with gentamicin or streptomycin.[91]

Enterococcus faecalis, *Enterococcus faecium*, and *Enterococcus durans* are the major enterococcal species of clinical interest. For *E. faecalis*, MIC_{90} values of 1 mg/L for ampicillin and 2 mg/L for penicillin G and vancomycin have been reported, and ampicillin in combination with an aminoglycoside is considered as the first-line treatment option in *E. faecalis* endocarditis. *E. faecium* strains are typically resistant to β–lactams, whereas the MIC_{90} for vancomycin is still 2 mg/L. For teicoplanin, the lowest MIC_{90} to *E. faecalis* and *E. faecium* (0.5 mg/L) of all tested antibiotics has been reported, but the clinical experience of IE therapy with teicoplanin is still limited.[91,92]

Resistance to β–lactams has been attributed to intrinsic resistance traits of low affinity to PBPs and to β–lactamase production. Transferable resistance to glycopeptides was first reported in 1986 and has been recognized with rising frequency in nosocomial strains of *E. faecalis* and *E. faecium* from intensive care unit settings in both North America and Europe, and a 26-fold increase in vancomycin resistance nationwide in the US was documented between 1989 and 1993.[93] Enterococcal strains are also proportionally resistant to aminoglycosides, the average gentamicin and tobramycin MIC_{90} values being 8–64 mg/L, and high-level aminoglycoside resistance mediated by various enzymes is becoming a significant problem in some areas.[92,93]

Numerous studies have confirmed the *in vitro* synergy of penicillin G and gentamicin against enterococci, and subsequent *in vitro* studies focused on defining a minimum aminoglycoside concentration required to maintain synergistic activity and to reduce the risk of nephrotoxic

Table 5. Recommended antibiotic treatment for pediatric endocarditis sustained by viridans group streptococci, *Streptococcus bovis*, or Enterococci*[3,50]

Microorganisms	Regimens for native-valve endocarditis	S.R.	Regimens for prosthetic-valve endocarditis	S.R.
Penicillin-susceptible streptococci (MIC ≤ 0.12 μg/mL)	**Penicillin G**† (200,000 Units/kg IV daily in 4-6 equally divided doses) **or ceftriaxone** (100 mg/kg IV/IM daily) for 4 wk ***or*** **Penicillin G**† (200,000 Units/kg IV daily in 4-6 equally divided doses) **or ceftriaxone** (100 mg/kg IV/IM daily) ***plus*** **gentamicin**‡ (3 mg/kg IV/IM daily in 3 equally divided doses) for 2 wk	A1 A2	**Penicillin G**† (300,000 Units/kg IV daily in 4-6 equally divided doses) **or ceftriaxone** (100 mg/kg IV/IM daily) for 6 wk ***plus*** **gentamicin**‡ (3 mg/kg IV/IM daily in 3 equally divided doses) for 2 wk	A2
Streptococci relatively resistant to penicillin (MIC > 0.12 μg/mL and ≤ 0.5 μg/mL)	**Penicillin G**† (300,000 Units/kg IV daily in 4-6 equally divided doses) **or ceftriaxone** (100 mg/kg IV/IM daily) for 4 wk ***plus*** **gentamicin**‡ (3 mg/kg IV/IM daily in 3 equally divided doses) for 2 wk	A2	**Penicillin G**† (300,000 Units/kg IV daily in 4-6 equally divided doses) **or ceftriaxone** (100 mg/kg IV/IM daily) for 6 wk ***plus*** **gentamicin**‡ (3 mg/kg IV/IM daily in 3 equally divided doses) for 6 wk	A2
High-level penicillin-resistant Streptococci (MIC > 0.5 μg/mL), nutritionally variant viridans streptococci, or penicillin-susceptible enterococci[3]	**Penicillin G**† (300,000 Units/kg IV daily in 4-6 equally divided doses) **or ampicillin** (300 mg/kg IV daily in 4-6 equally divided doses) ***plus*** **gentamicin**‡ (3 mg/kg IV/IM daily in 3 equally divided doses) for 4-6 wk¶	A2	**Penicillin G**† (300,000 Units/kg IV daily in 4-6 equally divided doses) **or ampicillin** (300 mg/kg IV daily in 4-6 equally divided doses) ***plus*** **gentamicin**‡ (3 mg/kg IV/IM daily in 3 equally divided doses) for at least 6 wk	A2
Penicillin-resistant enterococci - β-lactamase-producing strain	**Ampicillin-sulbactam** (300 mg/kg IV daily in 4 equally divided doses) **or vancomycin** (30 mg/kg IV daily in 2 equally divided doses) ***plus*** **gentamicin**‡ (3 mg/kg IV/IM daily in 3 equally divided doses) for 6 wk	B3	**Ampicillin-sulbactam** (300 mg/kg IV daily in 4 equally divided doses) **or vancomycin** (30 mg/kg IV daily in 2 equally divided doses) ***plus*** **gentamicin**‡ (3 mg/kg IV/IM daily in 3 equally divided doses) for 6 wk	B3
-intrinsic penicillin resistance	**Vancomycin** (30 mg/kg IV daily in 2 equally divided doses) ***plus*** **gentamicin**‡ (3 mg/kg IV/IM daily in 3 equally divided doses) for 6 wk		**Vancomycin** (30 mg/kg IV daily in 2 equally divided doses) ***plus*** **gentamicin**‡ (3 mg/kg IV/IM daily in 3 equally divided doses) for 6 wk	

IV, intravenous; IM, intramuscular; PO, oral; MIC, minimum inhibitory concentration; S.R., strength of recommendation

** Recommended dosages are for patients with normal renal and hepatic function. Pediatric dose should not exceed that of a normal adult. The 2-week regimens are not recommended for patients with symptoms of infection > 3 months in duration, those with extracardiac focus of infection, myocardial abscess, mycotic aneurysm, creatinine clearance of < 20 mL/min, impaired eighth cranial nerve function, or infection with nutritionally variant viridans streptococci (Abiotrophia spp., Granulicatella spp., Gemella spp.).*

† Ampicillin (300 mg/kg IV daily in 4-6 equally divided dosages) may be used as alternative to penicillin G. Vancomycin (40 mg/kg IV daily in 2-3 equally divided doses) is recommended only for patients unable to tolerate penicillin or ceftriaxone.

‡ Gentamicin therapy should be used only with gentamicin-susceptible strains. Studies in adults suggest that dosage of gentamicin should be adjusted to achieve peak and trough concentrations in serum of approximately 3-4 and <1 μg/mL, respectively, when 3 divided doses are used. Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of IE exist.

§ For IE sustained by enterococci resistant to gentamicin, recommended treatment included penicillin G or ampicillin plus streptomycin (20-30 mg/kg IV/IM daily in 2 equally divided doses) for 4-6 weeks.

¶ Studies in adults suggest that 4-week treatment is sufficient for patients with enterococcal endocarditis with symptoms of infection of < 3-month duration; 6-week therapy is recommended for patients with symptoms of infection > 3-month duration.

effects. Regimens including a sustained penicillin G concentration of ≥5 μg/mL plus either 3 or 5 μg/mL of gentamicin were found to be equally synergistic *in vitro*.[94,95] Because of increasing prevalence of *E. faecalis* isolates with high-level resistance to aminoglycosides, some authors have explored the potential synergistic interaction between two β–lactam agents showing a significant bactericidal synergistic effect against enterococci, such as amoxicillin and cefotaxime or imipenem, or ampicillin and ceftriaxone. This synergy could be explained by the partial saturation of PBPs 4 and 5 by amoxicillin at low concentration (0.06 μg/mL), combined with the total saturation of PBPs 2 and 3 by cefotaxime at 4 μg/mL.[96]

The American Heart Association recommends for enterococcal endocarditis a combined treatment with penicillin G or ampicillin plus an aminoglycoside for a total duration of 4–6 weeks. Particularly, a 4-week combined therapy course is recommended for patients with symptoms of 3 months' duration, while a 6-week combined course is suggested for whose with longer symptom duration.[50]

Recently, some authors have evaluated the clinical outcome of enterococcal IE when the total duration of aminoglycoside therapy was reduced, in order to decrease the risk of aminoglycoside toxicity, which affects the elderly population more than any other. They concluded that reducing the administration of the aminoglycoside component to two weeks only would maintain clinical efficacy while decreasing potential nephrotoxicity. The theoretical explanation for these results after shortened synergistic aminoglycoside therapy in enterococcal endocarditis remains unclear. The sustained synergistic bactericidal concentrations during the first weeks of treatment might kill most of the tolerant or relatively resistant subpopulations, leaving minor populations which are sensitive to the relatively large doses of ampicillin or penicillin G that are employed in modern regimens.[91]

In IE sustained by enterococci susceptible to penicillin, aminoglycosides, and vancomycin, combinations of penicillin or ampicillin with gentamicin are preferred to combined vancomycin-gentamicin because of the increased risk of ototoxicity and nephrotoxicity associated with the latter. Thus, vancomycin therapy should be administered only in children unable to tolerate penicillin or ampicillin. Patients with either native-valve or prosthetic-valve endocarditis should receive at least six weeks of therapy.

In vancomycin-resistant enterococcal episodes, Q-D combined with an aminoglycoside or high-dose ampicillin may prove useful.[93,97] Oxazolidinones may be an effective alternative for the treatment of enterococcal endocarditis resistant to ampicillin, vancomycin, and streptogramins. Although the US Food and Drug Administration has not approved linezolid specifically for the therapy of IE, there are several reports of its use both in animal models and in patients with endocarditis due to vancomycin-resistant *E. faecium*.[98,99] Recently, successful treatment of *E. faecalis* prosthetic-valve endocarditis with linezolid was also reported,[100] but the effectiveness of this antibiotic in subjects with enterococcal bacteremia or endocarditis has not been formally assessed, and further clinical studies are needed (Table 6).[101]

Synergistic bactericidal activity *in vitro* and *in vivo* for *E. faecalis* strains has been demonstrated with double β–lactam combinations of imipenem and ampicillin or cephalosporin and ampicillin, probably as a result of the saturation of different penicillin-binding protein targets. These double β–lactam combinations have been used to treat endocarditis sustained by high-level aminoglycoside-resistant strains in experimental enterococcal endocarditis and in a small number of patients with endocarditis caused by a strain of multidrug-resistant *E. faecalis*. For endocarditis resulting from enterococci resistant to multiple antibiotics, a surgical approach may be recommended, and cardiac valve replacement may be the only chance of cure in some patients.[50]

Rare bacterial agents and fungi

Culture-negative endocarditis is not an uncommon clinical observation. In fact, sterile blood cultures have been noticed in 2.5% to 31% of patients with IE. Blood cultures are frequently sterile when antibiotic therapy has been administered before sampling and in subjects with subacute right-sided endocarditis, mural endocarditis, and endocarditis sustained by slow-growing or fastidious organisms, such as *Brucella* spp., *Bartonella* spp., *Legionella*

Table 6. Recommended antibiotic treatment for both native- and prosthetic-valve pediatric endocarditis sustained by enterococci resistant to penicillin, aminoglycosides and glycopeptides*[3,50]

Microorganisms	Regimens	S.R.
Enterococcus faecium	***Linezolid*** (30 mg/kg IV/PO daily in 3 equally divided doses) for at least 8 wk	C3
	or	
	quinupristin-dalfopristin (22.5 mg/kg IV daily in 3 equally divided doses) for at least 8 wk	C3
Enterococcus faecalis	***Imipenem-cilastatin*** (60-100 mg/kg IV daily in 4 equally divided doses) ***plus ampicillin*** (300 mg/kg IV daily in 4-6 equally divided doses) for at least 8 wk	C3
	or	
	ceftriaxone (100 mg/kg IV/IM daily in 2 equally divided doses) ***plus ampicillin*** (300 mg/kg IV daily in 4-6 equally divided doses) for at least 8 wk	C3

IV, intravenous; IM, intramuscular; PO, oral; S.R., strength of recommendation.
**Dosages recommended for patients with normal renal and hepatic function. Pediatric dose should not exceed that of a normal adult.*

spp., the HACEK group, *Mycoplasma* spp., *Coxiella burnetii*, *Abiotrophia* spp., *Chlamydia* spp., or anaerobe organisms.[102]

Although Brucellosis rarely causes endocarditis (0.3% to 0.6% of patients) it represents the most frequent cause of death. *Brucella* endocarditis is a destructive process, predominantly involving the aortic valve and perivalvular tissues, and evidence of underlying valvular disease (including prosthetic valve) is found in two-thirds of involved patients. The current recommendation is a combined medical and surgical treatment, especially when an infected prosthetic valve is of concern. The majority of authors suggest for pediatric brucellosis a combination of oral trimethoprim (4 mg/kg twice a day)-sulfamethoxazole (20 mg/kg twice a day) and intramuscular gentamicin (3 mg/kg daily) for one week, followed by oral trimethoprim-sulfamethoxazole and rifampin (10–20 mg/kg daily) for at least three months.[103]

Bartonella henselae and *Bartonella quintana* cause a subacute, insidious endocarditis, and most patients present with acute cardiac failure because the diagnosis is usually considerably delayed. Predisposing factors for *B. henselae* endocarditis include previous heart valve injuries, while *B. quintana* infection occurs mainly in alcoholics or homeless persons who have been exposed to body lice and who are without previous valve abnormalities. Although a standard regimen for the antibiotic therapy of *Bartonella* endocarditis has not been established, based on the relevant clinical data and the *in vitro* activity of antimicrobial compounds, a β-lactam agent (amoxicillin or ceftriaxone) in combination with an aminoglycoside for at least two weeks, or a β-lactam agent combined with rifampin for 6 weeks or more is recommended in children.[104]

HACEK group bacteria are fastidious, small, gram-negative bacilli (primarily members of the oropharyngeal flora), including *H. parainfluenzae*, *Haemophilus influenzae*, *Haemophilus aphrophilus*, *Haemophilus paraphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* spp.. HACEK bacteria are reported to cause around 3% of all episodes of endocarditis. Common epidemiological characteristics include previous dental procedures, infections in young- and middle-aged adults, previous underlying heart disease, and a preference for mitral valve. In the past, ampicillin plus gentamicin was the first-line therapy. However, emerging β-lactamase-producing organisms in this group have prompted a change in the treatment strategy, which should now include a β-lactamase-stable cephalosporin in place of ampicillin. The American Heart Association recommends a treatment of 4 weeks for native valve endocarditis, and of 6 weeks for prosthetic valve infections with ceftriaxone alone (preferred for outpatient treatment) or the association of ampicillin and gentamicin (Table 7).[46,105]

Fungal endocarditis in children is very uncommon, and medical therapy is usually unsuccessful. With the exception of neonates with mural endocarditis and, occasionally, older children, for most patients with fungal IE, surgery associated with antifungal treatment is

Table 7. Recommended antibiotic treatment for both native- and prosthetic-valve pediatric endocarditis sustained by HACEK microorganism and for culture-negative endocarditis*[3,50]

Microorganisms	Regimens	S.R.
HACEK microorganism	**Ceftriaxone** (100 mg/kg IV/IM once daily) for 4 wk	A2
	or	
	ampicillin-sulbactam (300 mg/kg IV daily in 4 equally divided doses) for 4 wk†	B2
	or	
	ciprofloxacin (20-30 mg/kg IV/PO daily in 2 equally divided doses) for 4 wk†	C3
Culture-negative, native valve	**Ampicillin-sulbactam** (300 mg/kg IV daily in 4-6 equally divided doses) ***plus*** **gentamicin** (3 mg/kg IV/IM in 3 equally divided doses) for 4-6 wk	B3
	or	
	vancomycin (40 mg/kg IV daily in 2-3 equally divided doses) ***plus*** **gentamicin** (3 mg/kg IV/IM in 3 equally divided doses) ***plus*** **ciprofloxacin** (20-30 mg/kg IV/PO daily in 2 equally divided doses) for 4-6 wk	B3
Culture-negative, prosthetic valve	**Vancomycin** (40 mg/kg IV daily in 2-3 equally divided doses) ***plus*** **cefepime** (150 mg/kg IV daily in 3 equally divided doses) ***plus*** **rifampin** (20 mg/kg IV/PO in 3 equally divided doses) for 6 wk ***plus*** **gentamicin** (3 mg/kg IV/IM in 3 equally divided doses) for 2 wk	B3

HACEK, Haemophilus parainfluenzae, H. aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae; IV, intravenous; IM, intramuscular; PO, oral; S.R., strength of recommendation.

** Dosages recommended for patients with normal renal and hepatic function. Pediatric dose should not exceed that of a normal adult.*

† The duration of antibiotic therapy should be 6 wk for prosthetic-valve endocarditis.

required. Amphotericin B remains the first-line antifungal agent for medical therapy, although it does not penetrate vegetations well. Long-term suppressive therapy with imidazoles (e.g., fluconazole and voriconazole) may be effective in patients with fungal infection and unable to undergo curative surgery, but there are no clinical data about their efficacy in childhood. Some authors recommend the addition of 5-fluorocytosine to amphotericin B for *Candida* endocarditis caused by strains susceptible to this drug, because of their synergistic activity which may potentiate fungal killing.

Finally, liposomal forms of amphotericin B may be employed in children with moderate to severe renal impairment or those with previously significant infusion-related adverse effects.[3] Novel antifungal agents approved for the treatment of visceral mycoses (e.g., caspofungin and voriconazole) are currently under study in the pediatric population.

SURGICAL TREATMENT

Surgical treatment is sometimes indicated in patients with IE, and several studies suggest that combined medical and surgical therapy can decrease mortality among subjects who present with congestive heart failure, perivalvular invasive disease, or uncontrolled infection despite appropriate antimicrobial therapy. In fact, surgical procedures in patients with IE have three different aims: to correct valvular dysfunction, to remove infected tissue, and to clear away mobile vegetations, which are the source of systemic embolisms.

Common indications for surgery include progressive heart failure, valvular obstruction, perivalvular extension of infection (periannular abscess), fungal endocarditis, persistent bacteremia despite appropriate antimicrobial therapy, metastatic infections, mycotic aneurysms, unstable prosthesis with dehiscence, ruptured sinus of Valsalva or ventricular septum, and significant embolic complications (mostly cerebral, pulmonary, renal, and coronary), especially when the aortic or mitral valve is involved.[106-108]

Congestive heart failure is the strongest indication for surgery and the hemodynamic

status of the patient at the time of valve replacement is the principal determinant of operative mortality.[109-111]

Congestive heart failure may occur acutely or insidiously and may be caused by abrupt structural changes, including perforation of a valve leaflet, rupture of mitral chordae or fistulous tracts, or from development of perivalvular leaks or dehiscence in children with prosthetic valves. Progressive congestive heart failure is usually caused by worsening valvular regurgitation, often associated with ventricular dysfunction. Urgent surgical treatment in patients with moderate to severe heart failure improves the likelihood of survival and preservation of cardiac function.[112-114]

Periannular extension of valvular infection increases the risk of congestive heart failure, with the greatest risk associated with aortic valve endocarditis. Moreover, periannular abscess may lead to fistulous tracts into the pericardium as well as between cardiac chambers or vascular structures. Intracardiac abscesses or fistulas generally do not respond to antimicrobial therapy alone and require surgical intervention. The extension of bacterial infection beyond valve leaflets are non-specific and include persistent fever with bacteremia, recurrent embolic events, development of new atrioventricular or bundle-branch block, and new pathologic murmurs or worsening congestive heart failure in patients treated with appropriate antibiotics.

Prosthetic-valve endocarditis is another common indication for surgical evaluation, especially in patients with perivalvular extension of infection and IE sustained by *S. aureus*. On the other hand, subjects with late onset of infection (more than 12 months after implantation of a prosthesis) and endocarditis caused by viridans streptococci, HACEK organisms, or enterococci can be treated with antimicrobial agents alone.[51] A potentially life-threatening complication observed in children with IE is the occurrence of infection in a surgically created shunt or conduit. Because these prosthetic devices are often Gortex or Dacon tubes, the likelihood of cure with antibiotics alone is reduced, and surgical treatment is frequently requested.[115,116]

Embolic complications may occur in any patient with IE, but they are more frequent in those with larger sized intracardiac vegetations. Even in the absence of previous embolization, vegetations with diameter > 10 mm seem to have a great predictive value for embolic events. The location of the primary vegetation is also a predictive factor for embolization: in adults, mitral lesions are associated with higher rates of embolization than aortic vegetations (25% *versus* 10%, respectively), and the highest rate of embolic events is associated with the vegetations attached to the anterior rather than the posterior mitral leaflet.[117]

With regard to the type of etiological agents, staphylococcal and fungal endocarditis carry the highest risk of embolism regardless of vegetation size or location. Most embolic events occur within the first 2 to 4 weeks after therapy is instituted, but embolization can occur also before diagnosis, at any phase of antibiotic therapy, or after therapy is completed. An increase in vegetation size during the fourth to the eighth week of therapy is predictive of embolization and abscess formation and may require a valve replacement.[3,4] Surgical therapy is generally advised for IE caused by some microorganisms refractory to medical treatment (such as *Pseudomonas aeruginosa*, *Brucella spp.*, *Coxiella burnetii*, *Candida spp.* and other fungi) and in subjects with uncontrolled sepsis in spite of maximal antimicrobial therapy.[115-117]

Mycotic aneurysms are another complication of IE. Such aneurysms may result from septic embolization or from the spread of infection from contiguous tissues to the adjacent arterial wall. In most cases, development of mycotic aneurysms is an indication for cardiac surgery, and overall mortality among patients with intracranial mycotic aneurysm is high.[4] The decision when to perform acute surgery in patients with IE is often difficult because of the frequent concurrent complications (such as cerebral hemorrhage or stroke, renal failure, or myocardial infarction) which remarkably increase the operative risk. The optimal time to perform surgery is before severe hemodynamic compromission or spread of the infection to perivalvular tissue has occurred. Surgery should not be delayed solely because a full course of antibiotic therapy has not been completed.

The operative mortality after valve replace-

ment due to active IE has varied from 5% to 30% in modern reports, and the short- and medium-term results after early surgery (i.e., surgery during antibiotic treatment) are comparable to those obtained by valvular surgery after the conventional period of antibiotic therapy.[118,119] The duration of antibiotic therapy after valve-replacement surgery for active IE has not been assessed in carefully controlled trials, and it should depend on the length of preoperative therapy, the presence of perivalvular infection, and the microbiological and pathological findings.[51,120] If the infant is considered too unstable for a complicated surgical intervention, the treatment options are limited, and these infants frequently succumb because of severe complications, such as persisting septic shock, dissemination of septic emboli, or destruction of infected valves.

Successful treatment with recombinant tissue plasminogen activator (r-TPA) has been reported in children with extremely low birth weight. Thrombolytic therapy in patients with IE acts by degrading the fibrin clots and disrupting valvular vegetations. The advantage of r-TPA over other thrombolytic agents is its high affinity for fibrin and low affinity for circulating plasminogen, allowing disruption of the thrombus without causing systemic anticoagulation.[121-123] In a recent, prospective, 3-year study, seven high-risk infants (one with congenital heart disease and six receiving prolonged parenteral nutrition via indwelling catheters) with IE who failed to respond to conventional medical therapy were treated with r-TPA. All infants responded promptly to treatment, with resolution of the intracardiac vegetations within 3 to 4 days of commencement and without any adverse complications. All patients survived without long-term cardiac morbidity, showing that r-TPA may offer a safe alternative to surgical intervention in the high-risk infants with IE.[121]

PROPHYLAXIS

Endocardial infection should be prevented whenever possible by the use of antimicrobial compounds because of the elevated morbidity associated with endocardial infection. However, prophylaxis of endocarditis is a complex issue, involving different aspects of medicine, microbiology, dentistry, surgery, epidemiology, and decision analysis, and it is not always possible. Certain health care procedures cause bacteremia with microorganisms often responsible for IE, and antibiotics should be given to patients with predisposing heart disease before these procedures, in order to prevent bacteremia and endocardial infection.

Determination of adequate prophylaxis implies establishing the spectrum of patients at risk, the procedures that might provoke bacteremia, the most effective prophylactic regimen, and a balance between the risk of side effects of prophylaxis and of developing IE. Patients at risk and procedures responsible for bacteremia have been identified by clinical studies, and recommendations for prophylaxis have been suggested in several countries, but the effectiveness of these methods has not been evaluated by randomized, placebo-controlled, clinical trials. Results of case control studies show that prophylaxis is effective, but prevents only a limited number of cases.[47,124-126]

For patients with prosthetic valves and subjects with earlier episodes of IE, the benefits of antibiotic prevention have been demonstrated, and a single-dose prophylaxis with amoxicillin is now widely accepted in European countries for these risk groups. On the other hand, recent studies have concluded that dental treatment does not seem to be a risk factor for IE, even in patients with valvular abnormalities.[127,128]

Prophylaxis is recommended in individuals who have a higher risk for developing endocarditis than the general population and is particularly important for subjects in whom endocardial infection is associated with higher morbidity and mortality rates. Certain cardiac conditions are followed by IE more often than others. Table 8 stratifies heart abnormalities into high-, moderate-, and negligible-risk categories primarily on the basis of potential outcome if endocarditis occurs. Procedures associated with the risk of bacteremia and endocarditis are listed in Table 9. The American Heart Association recommends antimicrobial prophylaxis only in subjects belonging to the high- and moderate-risk groups, or rather in children in whom endocarditis is associated with high morbidity and mortality. Individuals in the negligible risk category have no greater risk for developing endocarditis than does the

Table 8. Heart abnormalities associated with the risk of infective endocarditis[129]

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

Moderate-risk category
- Most other congenital cardiac malformations
- Acquired valvular dysfunction (such as rheumatic heart disease)
- Hypertrophic cardiomyopathy
- Mitral valve prolapse with valvular regurgitation and/or thickened leaflets

Negligible-risk category (prophylaxis not recommended)
- Surgical repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus (without residua beyond 6 mo)
- Isolated secundum atrial septal defect
- Previous coronary artery bypass graft surgery
- Mitral valve prolapse without valvular regurgitation
- Physiologic, functional, or innocent heart murmurs
- Previous Kawasaki disease without valvular dysfunction
- Previous rheumatic fever without valvular dysfunction
- Cardiac pacemakers and implanted defibrillators

Table 9. Procedures for which antibiotic endocarditis prophylaxis is recommended[129]

Dental procedures
- Dental extractions
- Periodontal procedures (such as surgery, scaling and root planing, probing, and recall maintenance)
- Dental implant placement and reimplantation of avulsed teeth
- Endodontic (root canal) instrumentation or surgery only beyond the apex
- Subgingival placement of antibiotic fibers or strips
- Initial placement of orthodontic bands but not brackets
- Intraligamentary local anesthetic injections
- Prophylactic cleaning of teeth or implants where bleeding is anticipated

Respiratory tract procedures
- Tonsillectomy and/or adenoidectomy
- Surgical operations involving respiratory mucosa
- Bronchoscopy carried out with a rigid bronchoscope

Gastro-intestinal tract procedures
- Sclerotherapy for esophageal varices
- Esophageal stricture dilation
- Endoscopic retrograde cholangiography with biliary obstruction
- Biliary tract surgery
- Surgical operations involving intestinal mucosa

Genitourinary tract procedures
- Prostatic surgery
- Cystoscopy
- Urethral dilatation

general population.

Antimicrobial prophylaxis in children with mitral valve prolapse is debated still today. Subjects with prolapsing and regurgitant mitral valve are at increased risk of endocarditis and are placed in the moderate-risk category. In two of the last three large clinical studies of pediatric patients with IE, mitral valve prolapse has been the underlying cardiac diagnosis in large numbers of patients. However, children without mitral valve regurgitation have not been demonstrated to be at higher risk than general population and are placed in the negligible-risk category.[6,12] Bacteremias usually occur during several daily activities, such as routine tooth brushing or chewing. Significant bacteremias considered for endocarditis prevention are only those caused by bacteria commonly responsible for IE and attributable to identifiable procedures.

The recommended antimicrobial prophylaxis for dental, oral, respiratory tract, or oesophageal procedures (mostly caused by viridans streptococci) is a single dose of oral amoxicillin (50 mg/kg), administered one hour before the procedure. In patients allergic to penicillin, a single dose of clindamycin, azithromicin, or clarithromicin could be employed.

Bacterial endocarditis following genitourinary and gastrointestinal tract surgery or instrumentation is most often sustained by enterococci, and prophylaxis is specified with regard to the category of risk. In high-risk patients, a combination regimen of parenteral ampicillin (50 mg/kg) and gentamicin (1.5 mg/kg) within 30 minutes of starting the procedure is suggested, followed by parenteral ampicillin (25 mg/kg) or oral amoxicillin (25 mg/kg), six hours later. In individuals at moderate risk, a single dose of oral amoxicillin (50 mg/kg) one hour before procedure or parenteral ampicillin (50 mg/kg) within 30 minutes of starting the

procedure is suggested. In patients which are known to be allergic to penicillins, the β-lactam agent could be replaced with vancomycin.[129] Despite a lack of convincing evidence, antibiotic prophylaxis is an A3 recommendation.[47]

CONCLUSIONS

In recent years, IE has shown an increasing frequency in childhood and is associated with a significant morbidity still today. Over the past decade, significant improvements in the diagnosis and treatment of IE have been made, and classical forms of endocarditis have been almost completely eradicated.

However, survivors of surgery for complex congenital heart abnormalities, children with implanted prosthetic valves or vascular grafts, and pediatric intensive care unit patients with indwelling venous catheters have significantly changed the epidemiology of pediatric endocarditis. As a consequence, the not uncommon observation of IE in children requires that primary care physicians, as well as specialists, consider this diagnosis in pediatric patients.

Numerous questions remain unanswered, including the most appropriate antimicrobial treatment for IE, the real efficacy of antibiotic prophylaxis, bacterial decolonisation, and antiadhesin vaccines, owing to the lack of clinical studies involving pediatric patients. Furthermore, the emergence of multidrug-resistant gram-positive and gram-negative bacterial isolates is associated with the need of a more appropriate choice of antibiotic regimens and newer and more effective antimicrobial compounds. While some clinical complications (such as heart failure) are well-known risk factors for death, the links to such factors as peripheral embolization, vegetation size or *S. aureus* infection remain controversial to date. In conclusion, further prospective, randomized, clinical studies concerning IE in childhood are certainly requested in order to provide definitive answers to these remaining questions, with particular regard to the most effective and safe antimicrobial therapy for this pediatric infection.

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