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Infective Endocarditis Prophylaxis: Update for 2007*

By JEREMY EDWARDS, MD, HOWARD LEONG-POI, MD, FRCPC

The prevention of infective endocarditis (IE) is a topic that attracts much interest and contention. A recent update of the guidelines for prevention of IE by the American Heart Association (AHA) represents substantial alterations to prior recommendations that had previously become standard practice. The changes involve restricting antibiotic prophylaxis only to patients with previous IE, a prosthetic heart valve, cardiac transplant recipients with valvulopathy, and a subset of congenital heart disease patients. The updated guidelines also include changes to the types of procedures for which antibiotic prophylaxis is recommended. This issue of *Cardiology Rounds* reviews the 2007 American Heart Association guidelines for the prevention of IE and discusses the rationale behind these changes.

The recent publication of the new IE prophylaxis guidelines in April 2007 led to much discussion amongst physicians, dentists, and their collective patients. Compared to the previous guidelines from 1997,[2] the 2007 guidelines[1] advocate antibiotic prophylaxis in a smaller group of select patients undergoing specific procedures. Thus, many patients who were previously advised to take antibiotic prophylaxis are no longer advised to do so.

For over 50 years, the AHA has been providing guidelines to physicians on how best to prevent IE. The rationale for updating the 1997 guidelines was based on the following observations:

- IE is less likely to occur after an invasive procedure than with exposure to random bacteremias associated with daily activities.
- Antibiotic prophylaxis, even if 100% effective, can only prevent a small number of cases of IE
- Antibiotic use is not without risk.
- The maintenance of good oral hygiene to prevent bacteremia from daily activities may contribute more to the prevention of IE than the use of prophylactic antibiotics.

While the previous 1997 AHA guidelines were endorsed by the American Dental Association (ADA), the current guidelines have been endorsed by the ADA, the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). This endorsement by many of the key societies involved with the prevention of IE adds to the credibility of these guidelines. The goal of this review is to summarize the current AHA infective endocarditis prophylaxis guidelines and discuss the rationale behind the changes in recommendations.

** A Review of the American Heart Association Guidelines for the Prevention of Infective Endocarditis*[1]

St. Michael's Hospital
30 Bond St.,
Suite 7049, Queen Wing
Toronto, Ont. M5B 1W8
Fax: (416) 864-5941

Pathogenesis of infective endocarditis

Understanding the pathogenesis of IE allows an appreciation of the rationale behind IE prophylaxis. The occurrence of endothelial trauma, which may result from turbulent flow, facilitates the aggregation of platelets and fibrin on the endothelial surface, this is called nonbacterial thrombotic endocarditis (NBTE). This nutrient-rich focus is at risk for bacterial seeding in the event of transient bacteremia, which is thought to arise from mucosal surfaces (eg, gingival, oropharyngeal, gastrointestinal, urethral, or vaginal mucosa).

Of particular interest are the transient bacteremias associated with gingival trauma. Once NBTE is exposed to transient bacteremia, bacteria can seed the NBTE through a variety of bacterial adherence properties. Viridans group streptococci are the pathogens in the majority of nonintravenous, drug-associated, native valve IE. Some viridans group streptococcal strains contain FimA protein that enable them to adhere to NBTE.[3] Other species of bacteria have their own adherence properties; for example, staphylococcal species exhibit staphylococcal adhesions. After bacterial adherence has occurred, there is further accumulation of platelets and fibrin. In effect, this seals off bacteria from host defenses and allows them to proliferate at rapid rates in the nutrient-rich NBTE, reaching microbial densities of 10^8 to 10^{11} colony-forming units per gram in left-sided lesions.[4] For reasons that are not clear, right-sided lesions tend to have lower microbial densities. In the past, the need to lessen or abolish this transient bacteremia with the goal to prevent seeding NBTE was, in part, the rationale for the use of antibiotics to prevent IE.

Infective endocarditis risk attributed to dental procedures

The oral mucosa was first recognized as a potential source of bacteremia and IE over 100 years ago. The majority of the literature regarding IE prevention tends to focus more on dental procedures over and above other invasive procedures. Because the incidence of IE is low, studies directed at IE prevention have focused on transient bacteremia as the final outcome, rather than the development of IE. Physicians are expected to infer that measures aimed at reducing the risk of transient bacteremia will also reduce IE risk, an assumption that is exceedingly difficult to prove.

To date, no clear evidence exists in the literature that proves a direct causal relationship between dental procedures and the development of IE, although there are many reports that often include cases where the time between a dental procedure and the development of IE is long, up to 3 to 6 months. Intuitively, it would seem that an "incubation" period of 3-6 months is not biologically plausible. This is supported by research published in 1977 that demonstrated that the timeframe between bacteremia and overt IE was <2 weeks in 80% of cases.[5]

Tooth extractions are generally accepted as being the dental procedure with the *highest* risk for transient bacteremia, with rates ranging from 10% to 100%. Other dental procedures have also been shown to carry a significant risk for the development of transient bacteremia.[6,7] Interestingly, bleeding at the time of a dental procedure has *not* been shown to increase the risk of transient bacteremia. Therefore, the question that arises is: What is the clinical significance of transient bacteremia associated with a dental procedure? Common daily activities such as chewing food, tooth brushing, flossing, toothpick use, and use of water irrigation devices all carry a risk of transient bacteremia. For example, the incidence of transient bacteremia after chewing food is estimated at up to 50%.[8] The annual *cumulative* risk of transient bacteremia associated with daily activities, such as chewing food and tooth brushing, greatly supersedes the risk associated with usually infrequent dental procedures. This is supported by the observation that the vast majority of patients with IE have not had a dental procedure within 2 weeks prior to onset of symptoms.[9,10] There is no information available on the magnitude of bacteremia required for the development of IE. Nonetheless, the magnitude of bacteremia associated with dental procedures appears to be fairly similar to that associated with daily activities, typically up to 10^4 colony-forming units per mL.[11] Intuitively, the longer the duration of bacteremia, the greater the risk of developing IE. However, this is very difficult to demonstrate scientifically. For the majority of dental procedures, the presence of bacteremia drops dramatically after 30 minutes.

The importance of dental hygiene with respect to the development of IE was first recognized over 80 years ago; however, it was never included in the AHA guidelines for the prevention of IE until 1997. In the 2007 guidelines, the significance of oral hygiene is once again stressed. In 1935, Okell demonstrated that patients with poor oral hygiene who had a tooth extraction had a 61% risk of viridans group streptococcal bacteremia.[12] It was later shown that rates of bacteremia in patients with poor oral hygiene were similar both pre- and post-dental procedure.[8] The burden of risk, therefore, is more enhanced by the level of oral hygiene in these patients, than by the dental procedure they are undergoing. Given the known risk of transient bacteremia associated with daily activities, the importance of good oral hygiene must be conveyed to patients, especially those

at increased risk, and may actually be of greater benefit in reducing the lifetime risk of IE than antibiotic prophylaxis prior to dental procedures.

Identifying patients who need antibiotic prophylaxis

The previous 1997 AHA guidelines for the prevention of IE focused on patients who had an increased lifetime risk of developing IE. This included those with valvular lesions such as aortic stenosis and mitral valve prolapse with regurgitation. The new 2007 AHA guidelines focus on patients who are at increased risk of developing an adverse outcome should they develop IE. Adverse outcomes mentioned in the 2007 AHA guidelines include death, severe valvular dysfunction, heart failure, multiple embolic events, and perivalvular extension, including abscess formation. This represents a significant change in the goal of antibiotic prophylaxis and has caused substantial debate among physicians. Many of the patients included in the 1997 guidelines no longer meet the criteria for antibiotic prophylaxis under the current guidelines. It is not because they are no longer at risk for the development of IE; rather, should they develop IE, they are not considered to be at increased risk of developing an adverse outcome. This is a very challenging concept to convey to a patient, especially after years of counseling by physicians about the importance of antibiotics for IE prophylaxis.

Patients with a prosthetic cardiac valve have a 20% risk of mortality from viridans group Streptococcus IE, compared to a 5% risk in patients with native valves. Clearly, patients with prosthetic valves are at an increased risk for an adverse outcome with IE. Similarly, patients who have had previous IE or a cardiac transplant with valvulopathy are at an increased risk of an adverse outcome with IE. A subgroup of congential heart disease (CHD) patients is also thought to be at increased risk of an adverse outcome with IE. This includes patients who have unrepaired cyanotic CHD (including palliative shunts and conduits), those with completely repaired congenital heart defects, but who have prosthetic material or devices during the first 6 months after the procedure, and those with repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (that inhibits endothelialization).

The rationale behind the change in focus towards targeting patients with increased risk of adverse outcome with IE stems from the knowledge that antibiotic prophylaxis has not been proven to prevent IE and that antibiotics are not without risks, including anaphylaxis and antibiotic resistance. Because of the tremendous increase in the incidence of antibiotic-resistant infections in recent years, especially enterococci that are resistant to penicillins, vancomycin, and aminoglycosides, the concern is that imprudent use of antibiotic prophylaxis can further increase drug resistance, making the treatment of IE more challenging when it does develop. Even if prophylaxis could reduce the risk of IE, only a small number of cases would be prevented in patients undergoing dental and other procedures. Hence, one should target only those patients who are likely to derive the greatest benefit from antibiotic prophylaxis, namely those at increased risk of developing an adverse outcome. Table 1 lists the patients who are at increased risk of developing an adverse event and who should receive antibiotics for endocarditis prophylaxis.

Table 1: Patients who are at increased risk of developing an adverse event and should receive antibiotics for endocarditis prophylaxis

- Prosthetic heart valve
- Previous infective endocarditis
- Congenital heart disease (CHD)
  - Unrepaired cyanotic CHD, including palliative shunts and conduits
  - Completely repaired congenital heart defect with prosthetic material or device, whether placed by catheter intervention or surgery, during the first 6 months after the procedure
  - Repaired CHD with residual defects at the site or adjacent to the site of prosthetic patch or device (which inhibit endothelialization)
- Cardiac transplantation recipients with cardiac valvulopathy

Dental antibiotic regimens

Patients described in Table 1 who are undergoing dental procedures that involve the gingival tissues or periapical region of a tooth, or procedures that perforate the oral mucosa, should receive antibiotic prophylaxis. The recommended antibiotic regimens are shown in Table 2.

Gastrointestinal and genitourinary procedures

Enterococci are the most likely pathogens to result in IE from a gastrointestinal (GI) or genitourinary source. Unfortunately, there is a paucity of information in the literature regarding the risk of IE associated with GI and genitourinary procedures and there are only anecdotal cases of patients undergoing GI and genitourinary procedures who develop IE. This implies that the incidence of IE related to GI and genitourinary procedures is fairly low. This, coupled with the growing

Table 2: Recommended antibiotic regimens

		Regimen: Single dose 30 to 60 min before procedure	
Situation	Agent	Adults	Children
Oral Unable to take oral medication	Amoxicillin Ampicillin **OR** Cefazolin or ceftriaxone	2 g 2 g IM or IV 1 g IM or IV	50 mg/kg 50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin – oral	Cephalexin*† **OR** Clindamycin **OR** Azithromycin or clarithromycin	2 g 600 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone† **OR** Clindamycin	1 g IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV

* Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
† Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

problem of antibiotic resistance towards enterococci species, has led the new 2007 AHA guidelines to no longer recommend the prescription of antibiotics solely for IE prophylaxis in patients undergoing GI or genitourinary procedures. In patients described in Table 1 who have a GI infection or who are already receiving antibiotics for wound infection or sepsis prevention, it may be reasonable to include coverage for enterococci species. Similiarly, patients described in Table 1 who have a known enterococci urinary tract infection or colonization, may benefit from enterococci eradication prior to instrumentation.

Respiratory tract procedures

Patients described in Table 1 who are undergoing respiratory procedures that involve incision or biopsy of the respiratory mucosa should receive antibiotic prophylaxis. This does *not* include routine bronchoscopy. The recommended antibiotic regimen is the same as that for dental procedures, as shown in Table 2. If patients described in Table 1 undergo an invasive respiratory tract procedure to treat an infection, there should be antibiotic coverage for virdans group streptococcus and for *Staphylococcus aureus* if suspected.

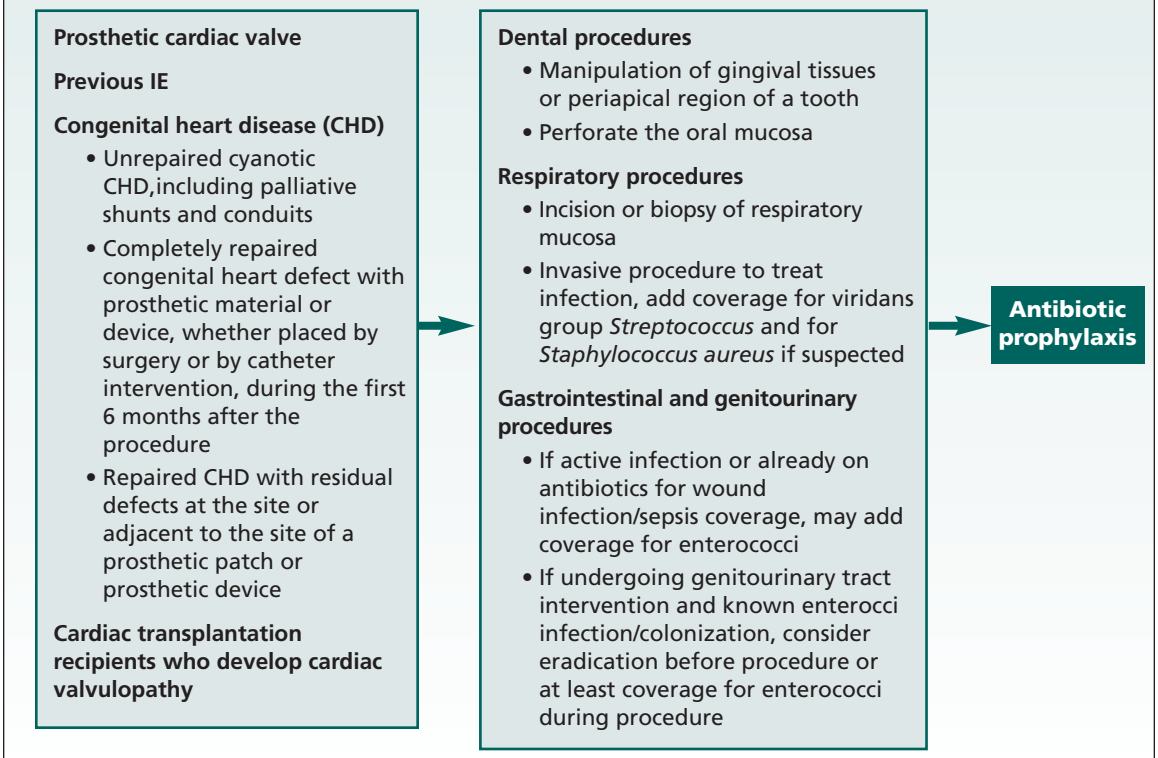
Conclusion

In many ways, the 2007 AHA guidelines for the prevention of IE have made antibiotic prophylaxis decision-making easier for the clinician. These guidelines are clearer and less ambiguous than the 1997 guidelines. It is important to recognize that the updated guidelines are not based on a wealth of new evidence; rather, there has been a conscious and considerate re-evaluation of existing evidence and changes in the philosophy and goal of treatment.

The major changes in the 2007 guidelines arise from the recognition that transient bacteremia arising from daily activities is more likely to lead to IE than dental, respiratory, or other invasive procedures. It has also been recognized that even if antibiotic prophylaxis is 100% effective, the magnitude of benefit remains small. The other major consideration in the new guidelines is that the focus has shifted away from patients at increased lifetime risk of IE, to just those who are at increased risk of an adverse outcome should they develop IE. Under the 2007 guidelines, only a select group of cardiac patients undergoing certain dental or respiratory procedures require antibiotic prophylaxis (Figure 1). The hope is that the new guidelines will promote a shift in emphasis away from focusing on dental procedures and antibiotic prophylaxis, towards a greater emphasis on improved access to dental care and oral hygiene in patients at the highest risk of adverse outcomes from IE and conditions that predispose to its development.

However, the dramatic change in the approach to the prevention of IE has also raised some interesting questions and concerns. It is appreciated that many physicians will require time to assimilate these guidelines and that patients will likely need even longer to feel comfortable with the changes. Concerns will always remain about higher-risk lesions, such as severe aortic stenosis, hypertrophic obstructive cardiomyopathy, or restrictive ventricular septal defects that do not require prophylactic antibiotics under the new guidelines.

Figure 1: Select group of cardiac patients undergoing dental or respiratory procedures that require antibiotic prophylaxis



On the other hand, these updated guidelines will be welcomed by those physicians who felt the data supporting the prior recommendations were scientifically weak and on the basis of large retrospective analyses, but who nevertheless commonly advocated the antiquated recommendations because of liability concerns. In the end, the uptake of these guidelines into routine clinical practice remains to be seen. However, the changes in the guidelines potentially open the door for well-designed, prospective, randomized, placebo-controlled, clinical trials – that may not have been able to be performed in the previous era – to evaluate the risk or benefit of antibiotics for the prevention of IE.

Dr. Jeremy Edwards is a cardiology trainee at St. Michael's Hospital.

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Abstracts of Interest

Prevention of Infective Endocarditis. Guidelines From the American Heart Association. A Guideline From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group.

WILSON W, TAUBERT KA, GEWITZ M, ET AL.

BACKGROUND: The purpose of this statement is to update the recommendations by the American Heart Association (AHA) for the prevention of infective endocarditis that were last published in 1997.

METHODS AND RESULTS: A writing group was appointed by the AHA for their expertise in prevention and treatment of infective endocarditis, with liaison members representing the American Dental Association, the Infectious Diseases Society of America, and the American Academy of Pediatrics. The writing group reviewed input from national and international experts on infective endocarditis. The recommendations in this document reflect analyses of relevant literature regarding procedure-related bacteremia and infective endocarditis, in vitro susceptibility data of the most common microorganisms that cause infective endocarditis, results of prophylactic studies in animal models of experimental endocarditis, and retrospective and prospective studies of prevention of infective endocarditis. MEDLINE database searches from 1950 to 2006 were done for English-language papers using the following search terms: endocarditis, infective endocarditis, prophylaxis, prevention, antibiotic, antimicrobial, pathogens, organisms, dental, gastrointestinal, genitourinary, streptococcus, enterococcus, staphylococcus, respiratory, dental surgery, pathogenesis, vaccine, immunization, and bacteremia. The reference lists of the identified papers were also searched. We also searched the AHA online library. The American College of Cardiology/AHA classification of recommendations and levels of evidence for practice guidelines were used. The paper was subsequently reviewed by outside experts not affiliated with the writing group and by the AHA Science Advisory and Coordinating Committee.

CONCLUSIONS: The major changes in the updated recommendations include the following: (1) The Committee concluded that only an extremely small number of cases of infective endocarditis might be prevented by antibiotic prophylaxis for dental procedures even if such prophylactic therapy were 100% effective. (2) Infective endocarditis prophylaxis for dental procedures should be recommended only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from infective endocarditis. (3) For patients with these underlying cardiac conditions, prophylaxis is recommended for all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa. (4) Prophylaxis is not recommended based solely on an increased lifetime risk of acquisition of infective endocarditis. (5) Administration of antibiotics solely to prevent endocarditis is not recommended for patients who undergo a genitourinary or gastrointestinal tract procedure. These changes are intended to define more clearly when infective endocarditis prophylaxis is or is not recommended and to provide more uniform and consistent global recommendations.

J Am Dent Assoc 2007;138(6):739-45, 747-60.

Use of echocardiography in the diagnosis and management of infective endocarditis.

CHU VH, BAYER AS. DURHAM, NC

The first use of echocardiography in infective endocarditis (IE) was described in 1973. Since then, echocardiography has emerged as a major tool for the diagnosis and management of this disease. In general, transthoracic echocardiography (TTE) is adequate for diagnosing IE in cases where cardiac structures-of-interest are well visualized. Specific situations where transesophageal echocardiography is preferred over TTE include the presence of a prosthetic device, suspected periannular complications, children with complex congenital cardiac lesions, selected patients with Staphylococcus aureus bacteremia, and certain pre-existing valvular abnormalities that make TTE interpretation problematic (eg, calcific aortic stenosis). Echocardiography is also useful for risk stratification. Evidence suggests that vegetation size can predict embolic complications, although the data are inconsistent. Careful clinical assessment is essential to the proper use of echocardiography in diagnosing IE, visualizing complications related to IE, and evaluating candidacy for surgical intervention.

Curr Infect Dis Rep. 2007;9(4):283-290.

Guidelines for the prevention of endocarditis: report of the Working Party of the British Society for Antimicrobial Chemotherapy

GOULD FK, ELLIOTT TSJ, FOWERAKER J, ET AL.

These guidelines have been produced following a literature review of the requirement for prophylaxis to prevent bacterial endocarditis following dental and surgical interventions. Recommendations are made based on the quality of available evidence and the consequent risk of morbidity and mortality for 'at risk' patients.

J Antimicrob Chemother 2006;57(6):1035-1042.

Upcoming meetings

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Canadian Cardiovascular Society – CCC 2007
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American Heart Association 2007
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Orange County Convention Centre
Contact: http://aha.orlandomeetinginfo.com

5-8 December 2007
EuroEcho 2007
European Society of Cardiology
Lisbon, Portugal
Contact: www.escardio.org/congresses/EE

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