INTRODUCTION AND HISTORICAL PERSPECTIVE

Infective endocarditis (IE) is a non-contagious, microbial infection of the valves and endocardium of the heart. The disease was first described by a French physician, Jean Francois Fernel, in his book Medicina in 1554. Almost 300 years later, in 1885, Sir William Osler gave a comprehensive account of endocarditis in three Gulstonian lectures. Osler astutely noted the host factors which predisposed to developing endocarditis, describing it “as a primary disease of the lining membrane of the heart or its valves, either attacking persons in previous good health or more often attacking the debilitated and dissipated and those with old valve lesions.”

DEFINITION

Infective endocarditis is defined as an infection of the endocardial surface of the heart, which may include one or more heart valves, the mural endocardium, or a septal defect. It is caused by a wide variety of bacteria and fungi. For this reason, IE requires a collaborative approach, involving primary care physicians, cardiologists, surgeons, microbiologists, infectious disease specialists, and frequently others, including neurologists, neurosurgeons, radiologists, and pathologists.

Changing Scenerio

IE is clearly an evolving disease, with changes in its microbiological profile, a higher incidence of healthcare-associated cases, elderly patients, and patients with intracardiac devices or prostheses. Conversely, cases related to rheumatic disease have become less frequent in industrialized nations. In addition, several new national and international guidelines or state-of-the-art papers have been published in recent years. Unfortunately, their conclusions are not uniform, particularly in the field of prophylaxis, where conflicting recommendations have been formulated.

ENDOCARDITIS PROPHYLAXIS

Infective endocarditis is a serious illness associated with significant morbidity and mortality. Its prevention by the appropriate administration of antibiotics before a procedure expected to produce bacteremia merits serious consideration. Experimental studies have suggested that endothelial damage leads to platelet and fibrin deposition...
and the formation of nonbacterial thrombotic endocardial lesions. In the presence of bacteremia, organisms may adhere to these lesions and multiply within the platelet-fibrin complex, leading to an infective vegetation. Valvular and congenital abnormalities, especially those associated with high-velocity jets, can result in endothelial damage, platelet-fibrin deposition, and a predisposition to bacterial colonization.

The principle of prophylaxis for IE was developed on the basis of observational studies in the early 20th century. The basic hypothesis is based on the assumption that bacteremia subsequent to medical procedures can cause IE, particularly in patients with predisposing factors, and that prophylactic antibiotics can prevent IE in these patients by minimizing or preventing bacteremia, or by altering bacterial properties leading to reduced bacterial adherence on the endothelial surface. The recommendations for prophylaxis are based in part on the results of animal studies showing that antibiotics could prevent the development of experimental IE after inoculation of bacteria.

However, many authorities and societies, as well as the conclusions of published studies, have questioned the efficacy of antimicrobial prophylaxis in most situations. Based on these issues AHA along with ADA (American Dental Association), IDSA (Infectious Disease Society of America) and AAP (Americal Academy of Pediatrics) after reviewing the relevant literature decided to change in some major recommendations for IE prophylaxis.

**The rationale for these revisions is based on the following:**

1. Infective endocarditis is more likely to result from frequent exposure to random bacteremias associated with daily activities than from bacteremia caused by a dental, GI tract, or GU procedure.
2. Prophylaxis may prevent an exceedingly small number of cases of infective endocarditis (if any) in individuals who undergo a dental, GI tract, or GU procedure.
3. The risk of antibiotic-associated adverse effects exceeds the benefit (if any) from prophylactic antibiotic therapy.
4. Maintenance of optimal oral health and hygiene may reduce the incidence of bacteremia from daily activities and is more important than prophylactic antibiotics for a dental procedure to reduce the risk of infective endocarditis.

**The major changes in the updated recommendations included the following:**

1. The committee concluded that only an extremely small number of cases of infective endocarditis may be prevented by antibiotic prophylaxis for dental procedures even if such prophylactic therapy were 100 percent effective.
2. Infective endocarditis prophylaxis for dental procedures is reasonable 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 reasonable for all dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of oral mucosa.
4. Prophylaxis is not recommended solely on the basis of 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 GU or GI tract procedure.

**Principles of the new ESC Guidelines**

Although recent guidelines proposed limitation of prophylaxis to patients at increased risk of adverse outcome of IE or even complete cessation of antibiotic prophylaxis in any patient groups, the Task Force decided:

- to maintain the principle of antibiotic prophylaxis when performing procedures at risk of IE in patients with predisposing cardiac conditions, but-
- to limit its indication to patients with the highest risk of IE (Table I) undergoing the highest risk procedures (Table II).

1. Patients with the highest risk of infective endocarditis (Table I):

**They include three categories of patients:**

(a) Patients with a prosthetic valve or a prosthetic material used for cardiac valve repair: these patients have a higher risk of IE, a higher mortality from IE and more often develop complications of the disease than patients with native valves and an identical pathogen.

(b) Patients with previous IE: they also have a greater risk of new IE, higher mortality and incidence of complications than patients with a first episode of IE.

(c) Patients with congenital heart disease (CHD), in particular those with complex cyanotic heart disease and those who have post-operative palliative shunts, conduits, or other prostheses. After surgical repair with no residual
defects, the Task Force recommends prophylaxis for the first 6 months after the procedure until endothelialization of the prosthetic material occurs.

Although AHA guidelines recommend prophylaxis in cardiac transplant recipients who develop cardiac valvulopathy, this is not supported by strong evidence. In addition, although the risk of adverse outcome is high when IE occurs in transplant patients, the probability of IE from dental origin is extremely low in these patients. The ESC Task Force does not recommend prophylaxis in such situations. Prophylaxis is not recommended for any other form of native valve disease (including the most commonly identified conditions, bicuspid aortic valve, Mitral valve prolapse, and calcific aortic stenosis).

### Table I. Cardiac conditions at highest risk of infective endocarditis for which prophylaxis is recommended when a high risk procedure is performed

<table>
<thead>
<tr>
<th>Recommendations : prophylaxis</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic prophylaxis should only be considered for patients at highest risk of IE</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>1. Patients with a prosthetic valve or a prosthetic material used for cardiac valve repair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Patients with previous IE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Patients with congenital heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. cyanotic congenital heart disease, without surgical repair, or with residual defects, palliative shunts or conduits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. congenital heart disease with complete repair with prosthetic material whether placed by surgery or by percutaneous technique, up to 6 months after the procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. when a residual defect persists at the site of implantation of a prosthetic material or device by cardiac surgery or percutaneous technique</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Antibiotic prophylaxis is no longer recommended in other forms or valvular or congenital heart disease III C

### Table II. Recommendations for prophylaxis of infective endocarditis in highest risk patients according to the type of procedure at risk

<table>
<thead>
<tr>
<th>Recommendations : prophylaxis</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>A - Dental procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic prophylaxis should only be considered for dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Antibiotic prophylaxis is not recommended for local anaesthetic injections in non-infected tissue, removal of sutures, dental X-rays, placement or adjustment of removable prosthodontic or orthodontic appliances or braces. Prophylaxis is also not recommended following the shedding of deciduous teeth or trauma to the lips and oral mucosa</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>B - Respiratory tract procedures:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic prophylaxis is not recommended for respiratory tract procedures, including bronchoscopy or laryngoscopy, transnasal or endotracheal intubation</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>C - Gastrointestinal or urogenital procedures:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic prophylaxis is not recommended for gastroscopy, colonoscopy, cystoscopy or transoesophageal echocardiography</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>D - Skin and soft tissue:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic prophylaxis is not recommended for any procedure</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
efficacy and the potential induction of resistance.

b. Other at-risk procedures:
There is no compelling evidence that bacteraemia resulting from either respiratory tract procedures, gastrointestinal or genitorinary procedures, dermatological or musculoskeletal procedures cause IE.

Thus, prophylaxis is not recommended in patients undergoing these procedures.

1. Respiratory tract procedures. Patients listed in Table 1 who undergo an invasive respiratory tract procedure to treat an established infection, e.g. drainage of an abscess, should receive an antibiotic regimen which contains an anti-staphylococcal penicillin or cephalosporin. Vancomycin should be given to patients unable to tolerate a β-lactam. Vancomycin or another suitable agents should be administered if the infection is known or suspected to be caused by a methicillin-resistant strain of S. aureus (MRSA).

2. Gastrointestinal or genitourinary procedures. In the case of an established infection or if antibiotic therapy is indicated to prevent wound infection or sepsis associated with a gastrointestinal or genitourinary tract procedure in patients described in Table I, it is reasonable that the antibiotic regimen includes an agent active against enterococci, e.g. ampicillin, amoxicillin, or vancomycin. Vancomycin should only be administered to patients unable to tolerate β-lactams. If infection is caused by a known or suspected strain of resistant enterococcus, consultation with an infectious diseases specialist is recommended.

3. Dermatological or musculoskeletal procedures. For patients described in Table I undergoing surgical procedures involving infected skin (including oral abscesses), skin structure, or musculoskeletal tissue, it is reasonable that the therapeutic regimen contains an agent active against staphylococci and β-haemolytic streptococci, e.g. an anti-staphylococcal penicillin or cephalosporin. Vancomycin or clindamycin may be used in patients unable to tolerate a β-lactam. If the infection is known or suspected to be caused by MRSA, vancomycin or another suitable agent should be administered.

4. Body piercing and tattooing. These growing social trends are a cause for concern, particularly for those individuals with CHD who are at increased susceptibility for the acquisition of IE. Case reports of IE after piercing and tattooing are increasing, particularly when piercing involves the tongue, although publication bias may overestimate the problem since millions of people are tattooed and pierced around the world and CHD concerns only 1% of the general population. Currently no data are available.

<table>
<thead>
<tr>
<th>Situation</th>
<th>Antibiotic</th>
<th>Single dose 30-60 minutes before procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adults</td>
</tr>
<tr>
<td>No allergy to penicillin or ampicillin</td>
<td>Amoxicillin or Ampicillin</td>
<td>2 g p.o. or i.v.</td>
</tr>
<tr>
<td>Allergy to penicillin or ampicillin</td>
<td>Clindamycin</td>
<td>600 mg p.o. or i.v.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Situation</th>
<th>Agent</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Amoxicillin</td>
<td>2g</td>
<td>50 mg/kg</td>
</tr>
<tr>
<td>Unable to take oral medication</td>
<td>Ampicillin or Cefazolin or ceftiazione</td>
<td>2 g IM or IV</td>
<td>50 mg/kg IM or IV</td>
</tr>
<tr>
<td>Allergic to penicillin or ampicillin</td>
<td>Cephalexin or Clindamycin</td>
<td>1 g IM or IV</td>
<td>50 mg/kg IM or IV</td>
</tr>
<tr>
<td></td>
<td>Clindamycin or Azithromycin or clarithromycin</td>
<td>600 mg</td>
<td>20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Clindamycin or Azithromycin or clarithromycin</td>
<td>500 mg</td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>Allergic to penicillins or ampicillin</td>
<td>Cefazolin or Ceftriazone OR Clindamycin</td>
<td>1 g IM or IV</td>
<td>50 mg / kg IM or IV</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>600 mg IM or IV</td>
<td>20 mg/kg IM or IV</td>
</tr>
</tbody>
</table>
on (a) the incidence of IE after such procedures and (b) the efficacy of antibiotics for prevention. Education of patients at risk of IE is paramount, and piercing and tattooing procedures should be discouraged. If undertaken, procedures should be performed under strictly sterile conditions though antibiotic prophylaxis is not recommended.

5. Cardiac or vascular surgery. In patients undergoing implantation of a prosthetic valve or intravascular prosthetic or other foreign material, peri-operative antibiotic prophylaxis should be considered due to the increased risk and adverse outcome of an infection. The most frequent microorganisms underlying early (>1 year after surgery) prosthetic valve infections are CNS and S. aureus. Prophylaxis should be started immediately before the procedure, repeated if the procedure is prolonged, and terminated 48 h afterwards. It is strongly recommended that potential sources of dental sepsis are eliminated at least 2 weeks before implantation of a prosthetic valve or other intracardiac or intravascular foreign material, unless the latter procedure is urgent.

6. Procedures causing health care-associated IE. They represent up to 30% of all cases of IE and are characterized by an increasing incidence and a severe prognosis, thus representing an important health problem. Although routine antimicrobial prophylaxis administered before most invasive procedures is not recommended, aseptic measures during the insertion and manipulation of venous catheters and during any invasive procedures are mandatory to reduce the rate of this infection.

**What is new in 2010?**

**Cardiovascular Implantable Electronic Device (CIED) Infections and Their Prophylaxis:**

Despite the greater ease of device implantation with pectoral rather than other routes and increasing experience with implantation, the rate of CIED infection has been increasing. Cabell et al 29 reported that among Medicare beneficiaries, the rate of cardiac device infections (PPMs, ICDs, valves, and ventricular assist devices) increased from 0.94 to 2.11 per 1000 beneficiaries between 1990 and 1999, a 124% increase during the study period. The rate of frank endocarditis was relatively unchanged (0.26 and 0.39 cases/1000 beneficiaries, respectively). The numbers of CIED infection-related hospitalizations increased out of proportion to rates of new device implantation. Moreover, CIED infection increased the risk of in-hospital death by more than 2-fold.

**Prophylaxis at CIED Implantation:**

Prevention of CIED infection can be addressed before, during, and after device implantation. Before device implantation, it is important to ensure that patients do not have clinical signs of infection. A parenterally administered antibiotic is recommended 1 hour before the procedure. Data from a meta-analysis 30 2 case-control studies that examined purported risk factors of CIED infection 31,32 and a large, prospective, randomized, double-blinded, placebo-controlled trial strongly support the administration of antibiotic prophylaxis for CIED implantation. Most experts continue to advocate a first-generation cephalosporin, such as cefazolin, for use as prophylaxis. Although not generally recommended, some advocate the use of vancomycin instead of cefazolin, particularly in centers where oxacillin resistance among staphylococci is high. Vancomycin also represents an alternative to a first-generation cephalosporin in patients who are allergic to cephalosporins. In patients who are allergic to both cephalosporins and vancomycin, daptomycin and linezolid represent prophylaxis options. Antibiotic prophylaxis is also recommended if subsequent invasive manipulation of the CIED is required. Preoperative antiseptic preparation of the skin of the surgical site should be done. Intraprocedurally, compulsive attention to sterile technique is mandatory. If a patient has limited subcutaneous tissue and/or poor nutrition and is at increased risk for erosion, a retroperitoneal pocket should be considered. In a survey of pediatric patients, 9 (13.8%) of 65 with subcutaneously placed device-pocket transvenous systems developed infection compared with none of the 82 who underwent retropectorally placed systems 34 Routine ambulatory care follow-up after CIED placement to detect early infectious complications has been performed in many centers. Recent data from 1 investigation 35 failed to demonstrate the utility of early follow-up and advocated that instead, patients should be instructed to call their implanting physician for development of fever or incision findings of inflammation. The writing group believes that both early follow-up in a clinic setting and thorough patient education should be conducted for early identification of CIED-related infectious complications. Currently, there are no data to support the administration of postoperative antibiotic therapy, and it is not recommended because of the risk of drug adverse events, selection of drug-resistant organisms, and cost.
Recommendations for Antimicrobial Prophylaxis for Invasive Procedures in Patients With CIEDs:

**Class III**

1. Antimicrobial prophylaxis is not recommended for dental or other invasive procedures not directly related to device manipulation to prevent CIED infection. (Level of Evidence: C)

**Limitations and consequences of the new ESC Guidelines:**

The Task Force understands that these updated recommendations dramatically change long-established practice for physicians, cardiologists, dentists, and their patients. Ethically, these practitioners need to discuss the potential benefit and harm of antibiotic prophylaxis with their patients before a final decision is made. Following informed review and discussion, many may wish to continue with routine prophylaxis, and these views should be respected. Practitioners may also have a reasonable fear of litigation should prophylaxis be withdrawn, though unnecessarily so since adherence to recognized guidelines affords robust legal protection. Finally, the current recommendations are not based on appropriate evidence, but reflect an expert consensus of opinion. As neither the previous guidelines nor the current proposed modifications are based on strong evidence, the Task Force strongly recommends prospective evaluation in the wake of these new guidelines to evaluate whether reduced use of prophylaxis is associated with a change in the incidence of IE.

**CONCLUSION**

In the latter half of the 20th century, regular revisions for infective endocarditis prophylaxis guidelines added more cardiac risk conditions and risk groups, more at risk procedures and more antibiotic regimens, adding to the complexity faced by a primary physician in both applying these recommendations to an individual patient and also in explaining the benefits and potential harm to the patient. The newer guidelines are much simpler to follow and could potentially overcome this serious concern. These Contemporary guidelines on infective endocarditis prophylaxis challenge previous recommendations based on a low level of evidence. However, explaining these drastic changes to a returning patient and to referral physicians who are more accustomed to old recommendations would be equally challenging, if not more. One of the bright spots in the recent AHA and ESC guidelines, is the reduction in the use of prophylactic antibiotics in cases where it can be avoided without serious adverse outcomes. The main recommendation is to underline that prophylaxis may often be based on adequate education without the administration...
of antibiotics. Limited use of prophylaxis will likely reduce the unwanted selection of antibiotic-resistant strains and their unintended consequences.

REFERENCES


