



Infective Endocarditis Prophylaxis and the Impact of Recent Guideline Changes; Literature Review

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ABSTRACT

Background: Infective endocarditis is a serious condition with a significant mortality rate, especially among people with previously damaged or malformed heart tissues or immunocompromised. Antibiotic prophylaxis before dental procedure was a common practice earlier, particularly in patients with high-risk. **Objective:** This study aimed to clarify the evidence of prescribing prophylactic antibiotics among a specific group of patients before dental procedures and investigating the effect of the recent guideline changes on the incidence of Infective Endocarditis. **Methodology:** We used the PubMed database to look for relevant articles to the topic. **Conclusion:** The old guidelines were not based on randomized clinical trials, and among years, the incidence of infective endocarditis was not shown to be significantly decreased. Transient bacteremia is reported in many daily routine practices rather than dental procedures itself. The recent guidelines recommended antibiotic prophylaxis in high-risk patients undergoing specific invasive dental procedures.

Key Words: Infective Endocarditis, Antibiotic prophylaxis guidelines, Infective endocarditis antibiotic prophylaxis, American Heart Association guidelines

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INTRODUCTION

Infective Endocarditis (IE) is a rare life-threatening disease with an annual estimated incidence of two to 10 cases per 100,000 patients per year [1, 2]. Despite improvements in the multidisciplinary treatment approach for IE patients, mortality is still between 15 to 30%, and the 5-year mortality rate reaches nearly 40% [1]. The infection commonly involves the previously damaged or malformed area of the heart [3]; subsequently, a specific group of patients is at high risk of IE due to intracardiac prosthetic device, abnormal blood flow, damaged cardiac endothelium, or immunocompromised [1]. For example, patients with a prosthetic valve, previous IE, or cyanotic

congenital heart disease have a 10 to 50 folds higher risk of IE than the general population [1]. Bacteria commonly cause IE, but it may be less frequently caused by fungi, particularly *Candida* species, which can enter the bloodstream through several portals [3, 4]. Once the endothelium becomes damaged and exposed, its highly thrombogenic properties lead to rapid platelet deposition and the formation of a fibrin network [5]. Bacteria circulating from transient bacteremia due to invasive methods attach to this sterile thrombus, providing secondary accumulation of platelets, which coat the bacteria leading to vegetation formation [5].

In the US, approximately 10,000 to 15,000 new IE cases are diagnosed annually, and it is becoming more common

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in the US [6]. IE usually involves the left side of the heart and the descending order valves: pulmonary, tricuspid, aortic, and mitral [6]. Important risk factors include congenital heart disease and rheumatic heart disease, bicuspid or calcified aortic valve, mitral prolapse, hypertrophic subaortic stenosis, and prosthetic heart valves [6-8]. A predisposing cardiac abnormality was recognized in 50% of cases in one study [5]. The most frequent predisposing condition was the prosthetic valve following acquired degenerative valvular changes such as mitral valve prolapse and previous IE [5]. There are particular concerns about the complications following the proliferation of IE, including heart failure induced by valvular dysfunction secondary to vegetation proliferation [6]. Embolism caused by small fragments of vegetation can damage organs and tissues, including the brain, lungs, coronary arteries, spleen, and peripheral vascular system [6].

IE following dental procedures remains a controversial topic since it affects patient health and involves medico-legal implications [9]. Although most international guidelines recommend a single, double dose of antibiotic administration before any invasive dental procedures in a specific group of patients, both children and adults, many continuous debates about the real need for antibiotic prophylaxis (AP) [9]. Effective preventive strategies for both community and healthcare-acquired IE in at-risk groups are needed [10].

History of Infective Endocarditis Prophylaxis:

In 1909, the oral cavity was recognized as a significant bacterial entry portal by Thomas Horder [10]. Oral streptococci are one of the oropharynx commensal flora and account for 10% to 30% of IE cases [10]. Transient bacteremia, which occurs following poor oral hygiene and periodontal disease, dental procedures in the form of routine daily activities (i.e., tooth brushing), is suggested to be the etiology behind some IE cases [10]. In 1923, Lewis and Grant first thought that IE may be caused by bacteria entering the bloodstream during a dental procedure [11]. In 1935, Okell and Elliot confirmed what Lewis and Grant brought to by isolating *Streptococcus viridans* in blood cultures of 84/138 (61%) of patients five minutes after completing tooth extraction under general anesthesia [11, 12]. Soon after, the first reported use of AP took place in 1955 [11]. In 1955, the American Heart Association (AHA) issued the first guidelines, stating that "It is good medical and dental practice to protect patients with rheumatic or congenital heart disease by prophylactic measures." [11]. Focal infection of oral origin can affect body organs, but IE is considered the most significant due to its prevalence and high morbidity and mortality [12]. The oral cavity is believed to be the portal bacterial entry in 14% to 20% of IE cases [12].

DISCUSSION

Oral Hygiene and The Role of Antibiotic Prophylaxis:

Dental hygiene and oral health play a significant role in the etiology of streptococcal endocarditis [13]. The improvement of modern populations' dental health is linked to the considerable decrease in streptococcal IE of buccal origin [13]. However, the analysis of these data cannot support the role of AP before dental procedures, which is currently still a topic of controversy [13]. Following this analysis, there is not enough evidence in the literature showing an effect of AP for oral streptococcal endocarditis before dental procedures [13]. There was an unexpected finding in seminal studies that showed isolation of streptococci from blood culture taken before the dental procedure [14]. The later result concluded that oral sepsis, rather than dental procedures on their own, might cause streptococcal bacteremia and endocarditis [14]. Also, endocarditis was reported following cleaning and filling of teeth [14].

Nonetheless, the fact that invasive dental procedures cause some IE cases cannot impede [15]. Improve oral hygiene is essential, as it is likely to reduce the risk of IE resulting from daily activities and invasive dental procedures [15]. In patients with a high risk of developing IE (**Table 1**) who require scaling and other periodontal treatments to improve their oral health, it may be crucial to educate them about the risk and benefits of AP cover for such procedures [15]. Dental procedures are commonly performed for various reasons, and bacterial contamination is thought to be responsible for procedure failure, particularly dental implantation [15]. AP is the use of antibiotics before, during, or after therapeutic, diagnostic, or surgical procedures to prevent infection consequences [16]. According to the AHA and the European Society of Cardiology (ESC) guidelines and the Australian expert group on IE prophylaxis, all dental procedures, which potentially result in bleeding, such as incision of the oral mucosa, or manipulation of the periapical region or gingival tissue of teeth, must be covered by AP [9]. This approach differs from prescribing antibiotics aiming to eradicate infection caused by colonizing micro-organisms [16]. According to the National Center for Disease Control and Prevention, about one-third of outpatient antibiotic prescriptions are considered unnecessary [16].

A prophylactic antibiotic is commonly used based on the resident bacteria in the oral cavity, which are the most frequent cause of wound infection in oral surgery, such as anaerobic rods, streptococci, and staphylococci [16]. Subsequently, broad-spectrum antibiotics are commonly prescribed, and amoxicillin is the most common choice by physicians [16]. Amoxicillin-resistant oral streptococci have been isolated in dental plaque specimens from adolescents and children at risk of IE (20%), and healthy

adults (5%) [9]. Penicillin-resistant oral streptococci are also identified in patients who take amoxicillin before surgery [9]. First-generation cephalosporin and clindamycin are alternative options to amoxicillin [9].

Table 1: People at High Risk of Developing Infective Endocarditis

Patients with a previous history of infective endocarditis
Patients with any form of a prosthetic heart valve (including a transcatheter valve)
Those in whom prosthetic materials have been used to repair a cardiac valve
Patients with any cyanotic congenital heart disease
Patients with any type of congenital heart disease repaired with a prosthetic material, whether placed by percutaneous techniques or surgically, for the first six months after the procedure or lifelong if a residual shunt or valvular regurgitation remains

Antibiotic Resistance

The World Health Organization (WHO) has reported that antibiotics are the most common misused of all medications due to access availability, inexpensiveness, familiarity, and overall safe profile [16]. Unfortunately, this has led to the development of antimicrobial resistance (AMR), which becomes a global threat that could ultimately lead to antibiotic efficiency loss [16]. The Global Antimicrobial Surveillance (GLASS) program, run by WHO, revealed 500,00 people around 22 countries with suspected infections resulted in antibiotic resistance to microorganisms, such as *streptococcus pneumonia*, *staphylococcus aureus*, *Klebsiella pneumonia*, *Escherichia coli*, and *Salmonella* spp, showing high rates of antibiotic resistance [16]. The European Union (EU) AMR fact sheet estimates that antibiotic resistance results in annual death of approximately 25,000 and over 1.5 billion for the healthcare-related cost [16].

Evidence-Based Antibiotic Prophylaxis:

There is an ongoing debate about the efficacy of AP before invasive dental procedures, especially in the absence of randomized control trials [17]. It is clinically reasonable to balance the risk of giving and not giving AP [17]. Most current guidelines recommend AP only in patients with a high risk for developing IE (Table 1) [17]. Patients with prosthetic valves reported a high efficacy rate for AP before dental procedures [18]. For example, one study reported a 14-time higher incidence of infective endocarditis in unprotected prosthetic valves in comparison to native and protected prosthetic valves [18]. Another study reported no new cases in 229 protected patients with prosthetic valves in comparison to two (2%) new cases in 117 patients with unprotected dental procedures [18]. Generally, it is well established that dental

cares cause bacteremia with a predominance of streptococcal strains [19]. Therefore, it is considered to be logic to prescribe antibiotics before dental procedures to decrease the incidence of IE [19].

AHA initially published AP guidelines in 1955 for patients with rheumatic heart disease or congenital heart disease [20]. These guidelines were widely accepted and reported by the ESC in 1955 [20]. Conversely, in 2007 and 2009, the AHA and ESC guidelines were recommending AP restriction against IE based on a few considerations [20]:

1. First, the absence of randomized clinical trials supports the guidelines, and most of the current supporting data in the literature remain based on non-randomized controlled trials.
2. Second, the reported failure rate of AP that reached 50%.
3. Third, the importance of antibiotics misuse and resistance is getting widely recognized and appreciated.
4. Last, the importance of dental procedures as a cause of IE was questioned based on a few investigations that did not identify dental procedures as a major risk factor for IE.

The ESC new guidelines released in 2015, AP for IE must be prescribed only for 'high risk' patients with pre-existing heart conditions (i.e., previous history of infective endocarditis, prosthetic valves or CHD) undergoing 'high risk' or invasive/surgical gastrointestinal and genitourinary tract procedures [20]. Moreover, in the UK, the 2008 National Institute for Health and Care Excellence (NICE) guidelines strongly recommended against the routine administration of prophylactic antibiotics to all patients with potential IE risk [16, 20]. Also, the Canadian Cardiovascular Society and the Canadian Dental association adopted AHA revised guidelines [21]. Consequently, the base of AP for invasive dental procedures is not proven to be clinically significant [16]. These guidelines further suggested that AP used for IE before dental procedures are not shown to be cost-effective [16]. According to NICE, regular toothbrushing almost presents a higher risk of IE than a single dental procedure due to repetitive bacterial contamination with the bloodstream [16]. However, antibiotics use is appropriate for oral spreading infection (cellulitis, lymph node involvement, and swelling) or systemic involvement such as fever and malaise, according to the Scottish Dental Clinical Effectiveness Program [16].

The Impact of Recent Guidelines Changes:

For more than half a century, prophylactic antibiotics have been administered before dental procedures to reduce the risk of bacteremia and prevent IE in patients with the risk of developing IE [21]. One study showed that most

antibiotics were prescribed prophylactically before dental procedures were unnecessary [22]. This finding raised concern because dentists prescribed a significant proportion of antibiotics and the most frequent prescribers of clindamycin in the US [22]. These unnecessary antibiotic prescriptions have been associated with community-associated *Clostridium difficile* infection [22]. Nonetheless, antibiotics prophylaxis was significantly decreased over the study period, which may indicate the implementation of the 2013 guidelines for the prevention of prosthetic joint infections to patient care [22].

Recent studies investigated the impact of antibiotic prophylaxis restriction, and the outcome was conflicting [21]. In the UK, a study between 2004 and 2013 showed an increased incidence of IE due to a significant decrease in antibiotic prophylaxis after the guidelines change [21]. Various North American studies have shown a similar rise in the incidence of IE cases [21]. A population-based study showed a decrease in the rate of prescribing antibiotics for IE patients undergoing dental procedures in England [23]. Following the establishment of the 2008 NICE guidelines, monthly prophylactic antibiotic prescriptions have markedly decreased from 10,900 in 2004-2008 to 2236 in the period from 2008 to 2013 [23]. A retrospective cohort study in Canada concluded that the antibiotic prescription rate had declined around 44.9% after April 2008 among patients with low-risk congenital heart disease for whom prophylaxis is no more recommended by the AHA [23]. However, there was a decline in 9.3% in antibiotic prescription among high-risk patients in whom prophylaxis is still recommended [23].

Regarding the hospitalization rate, an initial report from a teaching hospital in the US reported no significant change in hospitalization rate for acute and subacute IE nine months following the introduction of the 2007 AHA AP guidelines [23]. Soon after that, several population-based studies have concluded similar findings [23]. In England, Thornhill and colleagues found no significant change in IE incidence or IE cases possibly related to oral streptococci 25 months following the introduction of 2008 NICE AP guidelines [23]. In France, Duval and colleagues reported no increase of IE caused by streptococci in 2008 compared to 1999 among patients with underlying native valve heart disease whom AP was not recommended by the 2002 French prophylaxis guidelines [23].

A study using the US Nationwide Inpatient Sample found an age-adjusted 2.4% annual increase in hospitalizations between 1998 and 2009, but no change in the incidence of IE caused by streptococci after comparison between the result in 1998 to 2006 and 2009 [24]. Nevertheless, studies with longer follow-up have shown an increase in IE incidence [24]. Using the Nationwide Inpatient Sample with longer follow-up, a study without performing formal change-point analysis reported a significant IE incidence

increase in streptococcal from 2000 through 2007 to 2008 through 2011 [24]. Likewise, in Germany, there was a relevant 26% rise in the annual rate of IE after the introduction of the 2009 European Society of Cardiology guidelines, with a more generous annual prevalence increase in 2001 to 2014 compared with 2006 to 2010 [24]. Besides, there was minimum evidence to support AP before certain medical procedures previously recommended for coverage (i.e., genitourinary, gastrointestinal, hepatobiliary, ear, nose, and throat, respiratory tract interventions) [25]. Following the 2007 AHA established recommendations, there was a significant decrease in AP prescription [25]. Following the new recommendations, a greater reduction was among moderate-risk patients for IE [25].

CONCLUSION

Infective endocarditis is a life-threatening disease with a significant mortality rate. A specific group of patients are considered to be at high risk secondary to previously damaged or malformed areas of the heart. Although it remains controversial, transient bacteremia caused by dental procedures is the most common culprit for infective endocarditis. Previously, antibiotic prophylaxis before, during, or after dental procedures was recommended for patients at risk of developing infective endocarditis. This recommendation was not based on randomized clinical trials, rather than expert consensus. Recently, the latest several guidelines recommended antibiotic prophylaxis restriction before dental procedures except for specific patients at high-risk. The effect of the latest guidelines changes remains doubtful across the nation, and more clinical trials are strongly recommended in the near future to establish the efficacy of antibiotic prophylaxis restriction before dental procedures.

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