We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Antibiotic Prophylactic Regimens for Infective Endocarditis in Patients Undergoing Dental Procedures

Miguel Castro, Javier Álvarez, Javier F. Feijoo,
Marcio Diniz, Lucía García-Caballero, Pedro Diz and
Jacobo Limeres

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/65255

Abstract

Up to date causal relationship has been demonstrated between dental manipulations and the onset of infective endocarditis (IE). However, since 1955, numerous expert committees have proposed antibiotic prophylaxis (AP) to prevent bacteraemia of oral origin. Controversy regarding the efficacy of AP prior to the dental procedures has intensified in recent years because of the lack of conclusive evidence on its efficacy for the prevention of IE and on its cost-effectiveness, as well as the possibility of allergic reactions and the emergence of antibiotic resistance. Accordingly, AP is now maintained exclusively for patients at highest risk and who require the manipulation of the gingival or periapical regions of the teeth or perforation of the oral mucosa. In the context of a restrictive policy, the National Institute for Health and Clinical Excellence (NICE) of the United Kingdom published a new guideline in 2008 stating that "AP against IE is not recommended for persons undergoing dental procedures", regardless of risk status and of the nature of the procedure to be performed. The NICE guideline has generated further controversy, and expert committees in other countries continue to publish prophylactic regimens for the prevention of IE secondary to dental procedures. In this chapter, we discuss the principal guidelines currently applicable in Europe, the USA and Australia, and we draw particular attention to the need for randomised clinical trials.

Keywords: infective endocarditis, bacteraemia, dental procedures, dentistry, antibiotic prophylaxis

1. Historical perspectives

In 1955, the American Heart Association (AHA) was the first medical society to establish the need for a prophylactic antibiotic regimen to prevent infective endocarditis (IE) in at-risk patients undergoing various surgical procedures, including tooth extractions and other dental manipulations that affect the gum.

In the pre-antibiotic era, reports based on clinical observations described cases of IE of streptococcal aetiology in which there was a history of professional dental manipulation. This suggested the possibility that "transient bacteraemia during dental procedures may lead to subacute endocarditis in subjects with abnormal heart valves" [1].

The 1955 AHA Committee on the Prevention of Rheumatic Fever and Bacterial Endocarditis concluded that patients undergoing dental procedures must be protected by high concentrations of antibiotic present in the blood at the time of the procedure. Penicillin administered parenterally was preferred, although oral penicillin V was introduced as second choice. In cases of sensitivity to penicillin, other antibiotics such erythromycin or tetracycline were recommended [2].

Since that time, the scientific community has universally accepted the need for antibiotic prophylaxis in patients susceptible to developing IE. Experimental models developed in the 1970s provided evidence of the efficacy of prophylaxis in animals and demonstrated the ability of antibiotics to prevent *Streptococcus sanguinis* endocarditis [3]. However, the different antibiotic regimens to prevent IE in dental patients were developed based on empirical criteria.

In 1982, the British Society for Antimicrobial Chemotherapy included amoxicillin in the prophylactic antibiotic regimen against IE [4]. Amoxicillin has a broad antibacterial spectrum and a more favourable pharmacokinetic profile than penicillin V for oral administration; this has made it the drug of choice in all current guidelines on the use of antibiotics to prevent IE.

The main inclusion criteria for the prophylactic regimens established by the first committees were the rheumatic heart disease and congenital malformations, but fundamental changes have been introduced since that time regarding "patients considered to be at risk of IE". The campaigns for the prevention of rheumatic fever, the increase in the prevalence of intravenous drug abuse and the growth in cardiovascular interventions have transformed the microbiological patterns of IE, with a relative decrease in the incidence of streptococcal endocarditis and a significant increase in endocarditis due to staphylococci and other less common organisms.

These changes make it difficult to draw reliable epidemiological conclusions on the efficacy of antibiotics for the prevention of IE. In general, the majority of studies indicate that, despite the universal implantation of antibiotic prophylaxis prior to the dental treatment, no global reduction in the prevalence of IE has been achieved [5].

This has been one of the main arguments put forward by the British health authorities to revoke the indications for antibiotic prophylaxis in patients undergoing dental, digestive tract or genitourinary interventions. A few years ago, the National Institute for Health and Clinical

Excellence (NICE) in the United Kingdom published a proposal that surprised the scientific community by considering that "antibiotic prophylaxis for IE was not recommended for persons undergoing dental treatment". This recommendation was even applicable to "high-risk patients, independently of the type of dental procedure they were to undergo" [6].

This scepticism of the British health authorities to the prophylactic efficacy of antibiotics in IE is not shared by other scientific societies, which continue to include antibiotic cover for dental procedures in patients at risk of developing IE.

Epidemiological observations and statistical analyses made after the cessation of prophylaxis in the United Kingdom suggest the need for antibiotic cover in patients at maximum risk of IE of poor prognosis. In this setting, current guidelines maintain the need for prevention for patients considered to be at high risk of developing IE, such as individuals with prosthetic heart valves, the presence of certain congenital cardiopathies and patients who have had a previous episode of IE.

2. Impact of the nice recommendations

In the controversial document published in 2008, NICE brought about the complete cessation of antibiotic prophylaxis for all patients at risk of IE undergoing dental interventions [6]. The main premises on which the British experts based this decision was the quantifiable risk of antibiotic administration to the individual patient, the potential appearance of unnecessary antimicrobial resistance and the economic analysis of the cost-effectiveness of prophylaxis.

The recommendation was based on the limited available evidence on antibiotic prophylaxis as an effective method to reduce the incidence of IE when given before an interventional procedure. Furthermore, the existence of transient bacteraemia during activities of daily living, such as toothbrushing or chewing, diminishes the significance of dental procedures as a cause of IE, making antibiotic prophylaxis virtually ineffective for preventing the disease.

Consequently, NICE did not recommend antibiotic prophylaxis against IE in persons undergoing dental procedures or digestive, respiratory or genitourinary tract interventions, except for manipulations at an infected non-dental site.

The expert committees across the rest of the world, including the AHA and the European Society of Cardiology (ESC), have continued to recommend antibiotic prophylaxis in high-risk individuals, and these protocols are followed by most cardiologists and cardiac surgeons.

The first studies on the epidemiological repercussions of the implementation of the NICE guideline showed a substantial reduction in the prescription of antibiotics in its area of influence and the data gathered showed no significant changes in the general upward trend in cases of IE [7].

In 2013, a case of IE was reported in which aetiological analysis suggested a very strong association with a previous dental intervention performed without antibiotic cover. The affected patient had a metallic aortic valve and developed a fatal episode of *S. sanguinis*

endocarditis 10 days after undergoing a dental procedure without antibiotic prophylaxis, following the NICE recommendations. The dental history of the patient showed that he had received antibiotic prophylaxis during dental sessions over the previous 10 years with no adverse outcomes [8].

The most recent epidemiological studies have identified a significant increase in the incidence of IE after implementation of the NICE guideline. A retrospective study was performed in England to investigate the effect of antibiotic prophylaxis versus no prophylaxis on the incidence of IE [9]. The data collected and the subsequent analysis suggested that after March 2008—the year of publication of the NICE guideline—the number of cases of IE increased significantly above the expected historical trend.

According to some experts, these data are mainly observational and do not prove that the lower level of antibiotic prophylaxis was the cause of the increase in IE. However, no other satisfactory explanation for this increase in the incidence of IE has yet been put forward [10].

Despite this, NICE has reviewed all evidence relating to the effectiveness of IE prophylaxis as a precaution but, at present, they have found no need to change any of the existing 2008 guideline. They have, however, made an additional research recommendations on antibiotic prophylaxis against IE as summarised in **Table 1**.

Field of research	Importance
1. National register of infective endocarditis	To provide a cohort of patients able to generate sufficient evidence from well-conducted national studies
2. Cardiac conditions and infective endocarditis	To use a population-based cohort study design to allow direct comparison between acquired heart valve disease and structural congenital heart disease to estimate relative and absolute IE risk
3. Interventional procedures and infective endocarditis	To determine the frequency and intensity of bacteraemia caused by non-oral daily activities
4. Antibiotic prophylaxis against infective endocarditis	A randomised controlled trial with long-term follow-up comparing antibiotic prophylaxis with no antibiotic prophylaxis in adults and children with underlying structural heart defects undergoing interventional procedures

Note: https://nice.org.uk/guidance/CG64/chapter/Recommendations-for-research#4-antibiotic-prophylaxis-against-infective-endocarditis

Table 1. NICE recommendations for research. Antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures (updated in 2015).

3. Current antibiotic protocols

Antibiotic prophylaxis protocols against IE have undergone relevant changes in recent years. There is no doubt that the categorical 2008 NICE recommendations and their implementation in their area of influence constitute an event with significant epidemiological repercussions

that will serve to evaluate the efficacy of antibiotic prophylaxis for the prevention of IE. The scientific societies responsible for this question continue detailed follow-up in order to incorporate their conclusions as relevant data arise.

Among the different prophylaxis guidelines proposed by expert committees around the world, those that represent their corresponding geographical areas stand out for their scientific relevance. In the USA, the AHA has been pioneer in the introduction of antibiotic prophylaxis against IE; its most recent guideline was published in 2007 [11]. In Australia, the Infective Endocarditis Prophylaxis Expert Group (AIEPEG) published a guideline in 2008 that has been supported by the principal health associations in its area of influence [12]. In Europe, the ESC published the 2015 review of its protocols in the European Heart Journal, stating the official position of that scientific society on this subject [13]. These three guidelines coincide on two major points:

- All propose amoxicillin as the antibiotic of choice.

- All propose clindamycin as the alternative antibiotic of choice to amoxicillin.

3.1. Amoxicillin as the antibiotic of choice for prophylaxis

The standard regimens of the three guidelines mentioned above recommend the oral administration of 2 g of amoxicillin between 30 and 60 min before a dental procedure in adults. In the case of children, the recommended dose is 50 mg/kg body weight. When oral administration is not possible, amoxicillin can be administered intramuscularly or intravenously at the same dose.

Amoxicillin was introduced into the IE prophylaxis protocols in 1982 [4] and since that time it has become the drug of choice in the prophylactic guidelines internationally. From a pharmacological point of view, amoxicillin has optimal characteristics due to its rapid absorption after administration by mouth, achieving maximum plasma concentrations within 1–2 h after ingestion, and therapeutic levels are maintained for a minimum of 6 h. Amoxicillin is highly active against streptococci and also covers anaerobes and gram-negative bacteria. It is thus effective against the majority of microorganisms present in bacteraemia of oral origin. However, it is considered that between 5 and 35% of the microorganisms detected in blood cultures from patients undergoing dental treatment can be resistant to the antibiotic. This finding, together with the increased prevalence of IE caused by penicillin-resistant staphylococci and other unusual microorganisms, could justify the introduction of antibiotics other than amoxicillin into standard prophylaxis protocols in the future in order to improve the antimicrobial spectrum in certain circumstances.

3.2. Alternative drugs to amoxicillin

The three guidelines incorporate cephalosporins for parenteral administration as an alternative to amoxicillin. The cephalosporins are also recommended in patients with penicillin allergy, though this proposal is accompanied by a warning that the use of cephalosporins is contraindicated in individuals with a history of anaphylaxis.

About 10% of patients attending dental consultations are allergic to penicillin and its derivatives, although a large majority of these reported allergic reactions are no more than minor side-effects or late hypersensitivity reactions presenting as pruritus or rash, but not IgE-mediated. Urticaria (hives) is IgE-mediated; it only accounts for 10% of all exanthematous drug reactions, but may be interpreted as a clinical sign of immediate hypersensitivity that could progress to an episode of acute (fulminant) anaphylaxis.

The main antigenic determinant of the anaphylactic reaction to penicillins is the β-lactam ring, a part of the molecule that is essential for its bactericidal activity and that also forms part of the chemical structure of the cephalosporins and clavulanates (clavulanic acid), among others. Drug-related anaphylaxis is a life-threatening medical emergency and, as a result, the administration of β-lactam drugs is contraindicated in patients who give a history of penicillin allergy until such time as allergy testing establishes the true risk of anaphylaxis in each individual case [14].

The three main guidelines coincide on the oral or intravenous administration of 600 mg of clindamycin as the antibiotic of choice in patients allergic to penicillins (**Table 2**). Clindamycin has intrinsic in vitro activity against streptococci, staphylococci and anaerobes, it rarely causes allergic reactions and it has a low incidence of side-effects, making it an ideal alternative antibiotic based on its antimicrobial spectrum and biosafety. However, some authors have demonstrated that it is ineffective in preventing bacteraemia following dental procedures [15].

Australia (AIEPEG)	Europe (ESC)	USA (AHA)
Clindamycin	Clindamycin	Clindamycin
Lincomycin		Azithromycin
Vancomycin		Clarithromycin
Teicoplanin		

Abbreviations: AIEPEG, Australian Infective Endocarditis Prophylaxis Expert Group; ESC, European Society of Cardiology; AHA, American Heart Association.

Table 2. Alternative antibiotics for prophylaxis against infective endocarditis in patients allergic to penicillins and their derivatives.

The 2007 AHA guideline describes in great detail specific situations that could require changes to the application of the prophylactic regimens in clinical practice. For example, intramuscular injections should be avoided in patients receiving anticoagulants. In patients attending the dental clinic whilst on treatment with penicillins for other causes, it is preferable to delay dental therapy for at least 10 days; it is accepted that viridans group streptococci in the oral cavity of patients on long-term antibiotic therapy could be relatively resistant to penicillin or amoxicillin, and the cessation of antibiotic therapy allows the usual oral flora to be re-established. When the dental intervention cannot be postponed, the health professional should select a different class of antibiotic rather than increase the dose of the current antibiotic; options include clindamycin, azithromycin and clarithromycin, though only for patients with the highest-risk cardiac conditions [11].

Azithromycin and clarithromycin are macrolides with similar activity to erythromycin on the oral streptococci, but they show better gastrointestinal tolerance and a more favourable pharmacokinetic profile. Erythromycin is unstable under acidic gastric conditions, shows poor absorption and has a limited spectrum of activity. Azithromycin, on the other hand, causes fewer gastrointestinal side-effects, rapidly reaches high tissue concentrations and displays a better antibacterial spectrum, making it a good candidate for IE prophylaxis [16].

The Australian guideline includes a parenteral regimen of lincomycin, vancomycin or teicoplanin for patients with penicillin hypersensitivity and for those on long-term penicillin therapy or who have taken penicillin or related β-lactam antibiotics more than once in the previous month [12].

Finally, the ESC guideline is the most restrictive, recommending clindamycin as the only alternative antibiotic. In contrast to the proposal of the Australian expert committee, the European guideline states that the glycopeptides, such as vancomycin and teicoplanin, are not recommended because their efficacy has not been fully demonstrated and there is a potential for the induction of resistance [13].

4. At-risk patients

In its conclusions, the 2007 AHA guideline states that IE prophylaxis for dental procedures is a reasonable practice only for patients with underlying heart conditions associated with the highest risk of an adverse outcome [11]. New pathophysiological concepts and risk-benefit analyses justify the current tendency of the scientific community towards more limited indications for antibiotic prophylaxis in IE (**Table 3**).

1.	Bacteraemia occurs repeatedly and frequently during routine daily activities such as toothbrushing, flossing or chewing, and even more frequently in patients with poor dental health.
2.	Most case-control studies did not report an association between invasive dental procedures and the occurrence of infective endocarditis.
3.	The estimated risk of infective endocarditis following dental procedures is very low.
4.	Although antibiotic administration carries a small risk of anaphylaxis, it may become significant in the event of widespread use.
5.	Widespread use of antibiotics may result in the emergence of resistant microorganisms.
6.	Although efficacy of antibiotic prophylaxis on bacteraemia and the occurrence of infective endocarditis has been proven in animal models, the effect on bacteraemia in humans is controversial.
7.	No prospective randomised controlled trial has investigated the efficacy of antibiotic prophylaxis on the occurrence of infective endocarditis.

Table 3. Arguments for the restriction of the indication for prophylaxis against infective endocarditis [13].

Epidemiological evidence also supports this restrictive policy, as the incidence of IE and its associated mortality have not varied in recent decades despite the use of antibiotic prophylaxis. At the present time, we are seeing an increase in the number of cases of IE due to *Staphylococcus*

aureus and of unknown aetiology and a fall in the incidence of cases of IE of streptococcal aetiology [17]. This has occurred despite the evident, considerable increase in the number of dental interventions and in the ratio of dentists to population in recent years.

In this context and awaiting relevant new data, NICE in the UK continues its recommendation to universally cease antibiotic prophylaxis for medical interventions, although the majority of cardiologists and cardiac surgeons consider antibiotic prophylaxis necessary for patients at highest risk of adverse outcomes from endocarditis [9].

- Isolated secundum atrial septal defect.

- Surgical repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus (without residua beyond 6 months).

- Previous coronary artery bypass graft surgery.

- Mitral valve prolapse without valvar regurgitation.

- Physiologic, functional or innocent heart murmurs.

- Previous Kawasaki disease without valvar dysfunction.

- Previous rheumatic fever without valvar dysfunction.

- Cardiac pacemakers (intravascular and epicardial) and implanted defibrillators.

Table 4. Patients in whom prophylaxis against infective endocarditis is not recommended [18].

The 1997 AHA guideline was the first to stratify cardiac conditions into high, moderate and low risk for IE [18]. AHA experts stated that the risk of suffering IE assumed by low-risk patients undergoing dental treatment could be considered negligible, no higher than in the general population, and, as a result, they recommended abolishing antibiotic prophylaxis for routine dental treatment in these patients. This 1997 recommendation was particularly helpful in clinical practice because heart murmurs, pacemakers and minor congenital defects were frequently reported by dental patients in their medical records. The establishment of a restrictive position on the part of the health authorities regarding antibiotic prophylaxis created a framework of medico-legal protection in dental practice. The 1997 AHA guideline thus provided dentists with a certain capacity to evaluate the prescription of prophylaxis in patients with a history of cardiac disease and moderate their natural tendency to prescribe universal antibiotic cover derived from a fear of missing one of the numerous indications (**Table 4**). This conceptual change was further strengthened 10 years later when the 2007 AHA committee eliminated antibiotic prophylaxis for patients considered to be in the moderate risk category in the 1997 guideline (**Table 5**), on the basis that "*previously published AHA guidelines for the prevention of IE contained ambiguities and inconsistencies and were often based on minimal published data or expert opinion, they were subject to conflicting interpretations among patients, healthcare providers, and the legal system about patient eligibility for prophylaxis and whether there was strict adherence by healthcare providers to AHA recommendations for prophylaxis*" [11].

The current result of this policy limiting the indications for antibiotic prophylaxis to the highest risk cardiac conditions is stated even more restrictively in the 2015 ESC guideline (**Table 6**). In

their recommendation, the ESC excludes prophylaxis even in heart transplant recipients who develop heart valve disease; this is considered a true high-risk condition in the AHA and Australian guidelines. The Australian recommendations also include rheumatic heart disease in indigenous Australians, a population in which unusually high prevalence and mortality related to this disease have been detected [19].

- Congenital cardiac conditions

    ✓ Ductus arteriosus

    ✓ Ventricular septal defect

    ✓ Ostium primum atrial septal defect

    ✓ Coarctation of the aorta

    ✓ Bicuspid aortic valve

- Acquired valve dysfunction

    ✓ Rheumatic

    ✓ Collagen vascular disease

    ✓ Others

- Hypertrophic cardiomyopathy

- Mitral valve prolapse with valve regurgitation and/or thickened leaflets

---

Table 5. Cardiac conditions that carry a moderate risk of infective endocarditis [18].

Finally, dental surgeons show a degree of concern over the need for prophylaxis when performing dental procedures on patients with implanted cardiac devices such as pacemakers, stents and implantable defibrillators. In 2007, Lockhart et al. published an interesting literature review on this subject, revealing widely differing opinions, a situation that usually leads dentists to contact physicians for advice on management. Interestingly, most physicians, surgeons and medical specialists want their patients to receive antibiotic prophylaxis for all invasive dental procedures to prevent distant site infection of organs, tissues or prosthetic materials, and a number of them do so for medico-legal rather than scientific reasons. The majority of the literature sources agree that there is no indication for prophylaxis in patients with cardiac devices. Bacterial seeding of a graft site via a haematogenous route is an uncommon event and most of infections occurring in the first 2 months are due to *Staphylococcus* spp. and non-oral bacteria, probably as result of the manoeuvres of graft placement [20].

Based on these premises, it could be stated that patients with implantable cardiac devices may be cautiously covered with antibiotic prophylaxis exclusively during the early post-implantation period, though this is mainly for medico-legal reasons. Considering the current IE prophylaxis guidelines, there is no reason for antibiotic use during routine dental treatment in patients with implantable cardiac devices, unless individual cases present concomitant diseases that could justify such a decision.

1. Patients with any prosthetic valve, including a transcatheter valve, or those in whom any prosthetic material was used for cardiac valve repair.

2. Patients with a previous episode of infective endocarditis.

3. Patients with congenital heart disease (CHD):

    a. Any type of cyanotic CHD.

    b. Any type of CHD repaired with 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.

Table 6. Cardiac conditions associated with the highest risk of adverse outcomes of endocarditis according to the European Society of Cardiology guideline [13].

5. Risk-related dental procedures

In 1935, Okell and Elliott detected positive blood cultures in more than half of patients undergoing dental manipulations, with a particularly high prevalence among those with deficient oral health. Since that time, the relationship between bacteraemia of oral origin and dental interventions constituted proof that endocardial infection could be precipitated by oral streptococci mobilised during dental manipulation [21].

Transient bacteraemia has been widely documented as a common finding during dental procedures, associated particularly with the manipulation of teeth and periodontal tissues. Non-surgical tooth extraction is the dental procedure that most frequently provokes bacteraemia of oral origin, with a detection rate of positive blood cultures of 58–100% (**Figure 1**).
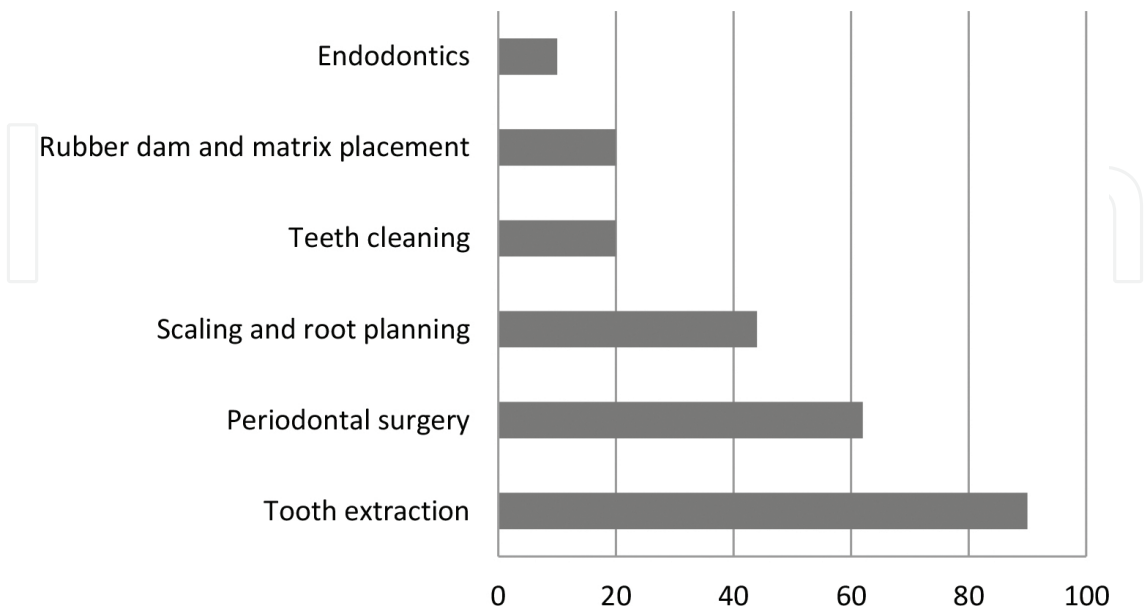
Figure 1. Prevalence of oral bacteraemia after dental procedures (inferred from [11]).

From early studies, it was generally accepted that the incidence and magnitude of bacteraemia of oral origin during dental procedures was directly proportional to the degree of inflammation and infection in the mouth. However, more recent series have found no relationship between the number of caries or the presence of periapical lesions and increased risk of post-intervention bacteraemia. Similarly, it is also accepted that the grade of gingival and periodontal health does not affect the presence or intensity of bacteraemia during interventions, and an increase in the prevalence of bacteraemia has only been demonstrated after tooth extractions in the setting of an acute infectious condition.

Studies that have investigated the bacteriological spectrum of bacteraemia of oral origin show a wide variability in their results due to the different sampling and detection techniques employed. However, *Streptococcus* spp.—the bacterial species most frequently implicated in IE of oral origin—is detected in at least 30% of cases [22]. This inoculum of streptococci that reaches the bloodstream has intrinsic pathogenic potential to colonise susceptible endocardial tissue in highest-risk patients. Structurally, streptococci have surface proteins (adhesins) that have been shown experimentally to have high affinity for the extracellular matrix, making the microorganisms capable of easily colonising vegetations and medical devices that become coated with matrix proteins after implantation. After colonisation, the bacterial biofilm acts as a propitious environment to perpetuate infection. The resulting fibrin and platelet deposition over the biofilm contributes to organise an actual bacteria-release clot which is able to create the recurrent bacteraemias that characterise IE.

A number of experimental studies have been able to reproduce these pathological events in animal models, but it remains to be seen whether oral bacteraemia secondary to dental interventions could promote identical results in humans [23].

A prospective study recently performed on patients diagnosed with IE appears to indicate that the mouth is a potential portal of entry (POE) for IE. A sample of 318 patients diagnosed with IE was examined prospectively by different specialists selected according to the natural habitat or site of colonisation of the causal diagnosed microorganism. A potential oral POE was detected by a stomatologist in 68 cases (21%), of which only 12% were considered possibly related to previous professional manipulation. Interestingly, the highest percentage of patients (88%) with oral and dental POEs was therefore made up of patients with no history of dental interventions. It was assumed that these patients presented a deficient state of oral health in the form of dental, endodontal or periodontal infection (**Table 7**).

These results agree strongly with those of Lockhart et al. [11] who presented a comparative study on the presence of bacteraemia in patients undergoing tooth extractions and toothbrushing. They found that the risk of oral bacteraemia was significantly associated with poor oral hygiene during toothbrushing. However, they did not find any association in the extraction group, even when performed without antibiotic cover. This is consistent with statements that patients at risk of IE have greater exposure to the action of oral bacteria during activities of daily living, such as toothbrushing or chewing, particularly if the individual has poor oral hygiene.

	N	%
Related to dental procedures (previous 3 months)	**8**	**12**
Tooth extraction	4	6
Scaling	1	1.5
Endodontics	1	1.5
No details	2	3
Not related to dental procedures	**60**	**88**
Dental focus of infection (decay, fracture, trauma)	9	13.3
Dental focus of infection (no further details)	22	32.1
Periodontal disease	7	10.3
Endodontal and periodontal disease	12	17.5
Radiological dental infectious focus with no clinical lesion	9	13.3
Vigorous tooth brushing with frequent bleeding	1	1.5

Table 7. Infective endocarditis patients with identified oral and dental portals of entry ($n = 68$) [24].

These observations highlight the importance of maintaining oral hygiene in patients at highest risk of IE, and provide an important argument that dental care could have greater repercussions than antibiotic prophylaxis on the incidence of IE of oral origin.

6. Evidence of the efficacy of antibiotic prophylaxis

Since the 1955 AHA statement, Ref. [2] antibiotic prophylaxis has been continuously recommended to clinicians for IE prevention among patients undergoing interventional medical procedures. Since that early paper, antibiotic prophylaxis for IE has been considered "good medical and dental practice" and it has been said that the "exact dosage and duration of therapy are somewhat empirical". Now, more than 50 years later, AHA experts continue to consider that the basis for the recommendations for IE prophylaxis are still not well established and that the quality of evidence is based on expert opinion, a few case-controlled studies, clinical experience and descriptive studies [11]. All these circumstances lead antibiotic prophylaxis against IE to be included in class C evidence (**Table 8**).

Level A	Data derived from multiple randomised clinical trials or meta-analyses
Level B	Data derived from a single randomised trial or non-randomised studies
Level C	Only expert consensus, case studies or standard of care

Table 8. Classification of the levels of evidence.

Despite this, intense research into this subject has been undertaken from three main perspectives:

- The prevention of bacterial endocarditis in experimental animal models.

- The efficacy of antibiotics for the prevention of bacteraemia secondary to dental procedures.

- Epidemiological studies.

6.1. The prevention of bacterial endocarditis in experimental animal models

The induction of IE in experimental animals was first achieved in 1970. The technique consisted of introducing a polyethylene catheter into the right side of the heart of the animal to induce a nonbacterial thrombotic endocarditis. Bacteria were then injected via the catheter to induce experimental bacterial endocarditis that served as a suitable model for the study of bacteriological, pathological and immunological aspects of IE [25].

Although experimental studies make it possible to investigate the efficacy of prophylactic antibiotic regimens against IE, there are difficulties associated with animal models both in their methodology and in the extrapolation of results. The plastic catheter acts as a foreign body delaying the successful treatment of established infection in animals, and the pharmacokinetics of antimicrobials in animals differ considerably from those in man [26].

The percentage of positive post-extraction blood cultures in experimental animals receiving antibiotic prophylaxis fell slightly with respect to the controls. However, it was observed that the administration of amoxicillin effectively prevented the onset of IE, allowing the researchers to suggest that the antibiotics had some protective mechanism over and above their bactericidal activity.

Animal research continues to be very useful for the preliminary evaluation of the efficacy and safety of drugs, and studies are being performed on the usefulness of other, alternative drugs to antibiotics for the prevention of IE in at-risk patients [27].

6.2. Efficacy of antibiotics in the prevention of bacteraemia secondary to dental procedures

The majority of studies show that amoxicillin is effective in the control of bacteraemia of oral origin, reducing the rate of positive blood cultures after dental interventions in a range that varies between 70 and 100%. There are a number of reports on the efficacy of alternative antibiotics to amoxicillin for the prevention of bacteraemia of oral origin. Results are heterogeneous as they are conditioned by numerous factors such as geographical situation, previous patient oral health status, blood culture sampling technique, microbiological analysis, resistance maps, etc.; however, in general, alternative antibiotics show a lower efficacy in the control of bacteraemia.

Interestingly, clindamycin constitutes the alternative antibiotic of choice to amoxicillin in the three main guidelines (AHA, ESC and AIEPEG). Although some studies have concluded that clindamycin was useful to reduce oral bacteraemia, more recently published studies have found that clindamycin prophylaxis does not produce a significant reduction in the incidence

of oral bacteraemia during dental procedures [15, 28, 29]. Some authors have proposed moxifloxacin as an alternative to amoxicillin, given its efficacy in experimental endocarditis [30] and in the prevention of bacteraemia following dental procedures in humans [15]. However, endocarditis expert committees appear to be ignoring this antibiotic at the present time.

S. aureus is now the most common pathogen in IE. This circumstance could justify the use of amoxicillin in association with a β-lactamase inhibitor, such as clavulanate, to broaden the bactericidal spectrum of antibiotic prophylaxis against IE. A recent study suggests that intravenous amoxicillin/clavulanate could be effective in the prevention of oral bacteraemia, virtually eliminating post-procedure inocula [29]. This observation opens the door to further research into the efficacy of oral amoxicillin/clavulanate in the prevention of bacteraemia. In any case, given its unusual demonstrated effectiveness in the elimination of oral bacteraemia, the intravenous prophylactic regimen of amoxicillin/clavulanate could be a high-efficacy alternative for patients with cardiac risk factors and severe systemic alterations, such as immune compromise, who require curative interventional dental treatment.

6.3. Epidemiological studies

Up to 2008, epidemiological studies did not support the hypothesis for the use of prophylactic antibiotics for medical procedures as a preventive method against IE. Case-control studies indicated that most IE events occurred independently of medical interventions and of the administration of antibiotic prophylaxis. A further argument was that despite the universal application of antibiotic prophylaxis, the incidence of IE and its associated mortality had not varied over decades [5].

In 2008, cessation of the NICE recommendation for antibiotic prophylaxis introduced a new epidemiological context into the study of IE, and analysis will serve to establish reliable conclusions in its area of influence. Implementation of the NICE guideline in England provides an opportunity for retrospective studies to investigate the comparative effect of antibiotic prophylaxis versus no prophylaxis on the incidence of IE.

Initially, the data suggest a significant increase in the incidence of IE after implantation of the NICE guideline, rising above the projected historical trend. This observation could lead to the hypothesis that the increased incidence of IE could be related to medical procedures in susceptible individuals performed without appropriate antibiotic cover. With regard to the dental procedures, we should observe an increase in the incidence of IE caused by oral viridans group streptococci but, at the present time, no data are available on pathogen-specific causal microorganisms [30].

7. Detractors of antibiotic prophylaxis

In view of the lack of scientific evidence on the prophylactic efficacy of the antibiotics for the prevention of IE, the British health authorities have focused their attention on the principle problems of the indiscriminate administration of antibiotics [6]:

- Quantifiable risk to the individual patient.

- Creation of unnecessary antimicrobial resistance.

- Economic burden.

However, a recent study on the incidence and nature of adverse reactions to antibiotics prescribed for endocarditis prophylaxis in England from 2004 estimates that reported adverse drug reaction rates from amoxicillin prescribed as antibiotic prophylaxis are low, without a single fatal reaction for nearly 3 million prescriptions [31].

The emergence of antibiotic resistance is a serious public health problem, but prophylactic antibiotic regimens for IE would only have a very limited effect as evidence shows that bacteria acquire resistance to antibiotics only after the administration of several consecutive doses.

With regard to the cost to the national health systems of the systematic administration of prophylaxis, cost-efficacy analyses of antibiotic prophylaxis for at-risk patients undergoing dental treatment provided contradictory results. In some countries, such as the USA, it has been estimated that prophylaxis constitutes a considerable expense, [32] but their results cannot be extrapolated to other countries in which the administration of prophylactic antibiotics to high-risk patients only represents a very small percentage of all the antibiotics that dentists prescribe.

Research into the control of bacteraemia shows that the administration of amoxicillin significantly reduces bacteraemia of oral origin, though it does not completely eliminate the possibility that this could occur. Alternative antibiotics such as clindamycin have shown poor results in the reduction of bacteraemia after dental interventions, leading us to deduce that the efficacy of prophylactic antibiotics in the prevention of IE in high-risk patients undergoing dental manipulations is limited.

8. Future research

Studies published to date on antibiotic prophylaxis against IE have a series of limitations that hinder their extrapolation, and attention must be focused on this aspect in future research:

- Regarding participants, it has been suggested that the prevalence of post-extraction bacteraemia may be related to age [33]. Age is also a determining factor in the pharmacokinetics of the antibiotic, and the efficacy of specific prophylaxis regimens may differ between children and adults. The oral health status may also influence the prevalence of post-dental manipulation bacteraemia, although this is still a controversial issue [34].

- The mode of anaesthesia, particularly general anaesthesia, can determine the appearance of post-extraction bacteraemia and prolong its duration. Comparative studies should therefore be performed using local and general anaesthesia [35].

- The prevalence of bacteraemia secondary to dental treatment and probably the predominant bacterial species are determined by the nature of the procedure. We therefore do not know whether antibiotic prophylaxis will be equally effective for different dental procedures [22].

- It is not known whether the dose and route of administration for the majority of current antibiotic prophylaxis regimens has a bearing on antibacterial activity.

- The fact that positive post-dental-manipulation blood cultures are not detected after the administration of antibiotic prophylaxis does not guarantee that bacteraemia does not occur due to bacteria that cannot be cultured in the usual culture media and/or whose inoculum is below the threshold of the method of detection employed.

Author details

Miguel Castro, Javier Álvarez, Javier F. Feijoo, Marcio Diniz, Lucía García-Caballero, Pedro Diz[*] and Jacobo Limeres

*Address all correspondence to: pedro.diz@usc.es

Special Needs Unit and OMEQUI Research Group, School of Medicine and Dentistry, Santiago de Compostela University, Santiago de Compostela, Spain

References

[1]   Elliot SD. Bacteraemia and oral sepsis. Proc R Soc Med 1939; 32: 747–754.

[2]   American Heart Association. Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections. Circulation 1955; 11: 317–320.

[3]   Pelletier LL Jr, Durack DT, Petersdorf RG. Chemotherapy of experimental streptococcal endocarditis. IV. Further observations on prophylaxis. J Clin Invest 1975; 56: 319–330.

[4]   British Society for Antimicrobial Chemotherapy. The antibiotic prophylaxis of infective endocarditis. Lancet 1982; 2: 1323–1326.

[5]   Prendergast BD. The changing face of infective endocarditis. Heart 2006; 92: 879–885.

[6]   National Institute for Health and Clinical Excellence. Prophylaxis against infective endocarditis. Antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures 2008. http://nice.org.uk/CG064

[7]   Thornhill MH, Dayer MJ, Forde JM, et al. Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study. BMJ 2011; 342: d2392.

[8]   Lopez R, Flavell S, Thomas C. A not very NICE case of endocarditis. BMJ Case Rep 2013: bcr2012007918.

[9]   Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB, Thornhill MH. Incidence of infective endocarditis in England, 2000–2013: a secular trend, interrupted time-series analysis. Lancet 2015; 385: 1219–1228.

[10] Thornhill MH, Dayer M, Lockhart PB, et al. Guidelines on prophylaxis to prevent infective endocarditis. Br Dent J 2016; 220: 51–56.

[11] Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis. Guidelines from the American Heart Association. J Am Dent Assoc 2007; 138: 739–745, 747–760.

[12] Moulds RF, Jeyasingham MS. Infective Endocarditis Prophylaxis Expert Group, Therapeutic Guidelines Limited. Antibiotic prophylaxis against infective endocarditis: time to rethink. Med J Aust 2008; 189: 301–302.

[13] Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015; 36: 3075–3128.

[14] Becker DE. Drug allergies and implications for dental practice. Anesth Prog 2013 Winter; 60: 188–197.

[15] Diz Dios P, Tomás Carmona I, Limeres Posse J, Medina Henríquez J, Fernández Feijoo J, Álvarez Fernández M. Comparative efficacies of amoxicillin, clindamycin, and moxifloxacin in prevention of bacteremia following dental extractions. Antimicrob Agents Chemother 2006; 50: 2996–3002.

[16] Addy LD, Martin MV. Azithromycin and dentistry—a useful agent?. Br Dent J 2004; 197: 141–143.

[17] Vogkou CT, Vlachogiannis NI, Palaiodimos L, Kousoulis AA. The causative agents in infective endocarditis: a systematic review comprising 33,214 cases. Eur J Clin Microbiol Infect Dis 2016; 35: 1227–1245.

[18] Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis: recommendations by the American Heart Association. Clin Infect Dis 1997; 25: 1448–1458.

[19] Davies SB, Hofer A, Reeve C. Mortality attributable to rheumatic heart disease in the Kimberley: a data linkage approach. Intern Med J 2014; 44: 1074–1080.

[20] Lockhart PB, Loven B, Brennan MT, Fox PC. The evidence base for the efficacy of antibiotic prophylaxis in dental practice. J Am Dent Assoc 2007; 138: 458–474.

[21] Okell CC, Elliott SD. Bacteraemia and oral sepsis with special reference to subacute endocarditis. Lancet 1935; 226: 869–887.

[22] Diz Dios P, Tomás Carmona I, Limeres Posse J. ***Bateriemias producidas por intervenciones odontológicas (chap. 13). In: Patología Periodontal y Cardiovascular. Coordinators: De Teresa E, Noguerol Rodríguez B. Editorial: Panamericana S.A., Madrid, 2011: 159–167.

[23] Veloso TR, Amiguet M, Rousson V, et al. Induction of experimental endocarditis by continuous low-grade bacteremia mimicking spontaneous bacteremia in humans. Infect Immun 2011; 79: 2006–2011.

[24] Delahaye F, M'Hammedi A, Guerpillon B, et al. Systematic search for present and potential portals of entry for infective endocarditis. J Am Coll Cardiol 2016; 67: 151–158.

[25] Garrison PK, Freedman LR. Experimental endocarditis I. *Staphylococcal endocarditis* in rabbits resulting from placement of a polyethylene catheter in the right side of the heart. Yale J Biol Med 1970; 42: 394–410.

[26] Petersdorf RG. Antimicrobial prophylaxis of bacterial endocarditis. Prudent caution or bacterial overkill? Am J Med 1978; 65: 220–223.

[27] Veloso TR, Mancini S, Giddey M, et al. Vaccination against *Staphylococcus aureus* experimental endocarditis using recombinant *Lactococcus lactis* expressing ClfA or FnbpA. Vaccine 2015; 33: 3512–3517.

[28] Maharaj B, Coovadia Y, Vayej AC. A comparative study of amoxicillin, clindamycin and chlorhexidine in the prevention of post-extraction bacteraemia. Cardiovasc J Afr 2012; 23: 491–494.

[29] Limeres Posse J, Álvarez Fernández M, Fernández Feijoo J, et al. Intravenous amoxicillin/clavulanate for the prevention of bacteraemia following dental procedures: a randomized clinical trial. J Antimicrob Chemother 2016; 71: 2022–2030.

[30] Sakka V, Galani L, Pefanis A, et al. Successful moxifloxacin prophylaxis against experimental streptococcal aortic valve endocarditis. J Antimicrob Chemother 2005; 56: 1160–1162.

[31] Thornhill MH, Dayer MJ, Prendergast B, Baddour LM, Jones S, Lockhart PB. Incidence and nature of adverse reactions to antibiotics used as endocarditis prophylaxis. J Antimicrob Chemother 2015; 70: 2382–2388.

[32] Lockhart PB, Blizzard J, Maslow AL, Brennan MT, Sasser H, Carew J. Drug cost implications for antibiotic prophylaxis for dental procedures. Oral Surg Oral Med Oral Pathol Oral Radiol 2013; 115: 345–353.

[33] Lockhart PB, Brennan MT, Kent ML, Norton HJ, Weinrib DA. Impact of amoxicillin prophylaxis on the incidence, nature, and duration of bacteremia in children after intubation and dental procedures. Circulation 2004; 109: 2878–2884.

[34] Lockhart PB, Brennan MT, Thornhill M, et al. Poor oral hygiene as a risk factor for infective endocarditis-related bacteremia. J Am Dent Assoc 2009; 140: 1238–1244.

[35] Barbosa M, Carmona IT, Amaral B, et al. General anesthesia increases the risk of bacteremia following dental extractions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010; 110: 706–712.