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Prevention of Infective Endocarditis: 2007 Guidelines from the American Heart Association (AHA)

Sharon Sam, Pharm.D.

Introduction: Infective endocarditis (IE) is an infection of the endocardial surface of the heart associated with high morbidity and mortality rates. The heart valves are most commonly affected but infection of the endocardium may also occur. Since the last publication on the prevention of IE in 1997, many authorities questioned the efficacy of antimicrobial prophylaxis in patients undergoing invasive procedures. The 1997 document also acknowledged that most cases of IE are not attributable to an invasive procedure but rather due to randomly occurring bacteremias from routine daily activities. This review outlines the revisions to the IE prophylaxis guidelines and an approach to IE prevention.

Pathogenesis: Endothelial damage on a cardiac valve causes the deposition of platelets and fibrin on the surface of the endothelium resulting in the formation of nonbacterial thrombotic endocarditis (NBTE). Trauma to mucosal surfaces, particularly the gingival crevice around teeth, oropharynx, gastrointestinal (GI) tract, urethra, and vagina, releases endogenous microflora colonizing the surface into the bloodstream allowing their adherence to the NBTE. Microorganisms adherent to the vegetation stimulate further deposition of fibrin and platelets on their surface concealing themselves from host defenses and proliferating their growth within the vegetation. The most common organisms involved in IE are *Staphylococcus sp*., *Viridans streptococcus*, and *Enterococcus sp*. (See Table 1).

Risk Factors: Prosthetic valvular heart disease, mitral valve prolapse with regurgitation, and congenital valvular heart disease are among the many risk factors that can predispose patients to an increased risk for IE (See Table 2). In addition, long-term hemodialysis with intravascular catheters and poor dental hygiene serve as sources of infection, which can lead to bacteremias and IE. Intravenous drug use also continues to be a risk factor for endocarditis, and *Staphylococcus aureus* is the usual pathogen in these individuals.

Prophylaxis Guidelines for IE: Since IE can be a life-threatening condition, the American Heart Association (AHA) developed guidelines for IE prophylaxis in patients with underlying cardiac conditions undergoing bacteremia-producing procedures. The basis for prophylaxis is endocarditis develops from transient bacteremias occurring in association with invasive dental, GI, and genitourinary (GU) tract procedures. Antibiotics administered prior to procedures can potentially prevent bacteremias and thus IE.

Table 1: Microogranisms of Infective Endocarditis

Microogranism	Colonization Site
Staphylococcus sp.	• Skin
Viridans streptococcus	• Skin • Oral mucosa • Respiratory tract • GI tract
Enterococcus sp.	• GI and GU tract

Table 2: Risk Factors for Infective Endocarditis

• Prosthetic valvular heart disease	• Hypertrophic cardio-myopathy
• History of infective endocarditis	• Surgically constructed pulmonary shunts or conduits
• Congenital heart disease	• Long-term hemodi-alysis
• Mitral valve prolapse with regurgitation	• Poor dental hygiene

Revision of 1997 Guidelines: Five fundamental principles are associated with the IE Guidelines: 1) IE is an uncommon but life-threatening disease and prevention is preferable to treatment; 2) certain underlying cardiac conditions predispose to IE; 3) bacteremia with organisms known to cause IE occurs commonly in association with dental, GI, or GU tract procedures; 4) antimicrobial prophylaxis was proven to be effective for prevention of IE in animal models; 5) antimicrobial prophylaxis was thought to be effective in humans for prevention of IE associated with invasive procedures. However, numerous publications questioned the validity of the fifth principle and suggested revision of the guidelines (See Table 3). The Guidelines were based largely on expert opinion, clinical experience, and limited case-control studies. The recommendations were often based on minimal published data and extrapolated from results in IE animal models. In addition, the Guidelines contained inconsistencies and ambiguities making it difficult for health care providers to determine what patients and procedures required prophylaxis. Over the past two decades, more clinical studies have evolved resulting in revisiting the appropriateness and effectiveness of IE prophylaxis in humans.

Table 3: Rationale for Revising 1997 IE Prophylaxis Guidelines

• Higher likelihood of IE developing from random bacteremias associated with routine daily activities (e.g., teeth brushing, flossing, chewing food) than from dental, GI, or GU tract procedures
• Only an extremely small number of IE cases may be prevented with antimicrobial prophylaxis in patients under-going dental, GI, or GU tract procedures
• The risk of antibiotic-associated adverse events outweighs the benefits of prophylactic antibiotic therapy
• Shifting an emphasis to improve oral hygiene and access to dental care rather than using prophylactic antibiotics to reduce the risk of IE

As the AHA Committee began updating the previous IE Prophylaxis Guidelines, three main issues were considered: 1) the underlying conditions that possess the highest risk in acquiring endocarditis; 2) the cardiac conditions associated with the highest risk of adverse outcomes from endocarditis; and 3) if recommendations should be based on one or both of these conditions.

In the past, rheumatic heart disease (RHD) was the most common underlying cardiac condition associated with endocarditis and is still common in developing countries. However, in developed countries and particularly the Western World, mitral valve prolapse (MVP) has become more prevalent than RHD. Although MVP is the most common underlying cardiac condition in patients with endocarditis, the incidence of developing endocarditis is extremely low for the entire MVP population. In addition, it is not usually associated with a high risk for detrimental outcomes. Consequently, the Committee decided to no longer recommend IE antimicrobial prophylaxis in patients with MVP.

Several published studies have confirmed that patients with underlying cardiac conditions other than MVP have a significantly higher lifetime risk of acquiring IE than individuals with no known underlying disease. The Committee defined a previous episode of IE, prosthetic cardiac valve, congenital heart disease, and cardiac transplantation as the conditions associated with the highest absolute risk of acquiring IE as well as the highest risk of developing adverse outcomes from IE (See Table 4). The revised Guidelines state that patients with these underlying conditions have high morbidity and mortality rates and will derive the greatest benefits from IE prevention for dental procedures despite the unknown effectiveness of antimicrobial prophylaxis.

Dental Procedures: Despite the association between Viridans streptococci bacteremia and dental extractions, the published data fail to demonstrate a benefit from antimicrobial prophylaxis. Transient bacteremias have been shown to occur frequently not only with manipulation of the teeth and periodontal tissues, but also with routine daily activities unrelated to dental procedures. A few published studies have demonstrated that the number of microorganisms present in the blood from a dental procedure is relatively low and comparable to the magnitude of bacteremia from performing routine daily activities (e.g., teeth brushing and chewing food). No clinical data have currently determined the absolute risk of IE from dental procedures, but published evidence have found that bacteremia-producing dental procedures cause an exceedingly small number IE cases. In addition, recommending IE prophylaxis for dental procedures but not during routine daily activities for the same patients would be inconsistent as well as impractical. As a result, the revised Guidelines recommend endocarditis prophylaxis only for high-risk patients undergoing dental procedures that involve manipulation of the gingival tissue or the periapical region of teeth or perforation of the oral mucosa (See Tables 4 and 5).

GI and GU Tract Procedures: The majority of published studies have focused on dental procedures as a cause of IE with few data existing on the risk and/or prevention of IE associated with GI or GU tract procedures. No published data have demonstrated a conclusive relationship between GI or GU tract procedures and development of IE, nor demonstrated the benefit of antimicrobial prophylaxis in preventing IE. Furthermore, the reported cases of IE related to a GI or GU tract procedure have been very small.

The revised Guidelines recommend against antimicrobial prophylaxis in patients undergoing GI or GU tract procedures except for high-risk patients. In addition, the Guidelines deemed an antimicrobial prophylaxis regimen, which contains an anti-enterococcal agent (i.e., ampicillin, vancomycin), reasonable in high-risk patients scheduled for a GI or GU tract procedure (See Tables 4 and 5).

Respiratory Tract Procedures: Similar to GI and GU tract procedures, respiratory tract procedures have been reported to cause transient bacteremias, but no published data has conclusively demonstrated a link between these procedures and IE. Antimicrobial prophylaxis is reasonable for high-risk patients who undergo an invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy. In high-risk patients who undergo an invasive respiratory tract procedure to treat an established infection, such as drainage of an abscess or empyema, antimicrobial prophylaxis is warranted as well. However, the guidelines do not recommend antibiotic prophylaxis for bronchoscopy unless the procedure involves incision of the respiratory tract mucosa (See Tables 4 and 5).

Skin, Skin Structure, or Musculoskeletal Tissue: Skin, skin structure, and musculoskeletal tissue infections are often polymicrobial and can cause bacteremias leading to IE. Similar to dental procedures, high-risk patients undergoing a surgical procedure that involves infected skin, skin structure, or musculoskeletal tissue should also receive antimicrobial prophylaxis (See Tables 4 and 5).

Table 4: High-Risk Patients for Adverse Outcomes from Endocarditis

- Prosthetic cardiac valve
- Previous infective endocarditis
- Congenital heart disease (CHD):
  - Unrepaired cyanotic CHD
  - Completely repaired with prosthetic materials for 6 months after procedure, allowing for endothelial formation
  - Incompletely repaired CHD with residual defects at prosthetic patches or devices
- Cardiac transplantation with valvular defects

Table 5: Invasive Procedures for Prophylaxis in High-Risk Patients

- Any procedure that involves the gingival tissue or periapical region of a tooth and for those procedures that perforate the oral mucosa
- Cystocopy or other genitourinary tract manipulation when the urinary tract is infected with *Enterococcus sp.*
- Drainage of established infections, such as empyema, abscesses, or phlegmons where *Staphylococcus aureus*, streptococci, or enterococci are likely or proven pathogens

Antibiotics for IE Prophylaxis*:* The Guidelines recommend the initiation of IE prophylactic antibiotics in eligible patients 30 to 60 minutes before the procedure. Amoxicillin is the preferred agent for antimicrobial prophylaxis due to good oral bioavailability and high serum concentrations. For individuals allergic to amoxicillin or penicillins, the recommended agents include cephalexin (Note: cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin), clindamycin, azithromycin, or clarithromycin. Lastly, the individuals who may not tolerate or cannot take oral therapy, the intravenous agents recommended for IE prophylaxis include ampicillin, ceftriaxone, or cefazolin (See Table 6).

Table 6: Antibiotics for Infective Endocarditis Prophylaxis (AHA 2007)

Situation	Agent	Regimen (30-60 minutes before procedure)
Oral	Amoxicillin	2 grams
Allergic to penicillin or ampicillin and able to take oral	Cephalexin Clindamycin Azithromycin Clarithromycin	2 grams 600 mg 500 mg 500 mg
Unable to take oral	Ampicillin Cefazolin Ceftriaxone	2 grams IM or IV 1 grams IM or IV 1 grams IM or IV
Allergic to penicillin or ampicillin and unable to take oral	Cefazolin Ceftriaxone Clindamycin	1 grams IM or IV 1 grams IM or IV 600 mg IM or IV

Specific Situations:

What is recommended if a patient is already on long-term antibiotic therapy prior to initiating IE prophylaxis for a dental procedure?
It is recommended to switch to an agent from a different antimicrobial class instead of increasing the dose of the current regimen.

What is the recommended IE prophylaxis regimen for patients on anticoagulants?
It is recommended to select an oral antimicrobial agent or an intravenous dosage form if the patient is unable to tolerate oral medications. However, it is recommended to avoid intramuscular injections of antimicrobials.

What is recommended for patients who undergo cardiac surgery?
Patients should have a careful dental evaluation prior to surgery. Surgical patients undergoing prosthetic heart valve placement are at a particular high risk of developing infections caused by *S. aureus*, coagulase-negative staphylococci, or diphtheroids. Antimicrobial prophylaxis should be administered immediately before the surgical procedure, repeated during prolonged procedures to maintain adequate drug concentrations in the serum, and continued for no more than 48 hours.

Summary: There is a long-standing belief that dental procedures, GI, and GU tract procedures cause IE; however, this assumption has been based largely on expert opinion and limited prospective, randomized studies. With increasing published data, the AHA Committee revisited the appropriateness and effectiveness of the IE Prophylaxis Guidelines in 2007. The 2007 IE Prophylaxis Guidelines no longer recommend antimicrobial prophylaxis for patients without underlying cardiac conditions undergoing dental, GI, or GU tract procedures and MVP patients undergoing dental procedures. However, patients with underlying cardiac conditions are at the highest risk for acquiring IE and adverse outcomes from IE. Although the effectiveness of prophylactic antibiotic therapy is unknown, these patients have the highest risk for morbidity and mortality and antimicrobial prophylaxis with dental, GI, or GU tract procedures is recommended. The revised Guidelines were intended to identify which patients and procedures required prophylaxis as well as stimulate additional prospective, randomized, placebo-controlled studies on the prevention of IE. The AHA 2007 Guidelines for Prophylaxis of Infective Endocarditis can be found in the Cleveland Clinic's Guidelines for Antimicrobial Usage.

References:

1) Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al. Prevention of infective endocarditis: recommendations by the American Heart Association. Circulation 2007;116:1736-54.
2) Dajani AS, Taubert KA, Wilson W, Bolger AF, Bayer A, Ferrieri P, et al. Prevention of infective endocarditis: recommendations by the American Heart Association. JAMA 1997;277:1794-1801.
3) Durack DT. Prevention of infective endocarditis. N Engl J Med 1995;323:38-44.

Formulary Update

The Pharmacy and Therapeutics Committee met on May 6, 2008, and the following decisions were made:

Additions:

1) **Budesonide/Formoterol Inhalation (Symbicort®):** This is a combination inhalational product containing a corticosteroid (budesonide) and long-acting beta-agonist (formoterol), similar to the current Formulary agent [fluticasone/ salmeterol (Advair®)], indicated for the long-term maintenance treatment of asthma in patients 12 years of age and older. Its FDA-approved indication is similar to that of Advair®, however, Advair® is also indicated for the treatment of asthma in patients age 4 and older, as well as for maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis. Symbicort® was added to the Formulary with the following **restrictions** (either criterion may be met): 1) continuation of home therapy, or 2) combination inhaled corticosteroid and long-acting beta-agonist in mechanically-ventilated patients.

A conversion chart will be placed on the online Formulary to assist when pharmacists receive questions about converting from Advair® to Symbicort® in mechanically-ventilated patients. Please note: There is NOT an automatic interchange from Advair® to Symbicort®.

2) **Triamcinolone acetonide injectable suspension (Triesence®):** This is a corticosteroid FDA-approved for treatment of sympathetic ophthalmia, temporal arteritis, uvetitis, and ocular inflammatory conditions unresponsive to topical corticosteroids. It is also approved for visualization during vitrectomy. Triesence® should NOT be administered intravenously (i.e., it is intended for ophthalmic administration). **This will be used mainly at the Cole Eye Institute.**

Deletions:

1) **Edetate Disodium (Endrate®):** The FDA has issued a Public Health Advisory due to confusion between edetate disodium (used for hypercalcemia) and edetate calcium disodium (used for high blood lead levels). Both are often referred to as "EDTA", and this may lead to medication errors. Due to the Advisory and lack of use at CC, edetate disodium is removed from the Formulary and will no longer be ordered or stocked by the inpatient pharmacy. Edetate calcium disodium will remain on the Formulary.

2) **IV colchicine:** The FDA has asked all manufacturers, including Bedford Laboratories, to cease manufacturing their injectable colchicine because it is not FDA-approved (a "grandfathered" medication marketed before laws required medications to undergo FDA review). Additionally, Bedford Laboratories (the only option for IV colchicine) has decided to discontinue it rather than submit a New Drug Application. There is no other manufacturer of IV colchicine. Therefore, IV colchicine is no longer commercially available and was removed from the Formulary.

New Restrictions:

1) **Intravenous haloperidol (Haldol®):** Due to a FDA warning about prolongation of the QT interval with the use of intravenous administration of haloperidol, the following restrictions are now in effect for IV haloperidol:

a. A patient must be in a monitored unit (ICU or telemetry) to receive IV haloperidol. The only exception is for a one time dose for an acutely agitated patient in a non-monitored unit. If the decision is made to continue the use of IV haloperidol after the one time dose, then the patient must be transferred to a monitored unit.
b. There will be NO restrictions on IV haloperidol if patients are in a monitored bed, or if the patient is Palliative Care located in a monitored or non-monitored unit.
c. Patients may receive IV haloperidol in M50 (BMT) with daily EKG monitoring.

2) **Dexmedetomidine (Precedex®):** Dexmedetomidine is now approved to be used by Ambulatory Anesthesia, specifically A60. Dexemdetomidine will be placed in the A60 pyxis machine.

3) **Albumin in the NeuroICU:** The criteria for albumin use in the NeuroICU include patients with severe/critical cerebral vasospasm after subarachnoid hemorrhage. Albumin 5% for these patients must be approved by Staff Physicians for 24-hour duration (i.e., discontinuation is considered on a daily basis).

Did You Know...

Availability of Hyoscyamine

In June 2006, the Food and Drug Administration (FDA) made their Unapproved Drug Initiative a top priority (See Pharmacotherapy Update newsletter May/June 2007). This initiative was established to emphasize the FDA's commitment to providing consumers with safe and effective medications.

All hyoscyamine (Levsin®, Levbid®) products are considered to be unapproved by the FDA. These products were on the market prior to the FDA's approval process that establishes safety and efficacy. Although the FDA has not taken action against any of the manufacturers of hyoscyamine, many manufacturers have voluntarily withdrawn their product(s) from the market to avoid a potential review by the FDA. This has resulted in an unexpected increase in demand on some companies, and thereby creates a shortage for the remaining products.

At the time of publishing of this newsletter, there are two manufacturers that have hyoscyamine products available and some hyoscyamine products are expected to return to the market by the end of July 2008. Aristos Pharmaceuticals currently has three hyoscyamine products available: Hyomax™ SL 0.125 mg, Hyomax™ SR 0.375 mg, and Hyomax™-FT chewable melt 0.125 mg. Alaven Pharmaceuticals currently has Levsin® 0.125 mg, Levsin® elixir 0.125 mg/5ml, Levsin® injection 0.5 mg/ml, and Levsin® oral drops 0.125 mg/ml available. Levsin® SL 0.125 mg and Levbid® 0.375 mg from Alaven are currently on backorder but expected to be available by the end of July 2008.

In the event that a patient's hyoscyamine product is unavailable, the patient should discuss alternative therapies with their pharmacist or physician.

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