ARTICLE

A Review of Bacterial Endocarditis and the Current Recommendations for Its Prevention

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ABSTRACT

Bacterial endocarditis is a rare but serious infectious disease for which prevention, specifically antibiotic prophylaxis, is important. In June 1997, the American Heart Association published revised recommendations for the prevention of bacterial endocarditis. Despite the existence of these guidelines, surveys of health-care practitioners and patients have demonstrated a significant lack of knowledge of important issues regarding antibiotic prophylaxis of bacterial endocarditis. The purpose of this article is to give pharmacists the information required to educate other health-care practitioners and patients about the appropriate use of antibiotic prophylaxis for this condition. The article reviews the incidence, pathophysiology, and clinical presentation of bacterial endocarditis and outlines the current recommendations for antibiotic prophylaxis. The risk factors for bacterial endocarditis, including cardiac conditions and procedures that cause bacteremia, are reviewed. The indications for antibiotic prophylaxis, based on the relative benefits and risks, are also discussed.

Key Words: bacterial endocarditis, antibiotic prophylaxis

RÉSUMÉ

L'endocardite bactérienne est une infection rare, mais grave pour laquelle la prévention, particulièrement l'antibiothérapie prophylactique, est importante. En juin 1997, l'American Heart Association a publié des recommandations révisées pour la prévention de l'endocardite bactérienne. Malgré l'existence de ces lignes directrices, des sondages auprès des professionnels de la santé et des patients ont démontré un manque considérable de connaissances des problèmes touchant l'antibiothérapie prophylactique. Le but de cet article est de donner au pharmacien l'information nécessaire pour informer les autres professionnels de la santé et les patients sur la pertinence de l'antibiothérapie prophylactique dans l'endocardite bactérienne. L'article analyse l'incidence, la pathophysiologie, et la manifestation clinique de l'endocardite bactérienne, et souligne les recommandations actuelles en termes d'antibiothérapie prophylactique. Les facteurs de risque d'endocardite bactérienne, y compris les états de santé et les interventions qui causent une bactériémie sont étudiés. Les indications pour l'antibiothérapie prophylactique, fondées sur les avantages et les risques relatifs, sont aussi passées en revue.

Mots clés : endocardite bactérienne, antibiothérapie prophylactique

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INTRODUCTION

Endocarditis, although defined as inflammation of the endocardium, generally refers to infection of the heart valves. Because bacterial endocarditis (BE) is a serious and often life-threatening disease, prevention is important. Although relatively few pharmacists are involved in treating acute BE, many are involved in providing antibiotic prophylaxis to prevent the disease. Antibiotic prophylaxis is indicated in patients at significant risk for BE, such as those with cardiac abnormalities who are scheduled for procedures that might cause bacteremia. Recommendations from the American Heart Association (AHA) have been revised and published in the *Journal of the American Medical Association*.[1]

Surveys of health-care practitioners have shown that there is insufficient knowledge regarding the appropriate indications for antibiotic prophylaxis. A survey in the United Kingdom found that only two-thirds of physicians and dentists considered prosthetic heart valves a significant risk factor, and 85% of physicians and 38% of dentists incorrectly considered a history of rheumatic fever alone to be a significant risk factor.[2] Two surveys in the United States reported frequent use of antibiotic prophylaxis in cases without appropriate indications.[3,4]

Similar studies of high-risk patients have also demonstrated a poor understanding of issues related to the prevention of BE. A survey of patients attending a cardiac clinic found that only 49% recalled previously reviewed information on skin care, dental hygiene, and antibiotic prophylaxis.[5] Of those with prosthetic valves, only 14% were familiar with such information.[5] Another survey of patients with congenital heart disease found that none could list measures to prevent BE, although 80% knew that medication was required before dental procedures.[6] An Alberta survey of patients attending a congenital heart disease clinic also found a general lack of knowledge about antibiotic prophylaxis.[7]

In this article we review the incidence, pathophysiology, and clinical presentation of BE and discuss the current guidelines for antibiotic prophylaxis. Our purpose is to give pharmacists the information required to educate other health-care practitioners and patients about the appropriate use of antibiotic prophylaxis for BE.

Table I. Pathogens Associated with Infective Endocarditis[12,20,21]

Pathogen	Incidence (%)
Streptococcus viridans	40 to 50
Streptococcus bovis	10
Staphylococcus aureus	20 to 30
Staphylococcus epidermidis	<10
Enterococcus faecalis	10 to 20
Gram-negative bacilli	5 to 10
Fungi	<5

REVIEW OF BACTERIAL ENDOCARDITIS

Incidence

The incidence of infective endocarditis is relatively low, estimated at 10 to 60 cases per million annually.[8-12] Despite significant progress over the past 40 to 50 years in important areas such as reducing rheumatic heart disease, improving oral hygiene, and using antibiotic prophylaxis, the incidence of infective endocarditis has not changed considerably. This may reflect an increase in other high-risk populations, better diagnostic techniques, or inadequate prevention.[9,13,14]

Although some studies have reported up to twice the incidence of infective endocarditis in males relative to females, others have found no difference.[8,9,12,15,16] The elderly population is at higher risk for infective endocarditis, and the mean age at diagnosis has increased from less then 30 years in the 1920s to over 50 years in the 1990s.[14,17] One study, which reviewed cases of infective endocarditis over a 5-year period during the 1980s, reported a median age of 69 years.[12] The fact that the incidence of endocarditis has also risen in children may reflect the improved survival rates of infants with congenital heart disease.[18]

Pathophysiology and Etiology

A pre-existing cardiac condition such as rheumatic heart disease, congenital lesions, prosthetic heart valves, or trauma is usually the first step in the development of infective endocarditis. The mitral valve is affected in 66% to 86% of cases,[19] whereas the aortic valve is less commonly involved. Infection of the tricuspid valve, leading to right-sided endocarditis, is most commonly associated with intravenous drug abuse. Sterile platelet-fibrin thrombi, also known as nonbacterial thrombotic vegetations, form at abnormal or damaged sites. The next step involves a transient bacteremia, which allows bacterial adherence, invasion, and colonization of valvular vegetations.[8,17,19]

Table I lists the pathogens associated with infective endocarditis, as reported in studies conducted over the past 2 decades.[12,20,21] Bacterial infections account for the majority of cases, whereas fungal and viral pathogens are less common. Bacteria demonstrate different propensities to cause bacteremia and adhere to valvular vegetations.[22] The most prevalent pathogen, *Streptococcus viridans*, originates in the oral cavity and enters the bloodstream during dental manipulations, procedures, or trauma. Other bacteria, including *Streptococcus bovis* and *Enterococcus faecalis*, are normal flora of the lower gastrointestinal tract, whereas *Staphylococcus aureus* and *Staphylococcus epidermidis* originate on the skin. In less than 10% of cases a pathogen is not isolated.

Certain pathogens are more prevalent in specific populations. For example, early prosthetic valve endocarditis, which occurrs within 6 months of surgery, is most often associated with *Staphylococcus aureus* and *Staphylococcus epidermidis*.[20,23,24] Gram-negative pathogens are also more prevalent in infections of prosthetic valves than in those of native valves.[20,25] *Staphylococcus aureus* is the most common cause of infective endocarditis in intravenous drug users, although gram-negative bacteria such as *Pseudomonas aeruginosa* and *Serratia marcescens* are also observed in this population.[20,25,26]

Clinical Presentation and Complications

The symptoms of BE are often nonspecific and variable. In general, aggressive disease characterized by high fever, leukocytosis, and sepsis is associated with *Staphylococcus aureus* and the less common streptococcal pathogens. An insidious presentation with low-grade fever, arthralgias, fatigue, anorexia, and anemia is more typical of *Streptococcus viridans* and *Staphylococcus epidermidis* infections. Other symptoms of BE include splenomegaly in 20% to 60% of cases, neurological signs such as headache and seizures in 20% to 40%, and heart murmurs in over 80%. Embolic manifestations on the skin including petechiae, Janeway lesions, and Osler nodes or retinal Roth's spots may also be observed.[19]

The diagnosis of BE is based on clinical findings, especially heart murmurs and blood culture, which yields positive results in over 90% of cases. Echocardiography, which allows visualization of valvular vegetations, is also used.[27,28]

BE, a serious disease with severe complications, can be difficult to eradicate.[29] Effective treatment requires intravenous administration of antibiotics for 2 weeks for uncomplicated cases and for 4 to 6 weeks or longer in complicated situations. Surgical intervention may also be required. The complications of BE include visual impairment, pulmonary embolism, and renal deficiency. Valvular insufficiency and congestive heart failure can also occur.[19] The mortality rate associated with BE is 25% to 30%, depending on the patient, the pathogen, and the site of infection.[8,10,19] The leading causes of death include neurologic complications and sepsis.[21]

BENEFITS OF ANTIBIOTIC PROPHYLAXIS

Although BE is a serious disease with severe complications, it is relatively uncommon, and the benefit of antibiotic prophylaxis is controversial. The AHA recommendations propose indications for the use of antibiotic prophylaxis to prevent BE according to current knowledge.[1] The recommendations are based on identifying cardiac conditions associated with significant risk of BE, identifying procedures associated with significant risk of bacteremia, and selecting a cost-effective antibiotic with a low incidence of adverse effects.[1]

The benefit of antibiotic prophylaxis is based primarily on animal studies, which have demonstrated effectiveness in preventing streptococcal endocarditis in rabbits with catheter-induced valvular damage.[10,30-32] Prospective, placebo-controlled studies of antibiotic prophylaxis in humans are not available and are unlikely to be done.[10] However, antibiotic prophylaxis has been examined in some case-control trials[11,33,34] (Table II). One study examined a subset of patients who had undergone procedures less than 30 days before the onset of BE symptoms.[33] BE occurred in 20% of patients who had received antibiotic prophylaxis and 46% of the controls who had not.[33] Similarly, Lacassin and colleagues[11] reported infection rates of 33% in patients who had received prophylaxis and 48% in the controls who had undergone dental procedures during the previous 3 months. Finally, in another study, Imperiale and Horwitz[34] found a statistically significant difference in the rates of BE between the treatment and control groups of 6.3% and 44%, respectively. Studies in this area are limited by their design and relatively small sample sizes. In addition, the benefits of antibiotic prophylaxis were demonstrated only after subset analyses of high-risk patient groups. As a result, recommendations for the prevention of BE are based on identifying patients at high risk and providing antibiotic prophylaxis when most appropriate.

Table II. Effect of Antibiotic Prophylaxis on Bacterial Endocarditis (BE)

Study	No. of Cases of BE	No. of Cases without BE	Rate of BE (%)
Lacassin et al[11]			
With prophylaxis	3	6	33
Without prophylaxis	15	16	48
Van Der Meer et al[33]			
With prophylaxis	2	8	20
Without prophylaxis	13	15	46
Imperiale and Horwitz[34]			
With prophylaxis	1	15	6.3
Without prophylaxis	7	9	44*

*Statistically significant.

Table III. American Heart Association Guidelines: Cardiac Conditions for which Antibiotic Prophylaxis is Recommended*

High-risk category
Prosthetic cardiac valves
Previous bacterial endocarditis
Complex cyanotic congenital heart disease
Surgically constructed systemic pulmonary shunts or conduits
Moderate-risk category
Most other congenital cardiac malformations
Acquired valvular dysfunction (due to rheumatic heart disease)
Hypertrophic cardiomyopathy
Mitral valve prolapse with regurgitation or thickened leaflets

*Adapted, with permission, from Dajani and associates.[1]

CARDIAC RISK FACTORS

The AHA recommendations classify cardiac conditions into high-risk and moderate-risk categories (Table III). Valvular heart disease is the most prevalent condition warranting antibiotic prophylaxis. A history of rheumatic fever without valvular dysfunction and the presence of a pacemaker are not indications for antibiotic prophylaxis.[35] Although cardiac abnormalities are important predisposing factors for BE, they are not present in all cases. It has been estimated that approximately one-third of patients with BE have no identifiable cardiac risk factor.[8,17,25]

DENTAL PROCEDURES AND ANTIBIOTIC PROPHYLAXIS

The AHA recommendations suggest antibiotic prophylaxis for dental procedures associated with significant bleeding, such as extractions, periodontal procedures (for example, surgery, scaling and root planing, probing, and recall maintenance), placement of implants, root canals, and some cases of professional cleaning.[1] The British recommendations are more conservative and limit antibiotic prophylaxis to dental extractions, scaling, and gingival surgery.[36,37] Other dental procedures are believed to produce low-grade bacteremia similar to that induced by regular brushing or chewing.[36,37] The European recommendations are more liberal, suggesting antibiotic prophylaxis for most dental procedures.[38]

Table IV. Rates of Bacteremia Related to Dental Activities and Procedures

Activity or Procedure	Rate of Bacteremia (%)	References
Chewing	17 to 50	18, 39
Brushing, flossing, oral irrigation	0 to 58	10, 18, 19, 39
Extractions	18 to 85	10, 18, 19, 39, 40
Single	51	18
Multiple	68 to 100	18
Subgingival scaling	51 to 83	18
Gingivectomy	83	18
Root canal		
Intracanal instrumentation	0	18
Extracanal instrumentation	31	18

The rates of bacteremia after various dental procedures are given in Table IV. Bacteremia usually occurs within 1 to 5 min of the procedure, is low grade, and lasts for less than 30 min.[14,39] The extent of bacteremia is associated with the degree of trauma, the amount of inflammation, and local numbers of bacteria.[18,41] However, the relationship between gingival bleeding and bacteremia is unclear. One study examined the incidence of bacteremia after the removal of oral sutures.[42] Although a statistically significant correlation was found between bacteremia and the number of sutures removed, no relationship was found between bacteremia and gingival bleeding at the suture sites.

The AHA guidelines recommend a single 2-g dose of amoxicillin administered 1 h before the dental procedure.[1] In patients who are allergic to penicillin, clindamycin is recommended. Cephalexin and cefadroxil are also options for patients without immediate hypersensitivity reactions (such as urticaria or angioedema) or systemic IgE-mediated reactions (anaphylaxis). Azithromycin and clarithromycin are more expensive alternatives (Table V). The guidelines also provide recommendations for parenteral alternatives and pediatric doses.

Table V. American Heart Association Guidelines: Antibiotic Prophylaxis for Dental, Oral, and Upper Respiratory Tract Procedures*

Situation	Antibiotic	Adult (Child) Dosage Regimen
Standard prophylaxis	Amoxicillin	2 g (50 mg/kg) po 1 h before procedure
Patient unable to take drugs orally	Ampicillin	2 g (50 mg/kg) IM/IV within 30 min before procedure
Patient allergic to penicillin†	Clindamycin	600 mg (20 mg/kg) po 1 h before procedure
	Cephalexin‡	2 g (50 mg/kg) po 1 h before procedure
	Cefadroxil‡	2 g (50 mg/kg) po 1 h before procedure
	Azithromycin	500 mg (15 mg/kg) po 1 h before procedure
	Clarithromycin	500 mg (15 mg/kg) po 1 h before procedure
Patient allergic to penicillin and unable to take drugs orally†	Clindamycin	600 mg (20 mg/kg) IV within 30 min before procedure
	Cefazolin‡	1 g (25 mg/kg) IM/IV within 30 min before procedure

IM = intramuscularly, IV = intravenously.

* Adapted, with permission, from Dajani and associates.[1]

† The drugs listed represent a choice; only one should be administered.

‡ Not for patients with immediate hypersensitivity reactions (urticaria or angioedema) or systemic IgE-mediated reactions (anaphylaxis) to penicillins.

Amoxicillin is the most extensively studied antibiotic for the prevention of BE. Anaphylaxis is the most significant adverse effect, and mild gastrointestinal upset occurs in approximately 10% of patients.[40,43] Other adverse effects and drug interactions are rarely encountered with single doses of amoxicillin used for antibiotic prophylaxis. Although the risks associated with amoxicillin are extremely low, it is warned that indiscriminate use could outweigh the benefits of antibiotic prophylaxis for BE, a relatively rare disease.[44]

One significant change to the current AHA recommendations is the removal of erythromycin as an alternative for patients allergic to penicillin. The British recommendations eliminated erythromycin in 1990 because of reports of significant nausea and gastrointestinal intolerance.[36] Erythromycin, especially in the large doses used for prophylaxis, is associated with adverse gastrointestinal intolerence in 30% to 50% of patients.[45] Its variable pharmacokinetics, including erratic oral absorption, is also well documented.[45,46] Other alternatives, including clindamycin, azithromycin, and clarithromycin, are generally less extensively studied than amoxicillin but are equivalent to erythromycin in inhibiting the growth of *Streptococcus viridans* in vitro.[47] The recommended alternative in the current guidelines is clindamycin, which is associated with less gastrointestinal upset and more reliable serum concentrations than erythromycin.[48]

Another major change to the current AHA recommendations was the elimination of a second antibiotic dose. The previous recommended regimen consisted of a 3-g dose of amoxicillin before the procedure followed by a 1.5-g dose after the procedure. In comparison, a single 2-g dose before the procedure is equally effective for the treatment of transient bacteremia, is associated with fewer adverse effects, and is less expensive.[43] Another potential benefit of single-dose prophylaxis is a reduction in the development of bacterial resistance. The influence of antibiotic prophylaxis on the development of resistance and the eventual effects on the efficacy of prophylaxis are unclear.[49] One study in humans demonstrated that weekly doses of amoxicillin increased the number of resistant streptococci in saliva.[50] The resistant bacteria were evident after the second or third dose and persisted for 4 to 7 weeks. Weekly doses of erythromycin also led to resistant streptococci, which were present for 23 to 43 weeks.[47] However, an antibiotic prophylaxis study in animals demonstrated that amoxicillin was equally effective in preventing BE due to sensitive and resistant streptococci strains.[31] Although the relationship is unclear, the development of resistance is an important consideration that can be reduced by limiting the frequency and duration of antibiotic use.

The cost-benefit relationship is another consideration in the selection of antibiotic prophylaxis. In the case of antibiotic prophylaxis for BE, the cost of administering antibiotics to large numbers of patients must be weighed against the benefits of preventing relatively few cases of BE. The few cost-effectiveness studies that have been conducted are difficult to interpret because of variability in the estimates of the incidence, risks, complications, and mortality rates associated with BE.[44,51] The AHA recommendations suggest inexpensive first-line antibiotics such as amoxicillin or clindamycin.

OTHER PROCEDURES AND ANTIBIOTIC PROPHYLAXIS

The AHA recommendations also identify non-dental procedures that warrant antibiotic prophylaxis (Table VI). The guidelines take into account the cardiac risk categories (high or moderate) and are consistent with recommendations of the American Society of Gastrointestinal Endoscopy.[52] Diagnostic procedures such as endoscopy are associated with relatively low rates of bacteremia (less than 10%) and are not indications for antibiotic prophylaxis.[53] For other procedures with variable rates of bacteremia, the use of antibiotic prophylaxis is controversial. For example, the incidence of bacteremia can approach 50% after esophageal dilatation or sclerotherapy.[53-57] Furthermore, techniques such as cleaning dilators with povidone-iodine or glutaraldehyde can decrease the risk and degree of bacteremia.[54,58,59] For gastrointestinal tract procedures, antibiotic prophylaxis is recommended for high-risk cases and optional in moderate-risk cases.

Because of the similar normal flora in the oral cavity, respiratory tract, and esophagus, the AHA recommendations for respiratory tract and esophageal procedures are the same as those for dental procedures[1] (Table V).

Bacteremia originating from the lower gastrointestinal or genitourinary tracts is primarily due to Enterobacteriaceae, *Enterococcus faecalis*, and anaerobes.[60] *Enterococcus* is the pathogen most commonly associated with BE in these cases. Approximately half of patients with BE due to *Enterococcus faecalis* have recently undergone a genitourinary procedure.[27,61] A review of BE cases in obstetric and gynecological patients from 1940 to 1983 identified *Streptococcus* spp. in 56% of cases, *Enterococcus faecalis* in 17%, and *Staphylococcus aureus* in 10%.[62]

The AHA recommendations for antibiotic prophylaxis for gastrointestinal (excluding esophageal) and genitourinary procedures are outlined in Table VII. Surgical prophylaxis, which often consists of a cephalosporin, is not effective against enterococci.[63] As a result, antibiotic prophylaxis for BE requires additional or alternative antibiotics such as amoxicillin, which cover both streptococci and enterococci. Vancomycin is an alternative for patients allergic to penicillin.

COUNSELLING OF PATIENTS BY PHARMACISTS

The pharmacist has an important role in educating other health-care practitioners and patients on the appropriate use of antibiotic prophylaxis for BE. Of most concern are the results of surveys that have demonstrated that many health-care practitioners lack basic knowledge in these areas.[2-4]

The counselling of patients should include information on the appropriate indications for and use of antibiotic prophylaxis, as outlined in the current AHA recommendations. Counselling on other preventive measures, such as good oral hygiene and frequent visits to the dentist, is of equal importance.[13,64] Good oral care includes avoiding gum with sugar, reducing sugar intake, drinking fluorinated water, and brushing and

Table VI. American Heart Association Guidelines: Surgical Procedures for which Antibiotic Prophylaxis is Recommended*

Tonsillectomy, adenoidectomy
Surgery involving respiratory mucosa
Bronchoscopy with a rigid bronchoscope
Sclerotherapy for esophageal varices†
Esophageal dilatation†
Endoscopic retrograde cholangiography with biliary obstruction†
Biliary tract surgery†
Surgery involving intestinal mucosa†
Cystoscopy
Urethral dilatation
Prostatic surgery

* Adapted, with permission, from Dajani and associates.[1]

† Antibiotic prophylaxis optional for patients at moderate risk and recommended for those at high risk.

Table VII. American Heart Association Guidelines: Antibiotic Prophylaxis for Genitourinary and Gastrointestinal Procedures*

Situation	Antibiotic	Adult (Child) Dosage Regimen
Patient at high risk	Ampicillin plus	2 g (50 mg/kg) IM/IV†
	gentamicin plus	1.5 mg/kg (1.5 mg/kg) IM/IV†
	amoxicillin or	1 g (25 mg/kg) po 6 h after procedure
	ampicillin	1 g (25 mg/kg) IM/IV 6 h after procedure
Patient at high risk, allergic to penicillin	Vancomycin plus	1 g (20 mg/kg) over 1 to 2 h†
	gentamicin	1.5 mg/kg (1.5 mg/kg) IM/IV†
Patient at moderate risk procedure	Amoxicillin or	2 g (50 mg/kg) po 1 h before
	ampicillin	2 g (50 mg/kg) IM/IV†
Patient at moderate risk, allergic to penicillin	Vancomycin	1 g (20 mg/kg) IV over 1 to 2 h†

IM = intramuscularly, IV = intravenously.
* Adapted, with permission, from Dajani and associates.[1]
† Complete infusion within 30 min of procedure.[52]

flossing teeth frequently.[39] Patients with dentures should also be advised to avoid ill-fitting dentures, which may cause mucosal abrasions.[40]

CONCLUSION

BE is a serious disease associated with significant morbidity and mortality. The AHA guidelines outline the measures currently recommended for the prevention of BE. Although controversy exists regarding the relative benefits of antibiotic prophylaxis, it appears that the most important issue is the criteria used to appropriately select cases for prophylaxis. The AHA recommendations, which are based on considerations of risk and benefit, provide guidelines for determining the indications for prophylaxis and selecting the most appropriate antibiotic regimens. The pharmacist is an important source of information on this topic for both patients and other health-care providers.

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