

## **Controversies over Infective Endocarditis Prophylaxis and the Need for National Guidelines**

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### **Abstract**

Infective endocarditis (IE) is a relatively rare but invariably fatal disease if left untreated. Over decades, individuals with certain congenital or acquired heart defects were given antibiotic prophylaxis before certain procedures to prevent IE. However, controversies on this regimen have begun to grow since 2002 and in 2007-2008, three major international health organizations, the American Heart Association (AHA), the European Society for Cardiology (ESC), and the National Institute for Health and Clinical Excellence (NICE), UK published have their revised guidelines where AHA and ESC markedly shortened the list of indications for IE prophylaxis and NICE abandoned the concept of IE prophylaxis altogether. This has literally divided not only the medical practitioners around the world but practitioners within countries who used to follow either AHA, ESC or NHS guidelines in absence of their own national guidelines. This chaotic situation has also affected the medical teaching in those countries because of contradictory teaching from teachers having different views and belongingness on this issue. Even follow up review five years after the introduction of revised guidelines has failed to resolve the controversies and it deems unresolvable in near future. In such circumstances, every country needs to have own guideline for uniform medical teaching and practice.

### **Background**

Infective endocarditis (IE) is an infection that involves the endocardial lining of the heart, the heart valves, indwelling cardiac devices or prosthetic valves (Lauridsen TK, 2018; Cahill TJ, 2016).

IE is predominantly a bacterial infection caused mainly by viridans streptococci, staphylococci, and enterococci; however, rarely it can be caused by non-bacterial agents, such as fungus (Liesman RM, 2017; Wu Z, 2020). Although IE is a relatively rare disease but almost invariably fatal in consequences in untreated patients. In-hospital mortality is up to 30% despite treatment including surgical interventions with lasting morbidity among the survivors. These figures remain more or less unchanged over past two decades (Rajani R, 2020; Hoen B, 2013; Duval X, 2015; Chirouze B, 2012; Wang A, 2012; Gregor P, 2013).

### What makes IE a serious disease: the pathophysiology

Bacteremia is the key trigger in the pathogenesis of IE. Pathogens enter the bloodstream, for example from mouth cavity during dental procedure, and attach to the site of damaged endocardium, to the cardiac valves, or to an intracardiac device. At the site of adherence, infected vegetations are formed as a result of complex interactions between invading microorganisms and the host immune system. The matrix of the vegetations containing fibrin and platelet aggregates provide a safe sanctuary for the microorganisms where they proliferate and colonize. Moreover, the a vascular tissues of the cardiac valves make it hard for the antimicrobial agents to reach the site of infection and eradicate the microbes.

The vegetations harboring microorganisms can grow large enough to cause obstruction or may embolize to almost any organs in the body producing multiorgan dysfunction. This can give rise to grave complications such as ischemic stroke from cerebral embolism, infarctions and abscess formations. Its effects within the heart include infarction, severe valvular insufficiency, intractable congestive heart failure, and myocardial abscesses (Werdan K, 2014; Lauridsen TK, 2018; Hubers SA, 2020; Sullam PM, 1985).

### Who Can Get IE: The Risk Factors

Traditionally, it was believed that the cardiac endothelium in a normal healthy heart is resistant to bacteremia and hence development of endocarditis and IE can develop only at the sites of damaged cardiac tissues, particularly the valve leaflets. However, it is now established that infection with virulent *Staphylococcus aureus* entering the body through intravenous routes, such as indwelling intravenous or central venous lines or intravenous drug use, can affect a healthy heart and produce florid vegetations, rapid valve destruction, and cardiac abscess formation frequently leading to a fulminant course and devastating outcome (Ralston SH, 2018; Hoen B, 2013; Fowler VG, 2005; Han SM, 2017; Bouchiat C, 2015). In children, approximately 8% to 10% of IE develop in a structurally normal heart. This is most often associated with central lines required for critically sick children admitted in neonatal or pediatric intensive care units (Saiman L, 1993; Martin JM, 1997; Morris CD, 1998; Selton-Suty C, 2012)

On the other hand, it is unanimously agreed that almost all types of congenital or acquired structural cardiac defects, the prosthetic heart valves, or the implanted cardiac devices, such as pacemakers or cardioverter defibrillator, can predispose to the development of IE (Holland TL, 2016). In children, congenital heart disease is the commonest risk factor for IE, and the risk continues, although less than before, after surgical repair because the synthetic materials used in the surgical procedure can favor bacterial adhesion and infection (Rushani D, 2013; Niwa K, 2005; Di Filippo S, 2006).

Although all cardiac defects can predispose to IE, the cardiac defects that are more vulnerable to seedling the infection and develop IE include areas exposed to higher jet of blood, such as ventricular septal defect, mitral regurgitation, mitral valve prolapse, and aortic regurgitation. On

the other hand, low-pressure lesions, such as atrial septal defect has minimal chance of developing IE (Brusch JL, 2021; Wang A, 2007; Hoerr V, 2018).

### **Concept of Antibiotic Use in the Prevention of IE**

Historically, Winge in 1870 the first suggestion that IE might be caused by microorganisms was suggested by Winge in 1870 (Winge E, 1870) and in the late 1800s, Rosenbach, Wyssokowitsch, and others established that bacteria entering the blood could attach and colonize on the damaged heart valves (Rosenbach O, 1878; Wyssokowitsch, 1886). However, the concept that invasive dental procedures might lead to bacteremia and IE was first coined in 1923 by Lewis and Grant (Lewis T, 1923) which was later confirmed in 1935 by Okell and Elliott who isolated oral viridans Streptococci through blood culture in patients undergone teeth extraction (Okell CC, 1935). Subsequently, a series of observational studies continued to shed lights on this issue and in late 1940s, the first case-control study demonstrated lower streptococcal bacteremia in persons receiving penicillin prophylaxis compared to control (Hirsh HL, 1948). This influenced the American Heart Association (AHA) to come up with their first official guidelines on IE prophylaxis in 1955 (American Heart Association, 1955; Thornhill MH, 2017). In 1982, the British Society for Antimicrobial Chemotherapy set on the first UK guidelines on antibiotic prophylaxis (The British Society for Antimicrobial Chemotherapy, 1982; Gould FK, 2006) and also kept on reviewing periodically.

In the meanwhile, the provision of using pre-procedural antibiotic to suppress bacteremia and reduce IE risk firmly established in the clinical practice. The dental, urogenital and gastrointestinal procedures were considered high-risk for bacteremia and of them, invasive dental procedures associated with bleeding was being consistently considered the major trigger for IE by Streptococcus viridans with an affected rate between 40-100% (Brusch JL, 2021).

### **Debates and Controversies Surrounding IE Prophylaxis**

Early in the twenty-first century, debates and controversies started brewing on the justification of using antibiotic prophylaxis to prevent IE. There were many reasons behind that. Growing number of scientific studies evidenced that streptococcus viridans present in the oral cavity of healthy individual form biofilms when they enter the blood circulation which protect them from the antibiotic action (Chino T, 2009; Avila M, 2009). Moreover, most bacteremia was short-lived, without any consequences and, in fact, were unpreventable. The bacteria entering the body were removed from the circulation by various host defenses before they adhered to the damaged endocardial tissue and use of antibiotic did not add much benefit to it, rather predisposed to antibiotic resistance (Maharaj B, 2012; Loyola-Rodriguez JP, 2019). Another shaking information was spelled out by the AHA committee on review of the IE prophylaxis guidelines that only an extremely small number of cases of infective endocarditis can actually be prevented by antibiotic prophylaxis before dental procedures even if such therapy were 100% effective (Wilson W, 2007).

The first major disagreement became public in 2007-2008 when three pioneer bodies—the American Heart Association (AHA), the European Society for Cardiology (ESC), and the National

Institute for Health and Clinical Excellence (NICE) who produce guidelines for North America, for whole of Europe, and for the UK respectively, disclosed update of their guidelines. In the updated versions, AHA and ESC guidelines stopped antibiotic prophylaxis for at risk persons before gastrointestinal and urogenital procedures but continued for invasive dental procedures (Embil JM, 2008; Thornhill MH, 2020). Both guidelines recommended antibiotic prophylaxis for individuals with a prosthetic valve or valve repaired with prosthetic material, previous history of infective endocarditis, unrepaired cyanotic congenital heart disease, or certain repaired congenital heart defects before invasive dental procedures involving the gingiva (Wilson W, 2007; Nishiura RA, 2008; Habib G, 2009).

On the other hand, the NICE guideline admitted the necessity for IE prophylaxis in selective conditions but completely abandoned the use of antibiotic prophylaxis for any person for any reason (NICE clinical guideline on prophylaxis against infective endocarditis, 2008). This put NICE guidelines in sharp contradiction with the other two major guidelines and at the same time, initiated one of the big controversies in contemporary medicine. While diagnostic strategies and treatment protocols for IE produced little or no debate, its prophylaxis did and still ongoing.

Moreover, NICE guidance on antibiotic prophylaxis against IE divided the practitioners in the UK; most (87%) dentists followed the NICE guidance, whereas many (39%) cardiologists and cardiothoracic surgeons did not; and more than half (56%) of the infection specialists adopted a middle course (Dayr MJ, 2013).

The policy changes by major organizations apparently originated from three considerations: the mounting concern of emerging bacterial resistance, potential adverse effects of the certain drugs (such as clindamycin given to penicillin-sensitive patients), and cost effectiveness—the cost of treating a large number of people (estimated 476) to prevent a single case of IE if prophylaxis was 100% effective (Thornhill MH, 2015; Kaya CT, 2018). Although the cost of antibiotic prophylaxis for a single person is not high, the cumulative cost is. In the USA, a cumulative cost of antibiotic prophylaxis for all illegible persons for dental procedure was estimated to \$145 million per year (Lockhart PB, 2013). Additional factors that led NICE to take an opposite stance include the unavailability of sufficient evidences in the published literatures to convincingly prove that antibiotic prophylaxis can reduce IE incidence when given before any dental and non-dental procedures (NICE, 2008; Stokes T, 2008). NICE also reasoned that only observational studies, not the randomized clinical trials (RCTs), were the sources of all previous and on going recommendations for IE prophylaxis which had low quality of evidences and therefore, not worth considering in terms of clinical and cost effectiveness (National Institute for Health and Care Excellence, 2015). This argument brought an ethical question in front—what to do if there is no RCT data available on any clinical issue, such as this (Mohindra RK, 2010; Mohindra RK, 2010). However, NICE has ignored the criticism and remained firm on the decision. Contextually, one of the primary roles of NICE is to evaluate the cost-effectiveness of drugs and to ensure effective use of available resources within the health care system in the UK (UK Government, 1999).

**Summary Table of Agreement and Disagreement in NICE, ESC and AHA Guidelines After Review in 2007-2008**

IE prophylaxis: Indications (whom to give)	
NICE guidelines (2008)	ESC & AHA guidelines (2007)
All cyanotic and acyanotic congenital heart defects except isolated atrial septal defect (ASD)	Unrepaired cyanotic congenital heart defects including palliative shunts and conduits
Surgically corrected or palliated conditions, but excluding repaired ventricular septal defect (VSD) or repaired patent ductus arteriosus (PDA), and closure devices that are judged to be endothelialized	Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure
Acquired heart diseases: valve stenosis or regurgitation	Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibits reendothelialization)
Valve replacement (i.e., prosthetic valves)	Prosthetic cardiac valves or any prosthetic material or device used for cardiac repair
History of previous infective endocarditis	History of previous infective endocarditis
Hypertrophic cardiomyopathy	Cardiac transplantation recipients with cardiac valvular disease
IE Prophylaxis: When to give	
No prophylaxis required for genitourinary or gastrointestinal procedures	No prophylaxis required for genitourinary or gastrointestinal procedures
No prophylaxis required for persons undergoing dental procedures	Antibiotic 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
No prophylaxis required for upper and lower respiratory tract procedures including ENT procedures and bronchoscopy	Antibiotic prophylaxis is recommended for invasive respiratory tract procedures that involve incision or biopsy of the respiratory mucosa including tonsillectomy, adenoidectomy. Simple bronchoscopy does not require prophylaxis.

### **Impact of the Changes in NICE Guideline**

Follow up studies evaluated the impact of changes in the NICE guidelines. In 2011, a study published in the British Medical Journal (Thornhill MH, 2011) concluded that there was a dramatic (78.6%) reduction in prescribing of antibiotic prophylaxis after changes in the NICE guideline and there was no significant increase in the incidence of IE cases. The article, in fact, covertly supported NICE's position while recommending on going monitoring and further clinical trials. This was further substantiated by an article (Franklin M, 2016) which estimated that changes in NICE guidelines for IE prophylaxis would save £5.5-8.2 million with gains of 2,687 quality-adjusted life years annually.

However, in March 2015, an article published in the Lancet (Dayer MJ, 2015) showed 88% reduction in antibiotic prescribing in England in five years since the introduction of changed NICE guidelines, but at the cost of significant increase in the incidence of IE cases which was over and above the projected historical trend what would have been expected had the previous trend continued. This pointed finger towards the changed NICE guidance as the cause of an upsurge of new IE cases and compelled NICE to announce another review in 2015. After the review, the NICE came up with a cautionary statement: "antibiotic prophylaxis against infective endocarditis is not recommended routinely for people undergoing dental procedures, but in individual cases, antibiotic prophylaxis may be appropriate" (National Institute for Health and Care Excellence, 2015). The UK practitioners welcomed even this little change in wordings because from a stance of total prohibition of antibiotic prophylaxis it gave a way to the practitioners to consider IE prophylaxis in a case-to-case basis (Thornhill MH, 2016).

At the same time, the ESC and AHA too announced a review of their guidelines in 2015 where ESC concluded 'the weight of evidence and opinion was in favour of the efficacy and usefulness of antibiotic prophylaxis in preventing IE in those at high-risk'. They also concluded that the risk of not giving antibiotic prophylaxis outweighed the risk of giving it and recommended continuing IE prophylaxis to all high-risk patients before invasive dental procedures (Habib G, 2015).

The recommendations of AHA were in parallel to the ESC guidelines. Both have concluded that their previous recommendations to continue antibiotic prophylaxis for the subset of patients at increased risk of developing IE were logical and should continue. Therefore, it had appeared that the disagreements between NICE and other guidelines prevailed and apparently not resolvable soon.

### **How These Disagreements has Affected the Other Countries of the World**

The disagreements reflected in the NICE, AHA, and ESC guidelines created a chaotic situation in the rest of the world where there is no national guideline. Medical professionals in these countries follow either guideline by own choice. Historically, many South Asian countries follow medical guidelines practiced in the UK; partly because many specialists in these countries receive postgraduate degrees from the UK, and partly medical teaching in these countries traditionally follow the UK curriculum. However, some also follow American or other guidelines as there is no national guidance. Contradictory positions on IE prophylaxis guidelines therefore put an awkward

situation on the medical and dental practitioners in these countries including the risk of being charged for medical malpractice due to contradicting practices in the same country. Furthermore, it equally affects the medical teaching in these countries because students learn contradictory information from the teachers. This literally has a lasting influence on the current and future medical practices and teaching in the countries because when students become doctor, they usually practice what they learnt as students and not too many of them update themselves regularly.

### **Conclusion and Recommendation**

Even the latest reviews on IE prophylaxis guidelines in 2015 have failed to resolve the contradictions among the major guidelines on IE prophylaxis. Uncertainty still remains if it still could not be resolved in the future. This will continue affecting the practitioners in countries outside of the UK, European Union, and North America unless they constitute and follow their own guidelines. A boat hit by counter-currents should have a safe port to anchor, a national guideline is expected to serve that purpose.

It's a demand of time that the medical councils of these countries prepare and follow own guidelines on medical practicing issues in view having major contradictory views in the global arena. Such guidelines are expected to bring uniformity in medical practice and teaching in those countries.

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