

Infective Endocarditis Prophylaxis in Patients Undergoing Oral Surgery

SUMMARY

Infective endocarditis (IE), an infection of the endocardium that usually involves the valves and adjacent structures, may be caused by a wide variety of bacteria and fungi that entered the bloodstream and settled in the heart lining, a heart valve or a blood vessel. The IE is uncommon, but people with some heart conditions have a greater risk of developing it. Despite advances in medical, surgical, and critical care interventions, the IE remains a disease that is associated with considerable morbidity and mortality. Hence, in order to minimize the risk of adverse outcome and achieve a yet better management of complications, it is crucial to increase the awareness of all the prophylactic measures of the IE.

For the past 50 years, the guidelines for the IE prophylaxis have been under constant changes. The purpose of this paper is to review current dental and medical literature considering the IE prophylaxis, including the new and updated guidelines from the American Heart Association (AHA, 2007 and 2015), the National Institute for Health and Clinical Excellence (NICE, 2015), the European Society of Cardiology (ESC, 2009 and 2015) and the British Society for Antimicrobial Chemotherapy (BSAC, 2006).

Keywords: Infective Endocarditis; Antibiotic Prophylaxis; Bacteraemia; Oral Hygiene

**M. Zoumpoulakis¹, F. Anagnostou³,
S. Dalampiras², L. Zouloumis², C. Pliakos⁴**

¹Postgraduate Program of Hospital Dentistry
Dental School of Aristotle University of Thessaloniki

²Department of OMFS

Dental School of Aristotle University of Thessaloniki

³National School of Public Health

⁴Department of Cardiology AXEPA Hospital
Thessaloniki, Greece

LITERATURE REVIEW (LR)

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Introduction

Dental practitioners, especially those working in hospitals, are often faced to provide dental care/treatment to patients with permanent or temporary underlying heart problems. Numerous medical procedures predispose these patients to bacteraemia-induced infections, such as infective endocarditis (IE). The IE is an uncommon but yet life-threatening infection.

Despite advances in diagnosis, antimicrobial therapy and surgical techniques, patients with the IE still have substantial morbidity and mortality related to this condition. Therefore, the increased awareness of all the prophylactic measures needed to minimize the risk of the adverse outcome, as well as management of complications, is required. The guidelines for the IE prophylaxis have been in a process of evaluation for more than 50 years.

This paper reviews current dental and medical literature considering the IE, including the new and

updated guidelines from: the American Heart Association (AHA, 2007¹ and 2015^{2,3}), the National Institute for Health and Clinical Excellence (NICE, 2015)⁴, the European Society of Cardiology (ESC, 2009⁵ and 2015⁶), and the British Society for Antimicrobial Chemotherapy (BSAC, 2006)⁷.

Definition of IE

IE is defined as an inflammation of the inner tissue of the heart (endocardium), which may include 1 or more heart valves, the mural endocardium or a septal defect, caused by infectious agents. However, in clinical practice, the definition extends to include infections on the arterio-venous shunts, arterio-arterial shunts and aortic coarctation, as the clinical presentation is often indistinguishable^{11,12}. Fungi, chlamydia, rickettsia, etc. can cause this infection; however, the most common

causes of this disease are bacteria, and this phenomenon is therefore also called bacterial endocarditis¹³. The IE can occur following the bacteraemia (bacteria in the bloodstream), not only on the congenital or the acquired structural cardiac abnormalities, but also on the normal, previously healthy valves.

Epidemiology of IE

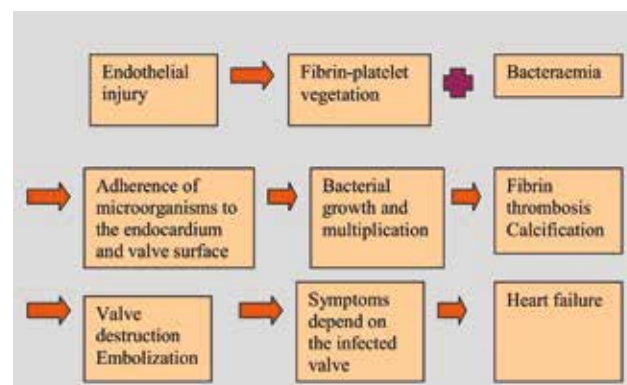
IE is a rare condition with significant morbidity and mortality if left untreated^{1,2}. Nowadays, it is characterized as the third or fourth most common life-threatening infection syndrome, after sepsis, pneumonia and intra-abdominal abscess². In industrialized countries, the annual incidence of IE is 3 to 7 cases per 100,000 persons². The male to female ratio is over 2:1¹⁴. There is an increased incidence of IE in persons 65 years of age and older, which is probably because people in this age group have a larger number of risk factors for IE^{13,15}. In recent years, over one third of the IE cases in the United States were healthcare-associated (invasive procedures and hospital infections). Another trend observed in industrialized countries is that chronic rheumatic heart disease accounts for <10% of the cases. So, even though the IE was previously associated with poor oral hygiene and rheumatic heart disease, many factors have altered its epidemiology, but have maintained its incidence: an aging population with the degenerative valvular disease, the injection drug use, increasing number of the valve replacements and medical interventions, i.e. the invasive vascular procedures¹⁶⁻¹⁸. Predominantly, it tends to develop on cardiac valves previously damaged, the mitral valve being the most frequent location, followed by the aortic and in rare occasions the pulmonary valve¹⁸. Although a history of valve disease has a significant association with the IE, 50% of all cases develop in people with no known history of the valvular disease. It is rare amongst the younger population with the exception of intravenous drug users. Among people who do not use intravenous drugs and have a fever in the emergency room, there is a less than 5% chance of occult endocarditis^{19,20}. Among people who do use intravenous drugs and have a fever in the emergency room, there is about a 10% to 15% prevalence of the endocarditis^{19,20}.

Pathophysiology

Several conditions must be met in order to develop the IE. According to the injury-thrombus infection theory, the trigger event is the endocardium damage. Endothelial injury is the most plausible factor leading to the platelet deposition. Injury develops as a result of the hemodynamic and mechanical stress to the endocardium.

The predilection site of IE is rough part of the valves due to high impact pressures following the closure of the leaflets. Also, the turbulent blood flow produced by the congenital or acquired heart diseases traumatizes the endothelium inducing apoptosis of the valve cells and leading to the tissue remodelling^{1,3,11,13,17}. This creates a predisposition for the deposition of platelets and fibrin on the surface of the endothelium, which results in the nonbacterial thrombotic endocarditis (NBTE). Invasion of the bloodstream with microbial species that have the pathogenic potential to colonize this site can then result in the IE^{1,3,11}. Mucosal surfaces in the mouth are populated by a dense endogenous microflora. Trauma to a mucosal surface, particularly the gingival crevice around teeth, oropharynx, gastrointestinal (GI) tract, urethra or vagina, transiently releases many different microbial species into the bloodstream. Transient bacteraemia caused by viridans group of *Streptococci* and other oral microflora, occurs commonly in association with dental extractions or other dental procedures or with routine daily activities. Although controversial, the frequency and intensity of the resulting bacteraemia is believed to be related to the nature and severity of the tissue trauma, the density of the microbial flora and the degree of inflammation or infection at the site of the trauma. Microorganisms adherent to the vegetation stimulate further deposition of the fibrin and platelets on its surface¹⁰. Within this secluded focus, the buried microorganisms multiply as rapidly as do bacteria in broth cultures to reach maximal microbial densities of 10² to 10¹⁶ colony-forming units per gram of vegetation within a short time on the left of the heart, apparently uninhibited by host defences in left sided lesions. Right-sided vegetation has lower bacterial density, which may be the consequence of host defence mechanisms active at this site, such as polymorphonuclear activity or platelet derived antibacterial proteins. The lack of blood supply to the valves and the blunted host immune system also have implications on the treatment, since drugs also have difficulty reaching the infected valve. The entry of microorganisms into the circulatory system leads to bacteraemia and ultimately converts the NBTE into the IE (Tab. 1)^{1,10,11,13,21}.

Table 1. Infective endocarditis: pathophysiology



Microorganisms

The number of microbial species entering circulation depends on the unique endogenous microflora that colonizes the particular traumatized site. The most common microorganisms that cause the IE include: *Streptococci*, *Staphylococci*, *Enterococci*, HACEK organisms (*Hemophilus parainfluenzae*, *Hemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* species and *Kingella* species) and fungi, with *Streptococci* keeping the first position^{1,14,18,22}. *Streptococci* of viridans group are the part of the normal skin, oral, respiratory and GI tract flora and they are cause of 30-65% of the IE^{12,14}. Approximately 30% of the flora of the gingival crevice is represented by *Streptococci*, predominantly of the viridans group¹⁻³. In healthy mouths, a thin surface of the mucosal epithelium separates potentially pathogenic bacteria from entering the bloodstream and lymphatic system. Anaerobic microorganisms are commonly responsible for the periodontal disease and frequently enter the bloodstream but rarely cause the IE and account 2-16% of all the cases¹. *Streptococci* of viridans group are antagonistic to the periodontal pathogens and predominate in a clean, healthy mouth. *Staphylococci* are responsible for 30-40% of the cases of IE¹⁶, with *Staphylococcus aureus* more often associated with the native valve IE than prosthetic valve endocarditis (PVE), whereas coagulase negative *Staphylococci* are more commonly seen in the PVE^{1,11,13,24}. On the other hand, the latest AHA guidelines (2015) state that *S. aureus* is now the most common microorganism that causes the IE². Furthermore, *Enterococcus spp.* usually leads to subacute form of the IE.

Candida and *Aspergillus* species cause the majority of the fungal IE. Intravenous drug abusers, prosthetic-valve recipients, and patients with long-term central venous catheters are at highest risk for the fungal IE.

The ability of various microbial species to adhere to the specific sites determines the anatomical localization of infection caused by these microorganisms (Tab. 2). Mediators of the bacterial adherence serve as virulence factors in the pathogenesis of IE. Some *Streptococci* of the viridans group contain a fimbrial adhesion protein (FimA), which is a lipoprotein receptor antigen I, which serves as a major adhesive to the fibrin platelet matrix of NBTE¹. *Staphylococcal* adhesive functions in at least two ways. In one, microbial surface components recognizing the adhesive matrix molecules facilitate the attachment of *Staphylococci* to the human extracellular matrix proteins and to the medical devices, which become coated with the matrix proteins after implantation¹. On the other hand, the bacterial extracellular structures contribute to formation of biofilm, localized on the surface of the implanted medical devices.¹

Table 2. The most common microbial species in IE cases

Frequencies and associations	Microbial species
30-65% of all cases of the IE	<i>Streptococci viridans</i>
30-40% of all cases of the IE	<i>Staphylococci</i>
2-16% of all cases of the IE	Anaerobic bacteria, i.e. <i>Actinobacillus actinomycetemcomitans</i>
PVE	Coagulase negative <i>staphylococci</i>
Subacute form of the IE	<i>Enterococcus spp</i>
Intravenous drug users (IVDU)	Fungi, <i>Staphylococcus aureus</i>
Long vegetations	Fungi, <i>H. parainfluenzae</i>
Fungal IE	<i>Candida</i> , <i>Aspergillus</i>

Signs and Symptoms

The clinical history of the IE is highly variable, depending on causative microorganism, the presence or the absence of pre-existing cardiac disease, the immunological status of the host and the mode of presentation. Thus, the IE should be suspected in a variety of different clinical situations, from a fulminant and acute attack to a chronic evolution¹¹.

Acute IE presentations are usually characterized by a toxic, unwell patient with high fevers and rigors in 80% to 95% of the cases¹⁴. Subacute or chronic presentations often occur weeks or months after the initial infection, and can be associated with a low-grade fever, night sweats, weight loss and anaemia (normochromic normocytic)¹¹. Patients may therefore consult a variety of specialists who may consider a range of alternative diagnoses including chronic infections, rheumatic and autoimmune disease, or even malignancy. The early involvement of a cardiologist and an infectious disease specialist to the list of therapists is highly recommended^{1,23,25}. Light pigmentation of the skin, the joints' pain or hepatosplenomegaly are typical; however, the main effect of endocarditis is the heart damage (valve destruction and heart failure)¹⁸. The progressive sign of the disability is related to changing murmurs showing the heart damage, the infection or embolic damage of various organs, especially of the kidneys. The liberation of emboli may have general effects from a loss of the peripheral pulse to the sudden death due to a stroke. Other associated symptoms and signs may include lethargy, anorexia, vague abdominal or flank pain, confusion, arthralgia, myalgia and finger clubbing (Tab. 3).

Table 3. Signs and symptoms per organic system

Organic system	Symptoms
Non-specific/general symptoms	Fever, rigors, weight loss, night sweats, anorexia
Skin	Light pigmentation of the skin, Janeway lesions, Osler's nodes, petechiae on the conjunctivae and buccal mucosa
Circulatory	Anaemia, murmurs, valve obstruction, para-valvular regurgitation, pericarditis, coronary artery embolism, mycotic aneurysms, vasculitis, heart failure
Eye	Roth spots
Neurological system	Embolic strokes, intracranial haemorrhages, lethargy, confusion
GI tract	Abdominal pain
Musculoskeletal system	Arthralgia, myalgia, finger clubbing, myocarditis
Lymphatic system	Splenic infarcts
GU tract	Glomerulonephritis

Peripheral manifestations as a result of an immunologically mediated vasculitis or septic embolization can give rise to^{1,6,11,12}:

- Petechiae of palpebral conjunctiva, buccal and palatal mucosa, and extremities;
- Osler's nodes (tender, subcutaneous nodules seen in the pulps of the digits);
- Janeway lesions (non-tender, erythematous or haemorrhagic macular lesions seen on the palms and soles);
- Splinter haemorrhages in the fingernails or toenails; petechiae on the conjunctivae and buccal mucosa;
- Focal glomerulonephritis and splenic infarcts;
- Mycotic aneurysms and occlusion involving any vessel, commonly seen in the cerebral arteries, abdominal aorta, coronary arteries, gastrointestinal arteries, limb arteries and renal arterioles;
- Retinal infarcts (Roth's spots), causing an oval-shaped haemorrhage with a pale centre;
- Neurological involvement in 30–40% of patients with the IE, the majority of which are embolic strokes, with intracranial haemorrhages occurring in 5%;
- Congestive cardiac failure as a result of the valve destruction or rupture of a chorda and, rarely intra-cardiac fistulae, myocarditis or coronary artery embolism;
- Peri-valvular extension beyond the valve ring either in the native or prosthetic valve IE, giving rise to the para-valvular regurgitation, valve dehiscence, septal and myocardial abscesses, fistulous tracts, pericarditis and conduction disturbances such as the first degree AV block;
- A change in the quality of the audible prosthetic clicks can reflect the valve obstruction by the vegetation overgrowth.

Table 4. Major (blood culture and echocardiographic) criteria and minor criteria²⁷

Major blood culture criteria	Major echocardiographic criteria	Minor criteria
2 blood cultures positive for organisms typically found in patients with the IE	Echocardiogram positive for the IE, documented by an oscillating intra-cardiac mass on a valve or on the supporting structures, or on the implanted material in the absence of an alternative anatomical explanation	Predisposing heart condition
Blood cultures persistently positive for 1 of the above organisms, from cultures drawn more than 12 hours apart	Myocardial abscess	Fever
3 or more separate blood cultures drawn at least 1 hour apart	Development of the partial dehiscence of a prosthetic valve	Temperature > 38°
Single positive blood culture for <i>Coxiella burnetii</i> or anti-phase 1 IgG antibody titre $\geq 1:800$	New-onset of the valvular regurgitation	Vascular phenomena or immunologic phenomena
		Microbiological evidence that does not meet a major criteria

Liberation of emboli may have general effects from a loss of the peripheral pulse to sudden death due to a stroke. About 35% of patients may develop the central nervous system effects such as transient ischemic attacks, stroke, toxic encephalopathy, and brain abscess²⁶. Renal

embolization may lead to the haematuria, while splenic emboli may cause the left upper quadrant pain. Septic pulmonary embolization of the right-sided valvular IE (frequently seen in IVDU-related IE) can give rise to a shortness of breath, haemoptysis, pleuritic chest pain

and pulmonary abscesses. Nowadays, due to widespread use of antibiotics, the incidence of classic presentation of the peripheral lesions are reduced substantially. Some of the peripheral manifestations are developed as a result of immunological activities, while the others are the result of the embolization.

Diagnosis of the IE is straightforward in those patients with classic manifestations: bacteraemia or fungemia, the evidence of active valvulitis, peripheral emboli, and immunologic vascular phenomena¹¹. In other patients however the classic peripheral stigmata may be few or absent. All this imposes the necessity for highly sensitive diagnostic algorithm that will be both sensitive for disease detection and specific for its exclusion across all the forms of the disease²⁶. The IE diagnostic criteria, cited as Duke criteria, have been validated by many other studies^{2,3,16}, comprise:

Diagnosis of reliable IE - *Pathological criteria* (microorganisms demonstrated by the culture or histological examination of a vegetation, a vegetation that has embolized, or an intra-cardiac abscess specimen) - *Clinical criteria* (2 major criteria; or 1 major criterion and 3 minor criteria; or 5 minor criteria);

Diagnosis of possible IE - 1 major and 1 minor criterion or 3 minor criteria (Tab. 4).

Dental Procedures Causing Bacteraemia

The large majority of published studies have focused on dental procedures as a cause of the IE and the use of prophylactic antibiotics to prevent the IE in risk patients. Transient bacteraemia is common with manipulation of teeth and periodontal tissues, and there is a wide variation in reported frequencies of the bacteraemia in patients resulting from dental procedures: tooth extraction (10-100%), periodontal surgery (36-88%), scaling and root planing (8-80%), teeth cleaning (up to 40%), rubber dam matrix/wedge placement (9-32%) and endodontic procedures (up to 20%)^{1,28,29,30,31}. Transient bacteraemia also occurs during the routine daily activities unrelated to a dental procedure: tooth brushing and flossing (20-68%), use of wooden toothpicks (20-40%), use of water irrigation devices (7-50%) and chewing food (7-51%)^{1,28,30,32,33,34,35,36,37}. Considering that the average person living in the United States has fewer than 2 dental visits per year, the frequency of bacteraemia from routine daily activities is far greater³⁰. The magnitude of bacteraemia resulting from a dental procedure is relatively low (< 10⁴ CFUs of bacteria per millilitre), similar to that resulting from routine daily activities, and is less than the one found in experimental animals' models (10⁶-10⁸ CFUs of bacteria/mL)^{1,22,29}. Although the infective

dose required to cause the IE in humans is unknown, the number of microorganisms in blood associated with dental procedures or daily activities is low. Additionally, the vast majority of patients with viridians *Streptococci* IE have not had a dental procedure within 2 weeks before the onset of symptoms of the IE^{4,38,39,40}. The role of the duration of bacteraemia on the risk of acquiring the IE is uncertain^{1,28}. It seems logical to assume that the longer the duration of bacteraemia, the greater the risk of the IE, but no published studies support this assumption. There may not be a clinically significant difference in the frequency, the nature, the magnitude and the duration of bacteraemia associated with a dental procedure compared with that resulting from the routine daily activities^{1,22}. Accordingly, it is inconsistent to recommend prophylaxis of the IE for dental procedures but not for the routine daily activities. Such recommendation would be impractical and unwarranted^{1,6}.

IE and Oral Hygiene

It is assumed that a relationship between poor oral hygiene and the extent of dental and periodontal disease, the type of dental procedure; and the frequency, the nature, the magnitude and duration of bacteraemia exists, but the presumed relationship is controversial^{1,6,22,23,32,33}. Nevertheless, the available evidence supports an emphasis on maintaining good oral hygiene and eradicating dental disease to decrease the frequency of bacteraemia from the routine daily activities, such as chewing food, tooth brushing or flossing^{1,25,41}. In patients with poor oral hygiene, the frequency of positive blood cultures just before the tooth extraction may be similar to those after the extraction^{28,41}. In patients with dental disease, the focus on the frequency of bacteraemia associated with a specific dental procedure and the AHA guidelines for prevention of the IE have resulted in an under-emphasis on the antibiotic prophylaxis and an over-emphasis on the maintenance of good oral hygiene and the access of the routine dental care, which are likely more important in reducing the lifetime risk of the IE than is the administration of antibiotic prophylaxis for a dental procedure^{1,2,3,6,25,41,42}; especially in patients with the underlying cardiac conditions associated with the highest risk of the adverse outcome of the IE.

It is mandatory that clinical examination, focused on the periodontal inflammation and caries, has been conducted in risk patients, as well as the full series of intraoral radiographs. There are 4 measures for the entire dental diseases prevention: (1) good oral hygiene for bacterial plaque removal; (2) dietary measures (elimination of sugar and carbohydrates); (3) the routine follow up and; (4) a daily use of toothpaste with high fluoride concentration².

Antibiotic Prophylaxis

Antibiotic prophylaxis is often administered to dental patients for prevention of harmful consequences of the bacteraemia, which may be caused by invasion of the oral microorganisms into an injured gingival or peri-apical vessel during the dental treatment. The administration of antibiotics for more than 12-24 hours is not considered as prophylaxis, but as antibiotic treatment⁸.

Indications for Antibiotic Prophylaxis

No published data demonstrate convincingly that the administration of prophylactic antibiotics prevents the IE associated with bacteraemia from an invasive procedure^{42,43,44}. However, the last AHA guidelines recommend that if the prophylaxis is effective, such therapy should be restricted to those patients with the highest risk of the adverse outcome of the IE who would derive the greatest benefit of prevention of the IE¹. In patients with the underlying cardiac conditions associated with the highest risk of the adverse outcome of the IE (Tab. 5), the IE prophylaxis for dental procedures is reasonable, even though we acknowledge that its effectiveness is unknown^{1,32,45,46}. If patients mentioned above undergo any dental procedure that involve manipulation of gingival tissue or periapical region of the teeth and for those procedures that perforate the oral mucosa, such as biopsies, suture removal and placement of the orthodontic bands, single or multiple tooth extraction, scaling (with expecting bleeding), curettage, periodontal surgery, apicoectomy, placement of the dental

implants and intraligamentary anesthesia^{1,6,13,45,46,47,48,49}. On the contrary, antibiotic prophylaxis does not include routine anaesthetic injections through non-infected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, placement of orthodontic brackets or the adjustment of orthodontic appliances^{1,13,48,49}. Finally, there are other events that are not dental procedures and for which prophylaxis is not recommended, such as shedding of the primary teeth and trauma of the lips and the oral mucosa^{1,13,45,46}.

Table 5. Cardiac conditions associated with the highest risk of the adverse outcome of the IE

Table 6. Antibiotic prophylaxis for dental procedures (BSAC, 2006)

Situation	Agent	Age			Dose timing
		>10 years	<5 years	≥5, <10 years	
Oral	Amoxicillin	3 g po	750 mg po	1,5 g	1h
Intravenous regimen expedient	Amoxicillin	1g IV	250mg IV	500mg IV	Just before the procedure or at induction of anaesthesia
Intravenous regimen expedient and allergic to penicillin	Clindamycin	300 mg IV*	75 mg IV*	150 mg IV*	Just before the procedure or at induction of anaesthesia
Allergic to penicillins or ampicillin (oral)	Clindamycin	600 mg po	150 mg po	300 mg po	1h
Allergic to penicillins or ampicillin and unable to take oral medication	Azithromycin	500 mg po	200 mg po	300 mg po	1h

IV: intravenously

*Given over at least 10 min

When a course of treatment involves several visits, the antibiotic regimen should alternate between amoxicillin and clindamycin. Pre-operative mouth rinse with chlorhexidine gluconate 0.2% (10ml for 1min)

Table 7. Regimens for a dental procedure (AHA, 2007)

Situation	Agent	Regimen: single dose 30-60 minutes before procedure	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin or Cefazolin/Ceftriaxone	2 g IV or IM 1 g IV or IM	50 mg/kg IV or IM 50 mg/kg IV or IM
	Cephalexin*,** or Clindamycin or Azithromycin/Clarithromycin	2 g 600 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg
Allergic to penicillin or ampicillin (oral)	Cefazolin/Ceftriaxone** or Clindamycin	1g IV or IM 600 mg IV or IM	50 mg/kg IV or IM 20 mg/kg IV or IM

IV: intravenously; IM: intramuscularly

* or other first-or second-generation oral cephalosporin in equivalent adult or paediatric dosage

** Cephalosporins should not be used in a person with a history of anaphylaxis, angioedema, or urticaria after receiving penicillin or ampicillin

In the UK, NICE (2015) has published guidelines stating that prophylaxis is not required, not only for dental procedures but also for the GI and genitourinary (GU) tract procedures, except where there is an evidence of active infection⁴. The Working Party of BSAC's (2006)⁷ guidelines are almost similar to those of AHA (2007, 2015, 2015)¹⁻³ and ESC (2009)⁵, but different in the proposed regimens (Tabs 6 and 7). Compared with the previous guidelines, under these revised guidelines, fewer patients would be candidates to receive the IE prophylaxis⁶. Additionally, restricting prophylaxis to only those patients with the highest risk of the adverse outcome should reduce the uncertainties among patients and providers about who should receive the prophylaxis^{1,42,43}. Finally, we should keep in mind that administration of the prophylactic antibiotics is not the risk-free^{6,43}. The widespread use of the antibiotic therapy promotes the resistant microorganisms most likely to cause endocarditis, such as *Streptococci* and *Enterococci*. The frequency of multidrug-resistant *Streptococci* of viridans group and *Enterococci* has increased dramatically during the past 2 decades.^{13,43,50} This increased resistance has reduced the efficacy and number of the antibiotics available for the treatment of the IE^{13,22}. Apart from this severe global development, at the individual level, the treatment with antibiotics correlates with the drug-related adverse reactions, such as diarrhoea or allergic reactions. Especially, if antibiotics are not indicated, these reactions outweigh any benefit of the prophylaxis^{6,9,18,22,51}.

Antibiotic Regimens

An antibiotic for the prophylaxis should be administered in a single dose before the procedure. If the dosage of the antibiotic has not been administered before the procedure, the dosage may be administered up to 2 hours after the procedure. However, administration of the dosage after the procedure should be considered only when the patient did not receive the pre-procedural dose. Some patients who are scheduled for an invasive procedure may have a coincidental endocarditis. The presence of fever or other manifestations of the systemic infection should be alert of the possible presence of IE. In these circumstances, it is important to obtain blood cultures and other relevant tests before the administration of the antibiotics intended to prevent the IE^{1,2,50}. Failure to do so may result in the delay of the diagnosis or treatment of a concomitant case of the IE.

Amoxicillin is the preferred choice for the oral therapy because it is well-absorbed in the GI tract and provides high and sustained serum concentrations^{1,2,6,7,22,50}. For patients who are allergic to penicillin or amoxicillin, the use of clindamycin, azithromycin or clarithromycin is recommended^{1,2,6,7,22,42,50}. No data show superiority of one oral cephalosporin over another for prevention of the IE, and the generic cephalexin is widely available and is relatively inexpensive⁴⁴. Because of the possible cross-reactions, a cephalosporin should not be administered to patients with a history of anaphylaxis, angioedema or urticaria after the treatment with any form of penicillin,

including ampicillin or amoxicillin^{1,2,6,50}. Patients who are unable to tolerate an oral antibiotic may be treated with ampicillin, ceftriaxone or cefazolin administered intramuscularly or intravenously. For patients who are allergic to ampicillin and are unable to tolerate an oral agent, recommended therapy is cefazolin, ceftriaxone or clindamycin (parenterally)^{1,2,6,7,50}. Table 7 shows the agent and the proper dose for each patient's condition.

Special Cases

If a patient is already receiving a chronic antibiotic therapy with an antibiotic that is also recommended for the IE prophylaxis for a dental procedure, it is prudent to select an antibiotic from a different class rather than to increase the dosage of the current antibiotic. If possible, it would be preferable to delay a dental procedure until at least 10 days after completion of the previous antibiotic therapy. This time may allow the usual oral microflora to be re-established.

Patients receiving parenteral antibiotic therapy for the IE may require dental procedures during the antimicrobial therapy, particularly if the subsequent cardiac valve replacement surgery is anticipated. In these cases, the parenteral antibiotic therapy for the IE should be continued and the timing of the dosage adjusted to 30 to 60 minutes before the dental procedure. This parenteral antimicrobial therapy is administered in such high doses in order to overcome any possible low-level resistance developed among oral microflora (unlike the concentration that would occur after the oral administration). Intramuscular injections for the IE prophylaxis should be avoided in patients who are receiving the anticoagulant therapy^{1,2,50}. A careful dental evaluation is recommended so that required dental treatment may be completed whenever possible before the cardiac valve surgery or replacement or repair of CHD^{1,41,44,47}. Such measures may decrease the incidence of the late PVE caused by viridans group *Streptococci*.

Discussion

The IE, despite improvements in its management, remains a lethal disease. The need for a collaborative approach involving primary care physicians, cardiologists, surgeons, microbiologists, infectious disease specialists and frequently other specialists - namely the "Endocarditis Team" - has been underlined. Echocardiography (TTE and TOE), positive blood cultures and clinical features remain the cornerstone of the IE diagnosis. The sensitivity of the Duke criteria can be improved by new imaging modalities (magnetic resonance imaging, nuclear imaging, multi-

slice computed tomography) that also allow the diagnosis of embolic events. Successful treatment of the IE relies on microbial eradication by the antimicrobial drugs. Surgery contributes by removing the infected material. The bactericidal regimens are more effective than the bacteriostatic therapy.

The IE still remains a threat for the patients with the heart problems. The critical question is how much dental practice is involved in the onset of this infection. Probably, dental procedures (scaling, endodontic treatment or simple tooth extractions) are not the causing factors for the disease, unless there is an established valve condition or a history of an infectious episode of endocarditis in the past. The American Heart Association guidelines for the prevention of the bacterial endocarditis in patients with valvular heart disease now only include antibiotic prophylaxis for the patients at the highest risk. Patients with the highest risk of the IE can be placed in 4 categories: (1) patients with a prosthetic valve or with prosthetic material used for cardiac valve repair, (2) patients with previous episodes of the IE, (3) patients with untreated cyanotic congenital heart disease and (4) the cardiac transplant recipients who develop a cardiac valvulopathy (although not recommended by ESC Task Force). The recent guidelines propose limiting antibiotic prophylaxis to patients at high-risk of the IE undergoing the highest-risk dental procedures, which are procedures requiring manipulation of the gingival or the periapical region of the teeth or perforation of oral mucosa. Antibiotic prophylaxis is not recommended for patients at the intermediate risk of the IE. However, both the intermediate and the high-risk patients should be aware of the importance of strict dental and cutaneous hygiene. Regular brushing, flossing, making sure that dentures fit properly and seeking professional dental care every 6 months, prevents the tooth and gum infections that could lead to endocarditis.

Endocarditis is more likely a result of a daily exposure to bacteria, rather than the exposure during a dental, gastrointestinal or genitourinary procedures. There may be greater risks of the preventive antibiotic therapy than potential benefits, if any. Therefore, maintaining good oral health is generally more effective in reducing the risk of the bacterial endocarditis than taking preventive antibiotics before certain procedures.

Conclusions

The major changes in the latest recommendations pertain to the following:

(a) Even if prophylactic therapy for dental procedures is totally effective, only an exceedingly small number of cases of the IE might be prevented;

(b) The IE prophylaxis for dental procedures should be recommended only for patients with underlying cardiac conditions associated with the highest risk of the adverse outcome from the IE;

(c) For these patients prophylaxis is recommended for all dental procedures that involve manipulation of the gingival tissue, or the periapical region of the teeth, or perforation of the oral mucosa;

(d) Prophylaxis is not recommended based solely on an increased lifetime risk of acquiring of the IE;

(e) Last but not least, there should be a shift in the emphasis away from a focus on the antibiotic prophylaxis toward a greater emphasis on the improved access to the dental care and the oral health in patients.

Dissemination of the new recommendations and their rationale underpinning is a prerequisite to their acceptance by the patients and their healthcare professionals.

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Corresponding Author:

Michail Zoumpoulakis
 Grigoriou Afxentiou 2, 40 ekklisies
 54636, Thessaloniki
 Greece
 E-mail: zmike251987@windowslive.com