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Review Article

Infective Endocarditis: Disease Burden and Updated Clinical Perceptive in Prophylaxis

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Abstract

Infective endocarditis is the most common cause of heart infections. The epidemiology, pathophysiology, clinical presentation, diagnosis, management and prevention have evolved in the past several years due to the increasingly-recognized healthcare associated infective endocarditis and advancements in cardiac devices. Prevention of infective endocarditis has been an important issue for the cardiovascular societies across the world, leading to updates in the guidelines of infective endocarditis prevention. The effective use of antibiotics prophylaxis in IE is still been a challenge as there is a threat of antibiotic resistance by widespread use of antibiotics, an important issue today, as well as needlessly exposing patients to antibiotic side effects. In this article, we are discussing the medical literature on infective endocarditis, mainly addressing its burden, the evolving causative micro-organisms and endocarditis prevention guidelines.

Keywords: *Infective Endocarditis; Prophylaxis*

Introduction

Infective endocarditis is an infection of the heart. It affects the inner membrane of the heart (endocardium). There is a prevalence of infective endocarditis in both children and adults and the risk of cardiovascular morbidity and mortality are significantly high in patients from developing countries [1]. Infective endocarditis is associated with older patients with co-morbidities and its trend has also evolved to affect young patients with pre-existing structural heart disease [2].

Organisms involved and diagnostic criteria

Endocarditis affecting the normal heart valves impacts fifty percent (50%) of the cases. The most common causative microorganism are the *Streptococcus* species, while *Staphylococcus aureus (S. aureus)* commonly affects older patients and is also a common cause of healthcare associated IE. *Streptococcus viridans* is commonly seen in patients from developing countries. Other causative agents are *Staphylococcus epidermidis*, Diphtheroid, and microaerophilic *Streptococcus*. In recent years staphylococci, commonly associated with healthcare contact and invasive procedures, have seemed to overtake streptococci as the most common cause of IE [3].

The most common causative agent of culture-positive, native valve and prosthetic valve endocarditis are the following:

1. *Streptococcus viridans*
2. *Staphylococcus aureus*
3. Coagulase negative *Staphylococcus* species - *S. epidermidis*
4. *Enterococcus* species
5. Gram- negative Bacillus species
6. Diphtheroids
7. *Streptococcus pneumonias*

Practically, positive blood culture for typical infective endocarditis organisms is a major diagnostic criteria of infective endocarditis according to Duke's criteria. Diagnostic can be decided by 2 major criteria and 0 minor or 1 major criteria and 3 minor criteria or 0 major criteria and 5 minor criteria.

In modified Duke's criteria, following are major diagnostic criteria:

1. Positive blood culture for typical infective endocarditis organisms (*S. viridans* or *S. bovis*, HACEK organisms, *S. aureus* without other primary site, *Enterococcus*), from 2 separate blood cultures or 2 positive cultures from samples drawn > 12 hours apart, or 3 or a majority of 4 separate cultures of blood (first and last sample drawn 1 hour apart).
2. Echocardiogram with oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or abscess, or new partial dehiscence of prosthetic valve or new valvular regurgitation.
3. Single positive blood culture for *Coxiella burnetii* or anti-phase 1 IgG antibody titer > 1:800.

In minor diagnostic criteria:

1. Predisposing heart condition or intravenous drug use.
2. Temp > 38 degrees C (100.4 degrees F).
3. Vascular phenomena: arterial emboli, pulmonary infarcts, mycotic aneurysms, intracranial bleed, conjunctival hemorrhages, Janeway lesions.
4. Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor.
5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with endocarditis (excluding coagulative negative staph, and other common contaminants).

IE caused by *Staphylococcus aureus* is usually from the organism's skin entry such as those seen in dermatitis, Intravenous injections, renal failure, organ transplantation, diabetes mellitus, and post-operative wound. Other gram negative bacteria that can cause IE are *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella, Coxiella burnetiid, Chlamydia, fungi, Candida, Aspergillus* and *Histoplasma* [4]. According to the statistical analysis done by Thomas L. Holland and co-workers from Division of Infectious Diseases, Duke University Medical Center, they reported global epidemiology of causative pathogens involved in IE study divided the world into 4 world regions as shown figure 1.

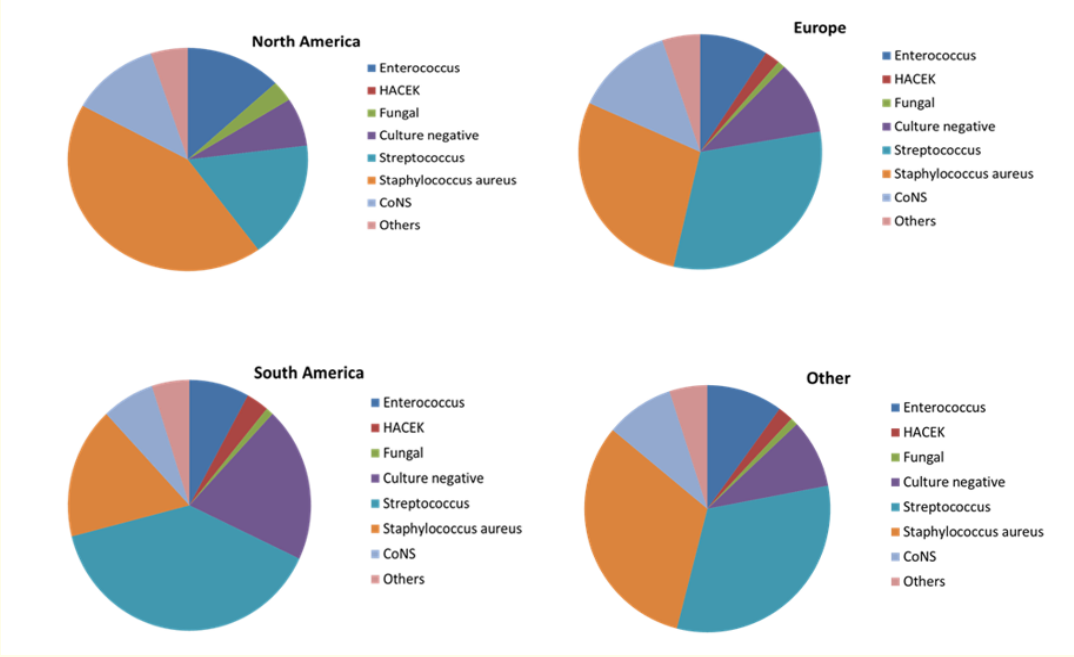

Figure 1: *Global epidemiology of causative pathogens involved in IE, CoNS: Coagulative Negative Streptococci.*

Burden of Infective Endocarditis in developing countries

In the developed countries, IE tends to affect patients between the ages of 50 - 60 years old while in developing countries, it commonly affects the 20 - 40 years old age group. This is primarily due to a more ageing society in developed countries that relies on increasing invasive medical care, the presence of degenerative valve disease, and other co-morbidities. In developing countries, rheumatic heart disease is still the most common predisposing cause of IE. About 50% of IE in developing countries occurs in patients with no known history of valve disease. There is limited data regarding the trend of disease pattern of IE in Southeast Asia but Mariana Mirabel., *et al.* reported Rheumatic heart disease remains a major predisposing factor of IE in Pacific tropical islands [5].

According to the Global Burden Disease 2013 Study of sixteen poorest countries*, Infective endocarditis' impact to the rate of DALY (disability-adjusted life-year) per 100,000 in this regions was 1.7% [6]. This data showed IE has been a great burden in these countries.

*[Sixteens poorest countries: Niger, Ethiopia, South Sudan, Chad, Burkina Faso, Somalia, Sierra Leone, Guinea-Bissau, Guinea, Mali, Burundi, Central African Republic, Democratic Republic of the Congo, Mozambique, Liberia and Uganda].

In developing countries, IE is predominantly a disease of young patients with rheumatic heart disease. Although the microbiological features of IE in Africa are similar to those of economically wealthier nations of the world, about 50% of IE in developing countries occurs in patients with no known history of valve disease [7,8].

Infective endocarditis prophylaxis

With the absence of randomized controlled trial (RCTs) that demonstrated the efficacy of antibiotic prophylaxis to prevent infective endocarditis (IE), the practice of antibiotic prophylaxis has been questioned by national and international medical societies. According to

the 2007 revised American Heart Association (AHA) Guideline, the use of antibiotic prophylaxis in IE before surgical procedures, dental and endoscopic procedures has changed over the few years [9,10].

Infective endocarditis after interventional, dental, or other procedures is uncommon because IE is much more likely to be obtained from exposure to random bacteremia associated with daily activities than from bacteria caused by gastrointestinal (GI) tract, genitourinary (GU) tract, and dental procedure. As the trend of antibiotic resistance is dramatically increasing around the world, it is recommended that optimal oral hygiene and oral health care be more effective and may reduce the incident of bacteremia [11].

Antibiotic prophylaxis alone is not recommended to prevent IE because there is no strong association between having an interventional procedures and development of IE. Preventive antibiotics are no longer recommended for any other congenital heart disease but may be considered in high-risk cardiac conditions.

Cardiac conditions with increased risk of IE
• Previous IE • Native valvular heart disease including established rheumatic heart disease • Cardiac Operations; Prosthetic material used for cardiac valve, Cardiac transplant recipients who develop cardiac valvulopathy or repair Prosthetic cardiac valves • Unrepaired cyanotic CHD, including palliative shunts and conduits • Completely repaired defects with prosthetic material or devices during the first 6 months after the procedure • Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or device (which inhibit endothelialization).

**Approved and adapted from American Heart Association and Cardiac Society of Australia, South Africa and New Zealand infective endocarditis guidelines.*

Both European Society of Cardiology (ESC) and American College of Cardiology (ACC)/American Heart Association (AHA) guidelines still recommended that IE prevention with antibiotics for prosthetic valve, previous IE, and congenital heart disease (IIA/B, C). The 2015 ESC guideline no longer recommends the use of prophylaxis for cardiac transplant with valvulopathy. Both ESC and ACC/AHA recommend IE prophylaxis for Dental Procedure [Class IIb, LOE C].

Dental procedures involve manipulation of gingival tissue of the periapical region of teeth or perforation of the oral mucosa. The estimated incidence of IE is about 1 per 150,000 dental procedures with antimicrobials prophylaxis and 1 per 46,000 for procedures unprotected by antimicrobials. Antimicrobial prophylaxis is recommended for invasive dental procedures that involve manipulation of the gingival or periapical region of the teeth or oral mucosa. Routine antimicrobial prophylaxis is not recommended for all patients undergoing dental procedures. During routine oral hygiene, bacteremia occurs more frequently (e.g. toothbrushing) and the risk of relation between endocarditis and poor dental health is common rather than occasional high-grade bacteremia due to dental procedure [13].

Genitourinary and gastrointestinal tract procedures

Patients who are undergoing genitourinary (GU) or gastrointestinal (GI) tract procedures may need IE prophylaxis. Routine pre-procedural antimicrobial prophylaxis is no longer recommended. However, for high-risk cardiac patients who have an established

gastrointestinal or genitourinary infection, or for those who received antimicrobial therapy for surgical reasons, the antimicrobial regimen should include an agent active against enterococci, such as Ampicillin or Vancomycin. In the unique scenario in which a high risk patients may require elective urinary tract manipulation (e.g. cystoscope) and has established enterococcal urinary tract infection or colonization, antibiotic therapy to eradicate enterococci from the urine before the procedure maybe reasonable [9,10].

Respiratory tract procedures

Antimicrobial prophylaxis is recommended for patients with increased risk of IE who will undergo an invasive respiratory tract procedure that involve incision or biopsy of the respiratory mucosa. According to ACC/AHA recommendation, invasive procedures of the respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy or adenoidectomy needs prophylaxis. Routine prophylaxis for bronchoscopy is not recommended if the procedure does not involve incision of the respiratory tract mucosa. In procedures involving an established respiratory tract infection, the antimicrobial must be active against the causative microorganisms in addition to Viridans Group Streptococci (VGS) [12,13].

Other procedures

Antimicrobial prophylaxis is required for high risk cardiac patients undergoing these procedures: incision and drainage of local abscess in the brain, skin and subcutaneous tissue (e.g. boils and carbuncles), eye (e.g. dacryocystitis), epidura, lung, orbital area, perirectal area, liver (e.g. pyogenic liver), tooth, and surgical procedures through infected skin, and percutaneous endoscopic gastrostomy.

Heart surgery and device replacement

All patients who will undergo heart valve replacement or who will receive an intravascular graft or intracardiac device should receive periprocedural prophylaxis with an anti-staphylococcal antibiotic.

Prophylaxis always required	Prophylaxis required in some circumstances	Prophylaxis not required
Extractions Periodontal procedures including surgery, subgingival scaling and root planning Replanting avulsed teeth Other surgical procedures (e.g. implant placement and apicectomy)	Consider prophylaxis for the following procedures if multiple procedures are being conducted, the procedure is prolonged or periodontal disease is present: • Full periodontal probing for patients with periodontitis • Intraligamentary and intraosseous local anaesthetic injection • Supragingival calculus removal or cleaning • Rubber dam placement with clamps (where there is risk of damaging gingiva) • Restorative matrix band/strip placement • Endodontics beyond the apical foramen • Placement of orthodontic • bands or interdental wedges • Subgingival placement of retraction cords, antimicrobial fibres or antimicrobial strips	Oral examination • Infiltration and block local anesthetic injection • Restorative dentistry • Supragingival rubber dam clamping and placement of rubber dam • Intracanal endodontic procedures • Removal of sutures • Impressions and construction of dentures • Orthodontic bracket placement and adjustment of fixed appliances • Application of gels • Intraoral radiographs • Supragingival plaque removal

**Adapted from Infective Endocarditis Prophylaxis Expert Group. Prevention of endocarditis. 2008 update from Therapeutic guidelines: antibiotic version 13, and Therapeutic guidelines: oral and dental version 1. 2008.*

In National Institute for Health and Care Excellent (NICE) 2015 guideline**,** antibiotic prophylaxis against infective endocarditis is not recommended routinely for people undergoing dental procedures and people undergoing non-dental procedures at the following sites. NICE also does not recommend routinely to give IE prophylaxis for upper and lower gastrointestinal tract, genitourinary tract; this includes urological, gynecological and obstetric procedures, and childbirth**.** Chlorhexidine mouthwash should also not be offered as prophylaxis against infective endocarditis to people at risk of infective endocarditis undergoing dental procedures according to NICE guideline 2015.

ESC 2015 Recommendation

The European Society of Cardiology (ESC) recommends prophylaxis for cardiac conditions at highest risk of IE for which prophylaxis is recommended when a high-risk procedure is performed. This include:

- Patients with previous IE have a greater risk for new IE, higher mortality and develop more complications than patients with a first episode of IE.
- Patients with congenital heart disease (CHD):
    1. Any type of cyanotic CHD
    2. Any type of CHD repaired with prosthetic material, whether placed surgically, or by percutaneous technique, up to 6-months after the procedure or lifelong if residual shunt or valvular regurgitation remains.

High-risk is defined as those with underlying cardiac conditions associated with the greatest risk of adverse outcome from IE, and not necessarily those with an increased lifetime risk of endocarditis.

What is new and modified in ACC/AHA (2017) recommendation?

The risk of developing IE is higher in patients with underlying valvular heart diseases (VHD). IE has been reported to occur after transcatheter aortic valve replacement (TAVR) at rates equal to or exceeding those associated with surgical aortic valve replacement (AVR). One year mortality rate of TAVR and AVR is 75% [14,15]. IE may also be seen after valve repair in which prosthetic material is used, usually necessitating urgent operation, which has high in-hospital and 1-year mortality rates [16,17]. According to some data, the incident of IE seems to be more common in heart transplant recipients than in the general population [18]. IE appears to be highest risk in the first 6 months after transplantation because of endothelial disruption, high-intensity immunosuppressive therapy, frequent central venous catheter access, and frequent endomyocardial biopsies [18].

Thus, American College of Cardiology /American Heart Association modified that patients with transcatheter prosthetic valves and patients with prosthetic material used for valve repair, such as annuloplasty rings and chords, were specifically identified as those to whom it is reasonable to give IE prophylaxis (LOE updated from B to C-LD)* [19].

*LOE- Level of evidence, LD- Limited Data.

Drugs used for prophylaxis

The most common pathogen for oral and respiratory tract procedures related endocarditis is the alpha-hemolytic streptococci. Antimicrobial regimens for endocarditis prophylaxis are generally directed towards VGS (Viridans Group Streptococci). Prophylactic antibiotics for IE prevention should be administered in a single dose before the procedure. If the dosage is inadvertently not administered before the procedure, it may be given up to 2 hours after the procedure [20,21].

Prophylactic regimens for a dental procedure

Antibiotic regimens for dental procedures (single dose administered 30 minutes to 60 minutes before the procedure).

Oral - Amoxicillin [2G for Adult and 50 mg/kg for Children].

Unable to take oral medication

- Ampicillin [2G IM/IV for Adult and 50 mg/kg IM/IV for Children].
- Cefazolin or Ceftriaxone [1G IM/IV for Adult and 50 mg/kg IM/IV for children].

Allergic to Penicillin or ampicillin (oral)

- Cephalexin [2G for adult and 50 mg/kg for child].
- Clindamycin [600 mg for adult and 20 mg/kg for child].
- Azithromycin [500 mg for adult and 15 mg/kg for child].
- Clarithromycin 500 mg for adult and 15 mg/kg for child].

Allergic to Penicillin or ampicillin (unable to take oral medication)

- Ceftriaxone or Cefazolin [1G IM/IV for adult and 50 mg/kg IV/IM children] or Clindamycin [600 mg IV/IM for adult and 20 mg/kgIV/IM for child]. IM: Intramuscular; IV: Intravenous

Future Direction

There are many ongoing trials and analysis about antibiotic prophylaxis in the field of infectious disease medicine including infective endocarditis to improve effective treatment while reducing the occurrence of antibiotic resistance. Although prophylaxis for infective endocarditis significantly lowers the risk for infection, it is still challenging to follow up the outcome of effectiveness in case series from single-center analysis. It would also be a good idea to analyze the effectiveness of basic infection control hand washing, good oral hygiene) in preventing disease.

There is a threat of antibiotic resistance by widespread use of antibiotics for this purpose, an important issue today, as well as needlessly exposing patients to antibiotic side effects such as allergic reactions. For this reason, International Collaboration of Endocarditis (ICE) has been formed and large randomized clinical trials can be done by collecting various cohort data from multicenter internationally.

Conclusion

According to real world data analysis, there is no different strategy and special guidelines of IE prophylaxis in both developed and developing countries. This has still been a challenge due to the low incidence of the disease and small retrospective analysis or case series to revise the IE prophylaxis for particular region. The most common pathogenic organisms in many developing countries setting are the Streptococci, and the antibiotic choice should therefore be no different to that of the international guidelines. Prophylaxis before oral procedures should be addressed in countries where the incidence of streptococcal IE remains high. Overall, prevention of IE with antibiotic is needed to give clear information about the benefits and risks of antibiotic prophylaxis.

Conflict of Interest

The authors declare that there is no conflict of interest.

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