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Infective endocarditis prophylaxis: An update for clinical practice

Antibiotic therapy to prevent endocarditis is now considered unnecessary for minor dental procedures and routine bronchoscopy.

ABSTRACT: Infective endocarditis is an uncommon but potentially life-threatening infection of the inner heart that is presumed to be associated with invasive procedures that compromise mucosal integrity and lead to transient bacteria. Prophylaxis against infective endocarditis remains a goal of clinicians and has traditionally been based on the identification of high-risk patients and high-risk procedures. However, new insights into the pathogenesis of infective endocarditis have challenged this assumption and form the framework for some revised prophylaxis guidelines, which limit the use of antibiotics and emphasize the importance of good oral hygiene.

Infective endocarditis (IE) is an uncommon but potentially serious infection of the inner layer of the heart. As a heterogeneous disease IE has been associated with various pathogens and clinical presentations, and a significant mortality and morbidity burden. Typically the risk for developing IE is highest in those with complex congenital cardiac abnormalities, acquired valvular dysfunction (post-rheumatic or degenerative), valvular replacement, or mitral valve prolapse with valvular regurgitation with or without thickened leaflets. Individuals with increased rates of transient bacteremia such as intravenous drug users and those with poor dental hygiene are also at higher risk.[1-3] Likewise, numerous conditions such as advancing age, diabetes mellitus, hemodialysis, and immunosuppression may complicate IE and portend a poorer outcome.[1]

Background

The clinical presentation of IE may be acute or subacute. Acute IE is a rapidly progressive illness in patients with normal heart valves. This contrasts with subacute IE, which often involves abnormal or prosthetic heart valves and presents in a more indolent manner with low-grade fever, anorexia, myalgia, and weight loss. These nonspecific systemic manifestations can lead to a delay in diagnosis, with subsequent increases in morbidity and mortality.

Cardiac complications are not uncommon sequelae of IE. Valvular destruction results in regurgitant lesions that may progress to clinical heart failure, which is estimated to occur in up to 50% of patients.[4,5] Paravalvular extension of the infection, which is also estimated to occur in up to 50% of patients, may lead to conduction abnormalities and heart block.[4,5] Embolic complications such as stroke, peripheral arterial occlusion, and myocardial, renal, splenic, or pulmonary infarct are estimated to occur in up to 50% of patients. The majority of these complications occur prior to the initiation of appropriate antibiotic therapy. Subsequently, the embolic risk decreases over time from 15% after 1 week of treatment to 1% after 4 weeks of treatment.[4] Classic findings such as Janeway lesions (small, flat, painless hemorrhagic lesions on palms or soles), Osler's nodes

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Table 1. Modified Duke Criteria for diagnosing infective endocarditis.[6]

Major criteria
1. Blood culture positive for infective endocarditis (IE) a. Typical microorganisms consistent with IE from two separate blood cultures: i. *Viridans streptococci, Streptococcus bovis,* HACEK group, *Staphylococcus aureus*; or ii. Community-acquired enterococci, in the absence of a primary focus; or b. Microorganisms consistent with IE from persistently positive blood cultures, defined as follows: i. At least two positive cultures of blood samples drawn ≥12 hours apart; or ii. All of three or a majority of four separate cultures of blood (with first and last sample drawn at least 1 hour apart) c. Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer ≥1:800
2. Evidence of endocardial involvement
3. Echocardiogram positive for IE defined as follows: a. Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or b. Abscess; or c. New partial dehiscence of prosthetic valve
4. New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)
Minor criteria
1. Predisposition: predisposing heart condition, or injection drug use
2. Fever: temperature >38°C
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE
6. Echocardiographic minor criteria eliminated
Interpretation
Definite infective endocarditis • Pathologic criteria: – Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or – Pathologic lesions; vegetation, or intracardiac abscess confirmed by histologic examination showing active endocarditis • Clinical criteria: – Two major criteria; or – One major criterion and three minor criteria; or – Five minor criteria **Possible infective endocarditis** • Clinical criteria – One major criterion and one minor criterion; or – Three minor criteria **Diagnosis of infective endocarditis is rejected** • Firm alternate diagnosis explaining evidence of infective endocarditis; or • Resolution of infective endocarditis syndrome with antibiotic therapy for ≤4 days; or • No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤4 days; or • Does not meet criteria for possible infective endocarditis, as above

(small, painful raised nodules on fingertips), and Roth's spots (pale areas on the retina surrounded by hemorrhage) are rare in clinical practice and are indicative of subacute disease.

The diagnosis of infective endocarditis is established with clinical, laboratory, microbiologic, and echocardiographic findings and is most practically achieved by applying the modified Duke Criteria (**Table 1**). The major criteria include persistently positive blood cultures growing an organism known to cause IE, evidence of endocardial involvement, new valvular regurgitation, and/or echocardiographic findings confirming endocardial involvement, such as an extraneous echogenic target, perivalvular abscess, or partial dehiscence of a prosthesis.[6] Transthoracic echocardiography is usually adequate as a first test; however, a transesophageal study may be required to better visualize prosthetic valves, myocardial abscess, or small lesions.

Medical management of IE involves antibiotic therapy with close monitoring for development of complications. Most patients do reasonably well on appropriate antibiotics, but surgery may be required in up to 50% of cases.[5,7] Indications for surgery include factors related to the patient (prosthetic valve endocarditis), the organism (fungal endocarditis), or complications (heart failure resistant to medical therapy, persistent sepsis after 72 hours of appropriate antibiotics, recurrent septic emboli on appropriate antibiotics, myocardial abscess, or valvular dehiscence).[4]

Pathogenesis

The pathogenesis of IE involves a well-delineated sequence of events that offer an opportunity for preventive intervention. It has been postulated that turbulent blood flow across abnormal cardiac surfaces (heart valves

and mural endocardium) results in endothelial damage and subsequent formation of a sterile nonbacterial thrombus (NBT) composed of platelets and fibrin. A subsequent transient bacteremia may lead to adherence of bacteria to the precursor NBT through a variety of virulence factors, thereby transforming the sterile thrombus into an infectious nidus. This focus in infection can then attract fibrin and platelets and result in bacterial proliferation leading to clinical IE.

It is well known that invasive procedures commonly result in transient bacteremia. For example, periprocedural bacteremias have been observed in up to 20% of upper and lower GI procedures, up to 40% of prostatic procedures, and up to 100% of invasive dental procedures.[3] This fact, combined with the knowledge that transient bacteremia plays a pivotal role in the pathogenesis of IE, has spurred the development and evolution of antibiotic prophylaxis guidelines.

However, transient bacteremia also occurs frequently during routine daily activities such as toothbrushing and chewing food. For example, transient bacteremia that is qualitatively similar to that induced by dental procedures occurs in up to 68% of individuals as a result of toothbrushing and in up to 51% of individuals as a result of chewing.[3,8] As a result, the estimated cumulative monthly bacterium exposure with routine daily activities is over 5000 times greater than that immediately following extraction of a single tooth.[8] By extension, the cumulative yearly bacterium exposure caused by routine daily activities has been estimated to be 154 000 to 5.6 million times greater than the bacteremia caused by a single dental extraction.[9] It is now felt that IE is much more likely to result from routine bacteremias associated with daily activities than from bacteremia caused by an invasive procedure.

Concerns about prophylaxis

One of the reasons for limiting prophylaxis to the highest risk groups stems from the apparent lack of proven efficacy in preventing IE. Unfortunately, recent reports have noted that periprocedural antibiotic therapy is not always 100% effective at "preventing or reducing the frequency, magnitude or duration of bacteremia associated with a dental procedure."[3] In a small case-control study it was observed that 25% of IE cases occurred despite adequate antibiotic therapy, leading the authors to conclude that prophylaxis was not effective.[10]

Likewise, there is always the potential for adverse effects or undesired outcomes with prophylactic antibiotic therapy. On the individual level there is the possibility of developing an adverse reaction directly related to the drug (e.g., immediate or delayed hypersensitivity) or an adverse consequence of antibiotic use (e.g., antibiotic-associated colitis). As well, there have been increasing concerns over the past few years regarding the role of indiscriminate antibiotic use in the emergence of antibiotic-resistant organisms such as strains of *Streptococcus viridans,* methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus* (VRE).

2007 guidelines for antibiotic prophylaxis

Given the questionable role that invasive procedures play in the pathogenesis of IE, coupled with the apparent lack of efficacy of prophylactic antibiotics in preventing transient bacteremia, the American College of Cardiology/American Heart Association (ACC/AHA) updated their 1997 guidelines after concluding that in most cases "the risk of antibiotic-associated adverse events exceeds the benefit, if any, from prophylactic antibiotic therapy."[3] The main changes in the 2007 version of the ACC/AHA document (**Table 2**) involve a shift toward recommending prophylaxis only for those with the highest risk conditions who are undergoing the highest risk procedures.[3] The patients who meet the criteria in part A of **Table 2** and are undergoing a procedure listed in part B should be placed on the appropriate antibiotic regimen described in part C.

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Currently antibiotic prophylaxis is only recommended for patients most at risk of developing IE or having an adverse outcome should IE occur. This includes patients with a prosthetic cardiac valve, prosthetic material used for cardiac valve repair, a past history of IE, or cardiac valvulopathy

Table 2. High-risk conditions (A) and procedures (B) for endocarditis and antibiotic regimens (C) recommended for prophylaxis.

A. Conditions

- Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
- Previous IE
- Congenital heart disease (CHD)*
  - Unrepaired or incompletely repaired cyanotic CHD, including palliative shunts and conduits
    - Tetralogy of Fallot, transposition of the great vessels, Ebstein anomaly
    - Tricuspid atresia, total anomalous pulmonary venous return, truncus arteriosus
    - Hypoplastic left heart, critical pulmonary valvular stenosis, interrupted aortic arch
    - Pulmonary valve atresia, coarctation of the aorta, pulmonic stenosis
  - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the repair
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
- Cardiac valvulopathy following cardiac transplantation

B. Procedures

- All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth, or perforation of the oral mucosa
  - The following procedures and events do *not* need prophylaxis: routine anesthetic injections through noninfected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, and bleeding from trauma to the lips or oral mucosa
- Invasive procedures of the respiratory tract that involve incision or biopsy of the respiratory mucosa (Routine bronchoscopy without incision of the respiratory tract mucosa does *not* require prophylaxis.)
- Surgical procedures involving infected skin, skin structures, or musculoskeletal tissue

C. Antibiotic regimens

Clinical situation	Agent	Single dose 30–60 minutes preprocedure	
		Adults	Children
Patient able to take oral medication	Amoxicillin	2 g	50 mg/kg
Patient unable to take oral medication	Amoxicillin OR	2 g IM or IV	50 mg/kg IM or IV
	Cefazolin or ceftriaxone†	1 g IM or IV	50 mg/kg IM or IV
Patient allergic to penicillins or ampicillin but able to take oral medication	Cephalexin† OR	2 g	50 mg/kg
	Clindamycin OR	600 mg	20 mg/kg
	Azithromycin or clarithromycin	500 mg	15 mg/kg
Patient allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone OR	1 g IM or IV	50 mg/kg IM or IV
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

*Consider consultation with a pediatric cardiologist for prophylactic antibiotics prior to dental treatment.
†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.
Adapted with permission from Wilson et al.[3]

following cardiac transplantation. As well it is recommended that patients receive prophylaxis if they have an unrepaired cyanotic congenital heart disease, if they have residual defects at or adjacent to the site of a prosthetic patch or device, or if they have a congenital heart defect that has been completely repaired using prosthetic material or a device within 6 months of the high-risk procedure.

A change has also been made to the procedures that require prophylaxis. In the current iteration of the ACC/AHA guidelines, only the highest risk procedures require prophylaxis. These are generally defined as procedures that result in a compromise in oral-respiratory mucosal integrity. For example, only dental procedures that involve manipulation of gingival tissue or the periapical region of teeth, or perforation of the oral mucosa now require prophylaxis. Likewise, the only respiratory tract procedures that require prophylaxis are those that involve incision or biopsy of the respiratory mucosa. Prophylaxis is no longer recommended for routine dental care, routine bronchoscopy, or gastrointestinal or genitourinary procedures. IE prophylaxis remains recommended for surgical procedures involving infected skin, skin structures, or musculoskeletal tissue.

Finally, changes in the timing of antibiotic administration have been made in the updated 2007 guidelines. Amoxicillin still remains the first-choice prophylactic antibiotic, but the administration of this agent should be 30 to 60 minutes prior to the procedure rather than 1 hour prior. The choice and timing of antibiotics remain unchanged, reflecting current practice standards and data demonstrating no difference in earlier administration of antibiotic prophylaxis.

While the recommendations surrounding prophylaxis for dental pro-

cedures have become less inclusive, greater emphasis has been placed on the maintenance of oral hygiene. As discussed above, recurrent bloodstream "seeding" from routine activities is much more likely to be the initiating factor in the development of infective endocarditis. By preventing dental disease individuals will be able to decrease the burden and frequency of bacteremia associated with routine daily activities and limit their cumulative risk.

Conclusions

Based on the available evidence, significant changes have been made to the ACC/AHA guidelines for endocarditis prophylaxis. Specifically, prophylactic antibiotic therapy is only recommended for the highest risk groups of patients who are undergoing the highest risk procedures and good oral hygiene should be emphasized for all patients at risk of endocarditis.

While the recommendations surrounding prophylaxis for dental procedures have become less inclusive, greater emphasis has been placed on the maintenance of oral hygiene.

Competing interests

None declared.

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