Infectious Endocarditis Prophylaxis in Children

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Abstract: Infectious endocarditis (IE) is a rare illness with high morbidity and mortality. Incidence of IE is on the rise in industrialized countries, particularly as those with congenital heart defects are living longer and the use of indwelling central catheters increases. With the 2007 American Heart Association guidelines, there has been a shift in recommending antibiotic prophylaxis only to high-risk patient populations. This clinical review will highlight the changing epidemiology and etiology of IE, followed by an emphasis on the appropriate indications for antibiotic prophylaxis in high-risk populations undergoing specific procedures.

Key Words: infectious endocarditis, congenital heart disease, antibiotic prophylaxis

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TARGET AUDIENCE

The target of this review includes pediatric emergency physicians, general emergency medicine physicians, general pediatricians, pediatric hospitalists, and family medicine physicians.

LEARNING OBJECTIVES

After completion of this article, the reader should be better able to:

1. Analyze the epidemiology, pathophysiology, and etiology of infectious endocarditis in children
2. Assess high-risk patient populations and certain procedures that require infectious endocarditis prophylaxis
3. Propose appropriate prophylactic antimicrobial regimens for infectious endocarditis

CASE

A previously healthy 6-year-old boy with a history of repaired congenital cyanotic heart disease arrives to the emergency department after having fallen from his bicycle. He was helmeted. There is no reported loss of consciousness, and he is at his baseline mental status. His examination is remarkable for an intruded left upper central incisor with bleeding surrounding the intruded tooth. There is no other dental malalignment. There are no facial bone, skull, or neck injuries. His cardiac examination is remarkable for a holosystolic III/IV murmur. The remainder of the examination is unremarkable. The dental consultant is en route to the emergency for tooth extraction and asks if there is a plan to give antibiotics before the procedure.

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Background and Epidemiology

Infectious endocarditis (IE) is an infection of the endocardium and or heart valves that has a high morbidity and mortality.[1–3] It involves vegetations that serve as a nidus for infection, resulting in destruction of the endocardium and/or heart valves. Prompt diagnosis and treatment are crucial to avoid poor outcomes, and antibiotic prophylaxis has been the mainstay of IE prevention for more than 60 years. In 2007, the American Heart Association (AHA) authored guidelines pertaining to IE prophylaxis, with updates as recently as 2015 reinforcing the prior recommendations.[4–6]

The epidemiology of heart disease in children has changed over the past 50 years.[7–10] Before the 1970s, an estimated 30% to 50% of children with IE had underlying rheumatic heart disease.[11] With increased survival rates of children with congenital heart disease (CHD) and decreased incidence of rheumatic heart disease in developed countries, CHD is now one of the leading predisposing conditions of children with IE.[9,10,12,13] Approximately 35% to 60% of cases of IE in children occur in individuals with underlying CHD.[12,14,15]

In addition, rates of postoperative IE after cardiac surgery and also IE associated with indwelling catheter placement are on the rise.[9,10,16,17] Postoperative IE maintains long-term risk even after complex cyanotic CHD is corrected, especially in those with residual defects or prosthetic implants.[6] Morris et al[17] reviewed cumulative incidences of endocarditis for a number of congenital cardiac lesions and reported the highest annualized risk for IE in children with repaired *cyanotic* CHD as compared with other cardiac defects. Overall, recent reports suggest increasing incidence of IE with an annual rate between 0.05 and 0.12 cases per 1000 pediatric admissions from 2003 to 2010.[10]

Pathophysiology

In both human and animal studies, IE occurs in the presence of damaged cardiac endothelium.[6] Injury to the cardiac endothelium can occur in the presence of turbulent blood flow due to valvular defects or incompletely repaired cardiac CHD.[18] Alternatively, endothelial injury can be caused by the presence of an indwelling central catheter or implantable cardiac device, or from injection of solid particles (eg, with intravenous drug abuse).[19] Once the endothelium is damaged, platelet and fibrin deposition occurs to form a thrombus, which in turn can serve as a nidus for bacterial or fungal infection.[6]

Seeding of an intracardiac thrombus and subsequent IE is thought to be due to transient bacteremia.[20] Damage or disruption of the body's mucosal surfaces that are heavily colonized with bacteria can result in bacteremia. Dental, oropharyngeal, respiratory, gastrointestinal (GI), and genitourinary (GU) procedures have all been implicated.[20,21] In children, reported ranges of bacteremia were 30% to 65% after dental extraction, although positive cultures were found to be transient.[22–24] Nonetheless, the prevailing belief is that activities of daily living (eg, toothbrushing, flossing, chewing, etc) result in the bulk of transient bacteremia and therefore IE seeding events.[5] Maintenance of oral hygiene remains the most effective practice to prevent the occurrence of IE.[4–6]

TABLE 1. Modified Duke Criteria[31,32]

Definitive endocarditis diagnosis
- Histologic: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis
- Pathologic: demonstrated by culture or histology in a vegetation, or in a vegetation that has embolized, or in an intracardiac abscess
- 2 major criteria *OR* 1 major + 3 minor criteria *OR* 5 minor criteria

Major criteria
- Positive blood cultures: typical pathogens from at least 2 positive cultures or single positive blood culture with *Coxiella burnetti*
- Echocardiogram supportive of endocarditis
  - o Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation
  - o Intracardiac abscess
  - o New partial dehiscence of prosthetic valve
  - o New valvular regurgitation

Minor criteria
- Predisposing heart disease or intravenous drug abuse
- Fever >38°C
- Microbiologic evidence that does not meet the criteria above (eg, one positive blood culture, excluding coagulase-negative staphylococcus)
- Vascular phenomena: arterial emboli, mycotic aneurysm, Janeway lesions, conjunctival hemorrhages, septic pulmonary infarcts
- Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
- Echocardiographic findings consistent with endocarditis but does not meet major criteria

Etiology and Diagnosis

Most isolates in cases of IE are staphylococcal and streptococcal subspecies, with gram-negative, HACEK (*Haemophilus*, Aggregatibacter, *Cardiobacterium*, *Eikenella*, *Kingella*), enterococcal, and fungal pathogens occurring less commonly.[25–27] For adult populations, *Staphylococcus aureus* remains the most common causative agent, followed by streptococcal species.[28] In the past, studies have reported most pediatric IE cases due to viridans streptococci[18]; however, a recent study of 632 cases of IE in children reported the following pathogens: *S. aureus* (57%), viridans streptococci (20%), and coagulase-negative staphylococci (14%).[12] In addition, 5% to 7% of cases of IE have been reported as culture negative.[8,18] More recent data suggest an ever larger percentage of culture-negative IE in children ranging from 8% to 36% of cases.[29,30]

To diagnose IE, the modified Duke criteria have been validated for use in children.[31] The modified Duke criteria require 2 major criteria, or 1 major and 3 minor criteria, or 5 minor criteria (Table 1).[32] Clinical findings, blood cultures, and echocardiography are routinely used in the evaluation of suspected IE. In addition, complete blood count, inflammatory markers, and urinalysis may be useful. Depending on the index of suspicion for culture negative IE, consultation with infectious disease specialists for serologic testing (eg, polymerase chain reaction, nucleic acid amplification test, etc) may be warranted.[6] Treatment is prolonged and largely depends on the pathogen(s) identified.

Indications for Prophylaxis

Antibiotic use for the prevention of IE has been in practice for more than 60 years, and its concept is based on animal models and human observational studies. There remains a lack of robust data from randomized clinical trials on the use of prophylactic antibiotics to prevent IE. Over time, restricted recommendations of antibiotic prophylaxis for IE have arisen owing to cost-benefit analyses, new understanding of the pathophysiology of IE, sources of bacteremia, and concerns regarding antimicrobial resistance.

At the time of this review, both the European Society for Cardiology and the AHA continue to recommend prophylaxis in certain high-risk populations only.[4,33] Conversely, in 2008, the National Institute for Health and Clinical Excellence in the United Kingdom recommended against its use for any and all patient groups.[34] Since that time, the number of hospital discharges coded for IE in the United Kingdom has increased significantly above the projected historical trend.[33,35] In the United States, since the 2007 AHA guidelines restricted prophylaxis for high-risk patient and high-risk procedures alone, there has been no significant change in the incidence of IE in either adult or pediatric patient populations.[36,37]

High-Risk Patients

In 1993, Steckelberg and Wilson[38] categorized various moderate- and high risk-groups, including those with prosthetic heart valves, prior IE, rheumatic heart disease, cyanotic CHD, and degenerative valve disease. The more recent 2007 AHA guidelines for IE prophylaxis were updated and encompassed only those considered to be at the highest level of risk (Table 2).

Multiple studies demonstrate that patients with complex cyanotic CHD and those who have cardiac shunts, conduits, or prostheses sustain not only a high lifelong risk of IE but also high morbidity and mortality if IE occurs.[8,15,18] Cyanotic CHD also incurs a higher risk for infants and children younger than 2 years. Although there are limited data for the population, the AHA continues to recommend prophylaxis for cardiac transplants with

TABLE 2. High-Risk Cardiac Conditions for IE Prophylaxis[4]

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair

Prior infectious endocarditis

CHD
- Unrepaired cyanotic CHD, including palliative shunts and conduits
- Completely repaired CHD with prosthetic material or device (<6 months after the procedure)
- Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
- Cardiac transplantation recipients who develop cardiac valvulopathy

TABLE 3. Single-Dose Regimens for IE Prophylaxis

Situation	Antibiotic	Pediatric	Adult
Oral medication	Amoxicillin	50 mg/kg PO	2 g PO
Unable to take oral	Ampicillin	50 mg/kg IV	2 g IV
	Cefazolin	30 mg/kg IV/IM	1 g IV/IM
	Ceftriaxone	50 mg/kg IV/IM	1 g IV/IM
Allergy to penicillin	Cephalexin	50 mg/kg PO	2 g PO
	Cefazolin	30 mg/kg IV/IM	1 g IV/IM
	Azithromycin	15 mg/kg PO	500 mg
	Clindamycin	10 mg/kg PO/IV/IM	900 mg PO/IV/IM

IM indicates intramuscular; IV, intravenous; PO, oral dose.

valvular disease.[4] The European Society for Cardiology, based in Europe, provided similar recommendations to the AHA in 2015 but does not place cardiac transplant patients with valvulopathy in the high-risk category because of lack of data.[33]

In the adult population, mitral valve prolapse is the most common cardiac defect associated with IE; however, given the wide prevalence of mitral valve disease as whole, the absolute incidence of IE in these patients is extremely low.[4]

High-Risk Procedures

A variety of procedures have been implicated as sources of bacteremia and IE, including dental/oral, respiratory, GI, and GU. Durack[20] reported higher rates of bacteremia after periodontal surgery (88%), tooth extraction (60%), brushing teeth or irrigation (40%), and tonsillectomy (35%), and significantly lower rates of bacteremia associated with respiratory, GI, and GU procedures. Based on the current available data, the AHA designates a limited number of procedures to be high risk for IE.

Studies indicate that the overall risk of IE—not bacteremia—associated with dental procedures is low.[25,39,40] The AHA recommends antibiotic prophylaxis in high-risk patients undergoing any dental procedure that involve manipulation of gingival tissue, periapical region of teeth, or the perforation of the oral mucosa. The AHA designates a variety of dental procedures as low risk, including local anesthesia of uninfected tissue, radiographs, placement or adjustment of orthodontics, shedding of primary teeth, and bleeding from trauma to the lips or oral mucosa.[4]

It is well studied that the collective risk of bacteremia with daily activities such as chewing or brushing one's teeth has a much greater *cumulative* exposure of bacteremia as compared with a single dental procedure.[41,42] However, the frequency of bacteremia with IE-associated subspecies is much higher with a single-tooth extraction as compared with a single episode of toothbrushing (60.4% vs 22.5%, respectively).[43]

For other oropharyngeal or respiratory procedures, only those patients who undergo invasive procedures (eg, biopsy and tonsillectomy/adenoidectomy) should receive IE prophylaxis. With few exceptions, GI and GU procedures do not warrant antibiotic prophylaxis, unless there is an intercurrent active infection. In such cases, treatment for the infection should include activity against enterococcal species.[4]

Antimicrobial Prophylaxis Regimens

The focus of this review is antimicrobial prophylaxis and will not go in-depth on the treatment of confirmed IE. For adequate prophylaxis of IE, antibiotics should administered at least 60 minutes before the procedure, apart from vancomycin, which should be given 120 minutes prior.[44] The recommend prophylactic antibiotics are listed in Table 3. Dosing range guidelines are per the *American Academy of Pediatrics Red Book*.[45]

An exception to the recommended antibiotic regimens is when the patient is already receiving antibiotics from the class recommended for prophylaxis. In such cases, an antibiotic of a different class should be chosen.[4]

Safety and Cost-effectiveness

On the whole, IE is a rare disease despite its increasing incidence. In France, Duval et al[46] reported a risk of IE after dental procedures in high-risk adults was 1 in 11,000 for patients with prosthetic valves and no prophylaxis, 1 in 54,000 for patients with native valves and no prophylaxis, and 1 in 150,000 for patients who received prophylaxis.

Despite this, the cost-effectiveness of IE prophylaxis has been demonstrated in multiple studies, with a reported cost-effectiveness ratio of $3000 to $21,000 per year of life saved.[47–49] A single dose of antibiotics is often well tolerated and the risk is minimal. Adverse reactions to single-dose amoxicillin and clindamycin are rare, and fatalities are less likely.[4,33,50]

Case Wrap-up and Summary

In our initial case of a 6-year-old boy with a history of repaired cyanotic heart disease, your answer to the dentist is: yes, IE prophylaxis is indicated for this high-risk patient. Although IE is rare, the incidence in on the rise. The associated high morbidity and mortality of IE warrant attentiveness and caution. Despite the uncommon presentation to the emergency department, health care providers must be prudent in providing adequate IE prophylaxis to each and every high-risk patient undergoing a high-risk procedure.

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