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Review

INFECTIVE ENDOCARDITIS PROPHYLAXIS IN DENTISTRY: CURRENT PERSPECTIVE

ABSTRACT

Infective endocarditis (IE) is a important heart disease with high morbidity and mortality. Current guidelines suggest antibiotic prohylaxis (AP) to individuals having high risk of IE. These high risk patients include the patients with background of IE, biological or a mechanical prosthetic valve, or a surgically constructed systemic or pulmonary conduit/ shunt. The restriction of AP is due to concerns about increased comprehension regarding antibiotic resistance and daily incidence of bacteraemia. Many researchers have examined the effect of restricting AP on the incidence of IE and found different results. Since these studies are mostly observational, researchers could not establish a causal link between the limitation of AP and the change in the incidence of IE. Until the subject is clarified with randomized-controlled studies, dental professionals should periodically visit guidelines for updates on AP.

Keywords: Infective endocarditis, antibiotic prophylaxis, dentistry.

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INTRODUCTION

Although infective endocarditis (IE) is a form of endocarditis usually caused by bacteria, other microorganisms may also be involved. Annual incidence ranges from 3 to 9 cases per 100,000 of the population, based on results reported in developed countries.[1] IE affects newborns, infants, children, young adults, and pregnant women, and the incidence increases after the age of 30, exceeding 10 per 100,000 over the age of 50.[2] The clinical picture of IE is not specific and includes high fever, weakness, weight loss, shortness of breath, new or changed heart murmurs, and skin rash. Although findings such as Roth spots in the eyes and Osler nodes and Janeway lesions on the skin can be seen rarely in young children, extracardiac symptoms such as septic embolization and thromboembolic complications are common in young people.[3]

Because of the significant mortality and morbidity associated with increased IE, the first guideline was published in 1955 by the American Heart Association (AHA). To prevent IE, prophylactic administration of antibiotics is generally considered appropriate in patients with predisposing cardiac conditions who have undergone invasive procedures causing bacteraemia.[4] AP recommendations changed over time. Before 2007, AHA guidelines recommended AP for those who underwent invasive dental treatments considered to be high or intermediate risk for IE. In AHA and European guidelines published after 2007, it was reported that it should be given only to people at high risk.[4-7] However, in 2008, the UK's National Institute of Health and Clinical Excellence (NICE) guidelines took a more radical decision, recommending discontinuation of AP for all patients undergoing dental and other invasive procedures.[8] The decision to AP restrictions or to cease altogether is mainly based on the absence of placebo randomized controlled trial results to determine assessments on the effectiveness and cost of AP. Other reasons include the emergence of bacterial resistance strains and the risk of drug side effects.[7,9]

However, a trend towards an increased incidence of IE was reported in some studies done in the UK after the 2008 NICE guidelines and in the US and Germany following the implementation of the 2007 and 2009 guidelines. This suggests that invasive dental procedures may be effective in the development of IE.[10-12] The purpose of this review is to evaluate the change in the incidence of IE after guideline revisions since 2007 and the current antibiotic prophylaxis approach in dentistry.

METHOD

This review was prepared in accordance with the PRISMA statement.

Focus question; What is the result of the guideline changes after 2007 for AP of IE before invasive dental procedures in high-risk patients?

Search strategy; The systematic way was performed to look up for relevant information through several kinds of literature and search engines with great concern to main question. This investigation was accomplished in December 2019 and applauded with new information until April 2020. A web search was conducted with terms and/or different combinations (infective endocarditis, antbiotic prophylaxis, dentistry, guideline, incidence) through search engines such as PubMed, Ovid Medline, Clinical key, Google Scholar and Google.

Inclusion criteria; Articles, review, meta-analysis, randomised controlled trial, publications carried out on human subjects from offcial organisation and guidelines relased within 13 years from 2007 to 2020 with English Language.

Exclusion criteria; Articles that involved the different clinical applications of AP excluding dental treatments and case reports

Review articles; Articles were categorized into two main groups (free and restricted). Free-ones have been downloaded directly by the URLs generated from the database. The restricted group has been downloaded by the institutional access of the Sivas Cumhuriyet University library. Even though some articles didn't match the main idea, they have been reviewed again and decided to be

either relevant or irrelevant. The reference was checked to identify any studies that haven't been covered by electronic searches.

Epidemiology, Risk factors and Microbiology of Infective Endocarditis

IE is the fourth leading infectious cause of death worldwide, following sepsis, pneumonia and intra-abdominal abscesses[12] with the incidence of 3-9 cases per 100.000 people.[1] The incidence of IE varies significantly by countries and regions.[13] This may be sourced from genetic tendency, poor dental hygiene, immunologically host susceptibility, congenital and rheumatic heart disease, intravenous drug usage, degenerative or prosthetic valve disease, intracardiac devices, adherence of guideline rules and development state of countries. However, it is reported that 50% IE cases has not cardiac valvular lesion before.[14]

IE is an acute disease with a relatively high mortality rate and often characterized by Staphylococcus aureus infection. Given the antimicrobial resistance of Staphylococcus aureus, including vancomycin, this pathogen, which may be a potentially fatal infection source, is of concern.[15]

The incidence study of IE has not been conducted in Turkey, but it may be suggested to be higher. Because high-risk groups have frequent presence of predisposing cardiac disorders and higher rates of nosocomial bacteraemia. But, unlike developed countries IE more often seen in young population in Turkey.[16] A evalution of epidemiological characteristics of IE cases in Turkey and the USA and Europe is seen in Table 1.

Table 1: Evalution of epidemiological and clinical characteristics of patients with infective endocarditis in Turkey and USA/Europe[16]

Feature	Turkey	USA/ Europe
Age, years (mean)	47	61
Male (%)	60	65
Predisposing conditions (%)		
Acute rheumatic fever	37	1.85
Prosthetic valve	28	10-30
Intravenous drug use	2	24
Cardiac implantable electronic device	7	15
Chronic hemodialysis	9	13
Causative microorganisms (%)		
Staphylococcus auerus	21	32
Viridans streptococci	19	18
Coagulase negative staphylococci	10	11
Enterococcus spp.	9	11
Brucella spp.	7	-
Blood culture negative (%)	37	8
Nosocomial endocarditis (%)	25	25
Mortality (%)	24	19

The microbiology of IE has changed over time, and staphylococci, often associated with healthcare contact and invasive procedures, have surpassed streptococci as the most common cause of the disease.[17] The most common causative bacteria are Staphylococcus aureus, streptococci, coagulase-negative staphylococci, and enterococci, both in Turkey and USA/Europe (Table 1). Gram-negative bacilli and fungi are generally causative pathogens of healthcare-associated IE. For patients who have been implanted with an intracardiac prosthetic device such as a prosthetic heart valve in the last decade, Mycobacterium chimaera is a possible pathogen for IE.[14] Also, it is thought that the collagen binding protein of Streptococcus mutans that is

the cause of dental caries, may be one of the potential important factors associated with the pathogenesis of IE.[18]

Pathogenesis and Mortality of Infective Endocarditis

Normal healthy endocardium lining of the heart naturally is resitant to colonization by bacteria to adhere to the these surfaces. However, once endothelial injury occurs via turbulent flow of blood such as through a stenotic valve or congenital lesion, prosthetic heart valve, previous history of endocartditis, or may be provoked by electrodes, catheters, or repeated intravenous injections by drug users. These make release of inflammatory substances, including cytokines and other tissue factors, lead to platelet and fibrin-rich thrombus formation, which serves as a nidus for bacterial infection called nonbacterial thrombotic endocarditis (NBTE). Mucosal surfaces of the body are populated by endogenous microflora and damage to these surfaces (caused by dental or medical procedures or daily activities such as chewing or brushing) creates a pathway for microbes to enter the bloodstream. When bacteria are introduced into the bloodstream by this way, they can adhere to the platelet-fibrin thrombus and replicate within the NBTE. Bacteria also stimulate further fibrin and platelet deposition and endothelial injury, leading to formation of a vegatation. Complication and progression of the vegatation cause impaired valve function, valve perforation, abscess formation, chordal rupture, conduction system involvement, embolization and heart failure.[7,19]

In Turkey, the mortality rate in patients with IE is higher than in developed countries and is close to 30%.[20] It is doubtless that mortality rates can be reduced by eliminating the lack of knowledge of the physicians who follow these patients and by establishing and implementing standard diagnosis and treatment protocols. Moreover, the role of dentists in preventing this disease should not be forgotten.

The Impact of Changing Antibiotic Prophylaxis Guidelines after 2007-2008

The guidelines suggesting AP for prevention of IE are based on three main observation; 1- bacteraemia has been accepted as a reason of IE, 2- Viridans group streptococci (VGS) can be cause serious bacteremia and, 3- these microorganism are susceptible to commonly used antibiotics. But, there was no placebo randomized controlled trial evidence to support the efficacy of AP and their assesment of the lack of cost effectiveness and other reasons include developing of bacterial resistance strains and risk of adverse drug reactions.[7,9]

Due to the paradigm change that started in the guidelines on AP in 2007, some researchers have tried to investigate the effect of this change on the incidence of endocarditis. After the implementation of the new guidelines, some studies did not show an increase in the incidence of IE[21-25], although other studies have raised concerns about the increased incidence of IE.[10-12,26,27] After complete AP cessation in England with NICE guideline in 2008, the incidence of IE significantly increased within 5 years. Therefore, they made a subtle change in 2016 to indicate that AP shouldn’t be "routinely" recommended for dental procedures.[28] Because daily activities such as regular tooth brushing can cause recurrent bacteraemia from the oral flora, which almost certainly poses a greater risk of IE than a single dental procedure.[8]

In the studies dealing with VGS which is commonly accepted as a indicator of oral cavity etiology of IE, Bizmarck *et al.*[29] reported a significant increase in IE caused by VGS for ages 10 to 17 after guideline changes, but no impact on IE incidence comparing pre & post guideline in US in the period 2001–2012. Another study[11] from US in period of 2000 to 2011 reported significantly increase in IE incidence caused by streptococci. Also, it was reported an increase from Netherland in the years from 2005 to 2011.[26] However, there were no change or increase about VGS in the etiology of IE in other studies involving the impact of guideline changes.[23-25,30-32] Rheumatic heart disease caused by streptococci and acute rheumatic fever are important public health concerns worldwide, and there is still a significant burden of disease, especially in developing countries.[33] Most paediatric

cardiologists have encountered children with bicuspid aortic valve affected by IE, due to VGS, who showed a clinical course similar to that of high-risk patients and resulted in increased need for surgery. In the light of these data, Zegri-Reiriz *et al*.[34] reported that these patients should be considered as "high risk " group and should be treated under AP administration. However, all of the researches after guideline changes contain one or more shortcomings of the following: Small sample size, short follow-up time, subpopulation researches with different risk factors, or exposure to invasive dental treatments compared to the general population, difficulties in accurately identifying IE caused by oral VGS and lack of data on AP administration. So, it is difficult to shown any causal link between restriction of AP and incidence of IE from any one or a combination of these studies. However, Dayer *et al*. stated that the evidence was taken as a whole, and that it was impossible to exclude the possibility of AP's influence, albeit small. In addition, there are serious concerns about the development of antibiotic resistance (AR) and increasing healthcare costs. But AP is low-priced and the recommended doses of antibiotics are likely to minimise the development of AR. In other words AP, especially amoxicillin, appears to be safe.[35,36]

The American Academy of Pediatric Dentistry has published guidelines stating that it is preferable to complete all dental treatments before starting immunosuppressive therapy in patients who will be treated with immunosuppressive and/or radiation therapy. Also stated that elective dental care should not be performed during the period of immunity suppression.[37] The neutrophil count can guide the decision to necessity AP during dental treatments. It was recommended to consider AP in patients with absolute neutrophil counts between 1000-2000/mm^3 according to AHA guidelines. If the patient's neutrophil count is less than 1000/mm3, dental treatments should be delayed or it is recommended to discuss necessity of AP with the medical team before continuing treatment.[38] Also, chlorhexidine mouthwash alone should not be recommended as a prophylaxis against IE to patients at risk of IE undergoing dental procedures.[8]

According to current guidelines, intermediate and low risk patients should probably avoid AP for dental procedures that involve manipulation of the gingiva or periapical region of the teeth or involve perforation of the oral mucosa. But, AP is strongly recommended in high risk patients undergoing medical procedures with bacteraemia. The recommended regimen for AP is shown in Table 2.

Table 2: Current guidelines on antibiotic prophylaxis to prevent infective endocarditis (IE)[39]

2007 AHA Guidelines	**2015 ESC Guidelines**	**2015 NICE Guidelines with 2016 Amendment**
Those Recommended for Antibiotic Prophylaxis Cover		
Those at highest risk of an adverse outcome from IE	Those at highest risk of IE undergoing a high-risk procedure	Antibiotic prophylaxis against infective endocarditis is not recommended routinely for people undergoing dental [or other] procedures. ('routinely' added 2016)
Those at Highest Risk of Adverse Outcome from IE	**Those at Highest-Risk of IE**	**Those At Risk of Developing IE**
• Prosthetic cardiac valve or prosthetic material used for valve repair • Previous IE • Unrepaired cyanotic CHD, including palliative shunts and conduits • Completely repaired congenital heart defect with prosthetic material	•Patients with any prosthetic valve, including a transcatheter valve, or those in whom any prosthetic material was used for cardiac valve repair •Patients with a previous episode of IE •Any type of cyanotic CHD •Any type of CHD repaired with	• Acquired valvular heart disease with stenosis or regurgitation • Valve replacement • Structural congenital heart disease, including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect or fully repaired patent

or device, whether placed by surgery or catheter intervention 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 • Cardiac transplantation recipients who develop valvulopathy	a prosthetic material, whether placed surgically or by percutaneous techniques, up to 6 months after the procedure or lifelong if residual shunt or valvular regurgitation remains after the procedure	ductus arteriosus, and closure devices that are judged to be endothelialised • Previous infective endocarditis • Hypertrophic cardiomyopathy.
Moderate/Intermediate-Risk		
	•Patients with a previous history of rheumatic fever •Patients with any other form of native valve disease (including: bicuspid aortic valve, MVP and calcific aortic stenosis) •Patients with unrepaired congenital anomalies of the heart valves	
High-Risk Procedures for which Antibiotic Prophylaxis Should Be Considered		
• All dental procedures that involve manipulation of the gingival tissue or the periapical region of teeth or perforation of the oral mucosa*. • Procedures on respiratory tract or infected skin, skin structures or musculoskeletal tissue	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*.	Advice not given
Recommended Antibiotic Prophylaxis Regimen (for those not allergic to penicillin)		
Amoxicillin 2g orally 30-60 mins before the procedure**	Amoxicillin 2g orally 30-60 mins before the procedure**	Advice not given
Recommended Antibiotic Prophylaxis Regimen for those Allergic to Penicillin		
Clindamycin 600mg orally 30-60 mins before the procedure**	Clindamycin 600mg orally 30-60 mins before the procedure**	Advice not given

However, some dental procedures do not require AP. Examples of these are routine anesthetic injections into non-infected tissues, dental x-ray, placement of removable prosthesis or orthodontic appliances, adjustment of orthodontic appliances and placement of orthodontic brackets. Also, the dentists should emphasise the importance of maintaining good oral health to patients. For optimal oral health, moderate-risk patients are recommended to be examined once a year, while high-risk patients should receive professional dental care twice a years.[6]

CONCLUSIONS

Consequently, dentists may not always aware of the IE risk in their patients because of unavailable medical documentation and insufficient anamnesis. From the legal framework, a collaboration with cardiologist and follow up current guidelines is important to achive the goal of IE prevention in dentistry.

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CONFLICT OF INTEREST STATEMENT

None

ÖZ

Enfektif endokardit (EE), yüksek morbidite ve mortaliteye sahip önemli bir kalp hastalığıdır. Mevcut kılavuzlar, yüksek EE riski olan bireylere antibiyotik profilaksisini (AP) önermektedir. Bu yüksek riskli hastalar, EE geçmişi, biyolojik veya mekanik prostetik kapak veya cerrahi olarak oluşturulmuş sistemik veya pulmoner kanal/ şant olan hastaları içerir. AP'nin kısıtlanması, antibiyotik direnci ve günlük bakteremi insidansı ile ilgili artan kavrayışla ilgili endişelerden kaynaklanmaktadır. Birçok araştırmacı, AP'yi kısıtlamanın EE insidansı üzerindeki etkisini incelemiş

ve farklı sonuçlar bulmuştur. Bu çalışmalar çoğunlukla gözlemsel olduğundan, araştırmacılar AP'nin sınırlandırılması ile EE insidansındaki değişim arasında nedensel bir bağlantı kuramadılar. Konu randomize-kontrollü çalışmalarla netleşene kadar, diş hekimleri AP ile ilgili güncellemeler için periyodik olarak kılavuzları ziyaret etmelidir.

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