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Chapter 4

History of Antimicrobial Prophylaxis Protocols for Infective Endocarditis Secondary to Dental Procedures

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Additional information is available at the end of the chapter

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1. Introduction

For several decades, the haematogenous spread of bacteria from the oral cavity has been considered a decisive factor in the pathogenesis of 10% to 15% of episodes of infective endocarditis (IE), suggesting that certain dental procedures may represent a significant risk factor [1]. Nowadays, however, this statement has its detractors; their main argument is that not all patients with heart valves infected by bacteria that typically colonize ecological niches of the oral cavity have undergone dental procedures. Furthermore, there is little evidence to date on the genetic similarity between bacteria isolated from the heart valves, from the bloodstream, and from the oral cavity of patients with IE [2,3].

Apart from its possible involvement in the development of episodes of IE, bacteraemia of oral origin has become of particular interest in the past 2 decades because it has been associated with the progression of atherosclerosis and may thus be related to ischemic processes, although the mechanism of action has not yet been fully elucidated [4-6]. A number of published clinical studies have demonstrated an association between periodontal disease and cardiovascular disease [7-9], and oral bacteria have been detected on heart valves and in atherosclerotic plaques and aortic aneurysms [10-12].

In 1935, Okell and Elliot [13] were the first authors to detect bacteraemia caused by *Streptococcus* species (in 64% of cases) after performing dental extractions on 138 patients. A year later, Burket and Burn [14] inoculated pigmented *Serratia marcescens* into the gingival sulcus of 90 patients before performing dental extractions and they subsequently isolated this bacterium in 20% of post-manipulation blood cultures. Those results confirmed that microorganisms from the oral cavity could enter the bloodstream after dental extraction. Between the mid 1930s

and the early 1950s, numerous studies were published on the prevalence of post-dental extraction bacteraemia, with figures that varied between 2% and 83% [15-19]. In the early 1930s there was a growing awareness of the need for IE prophylaxis in patients with valvular heart disease undergoing certain dental manipulations, and the first guidelines recommending the use of certain sulfonamides to prevent IE of oral origin were published at the end of that decade. This chapter first provides a review of development of antimicrobial prophylaxis protocols for IE secondary to dental procedures between 1930 and 1955. Since the American Heart Association (AHA) published its first guideline for the prevention of IE secondary to dental procedures in 1955, several international committees formed mainly of cardiologists, infectious diseases specialists and pharmacologists have drawn up different prophylactic regimens based on findings published in the scientific literature. In the second part of this chapter we therefore review the changes in IE prophylaxis in the guidelines published by the AHA and the British Society of Antimicrobial Chemotherapy (BSAC) between 1960 and 2009, as well as those recently drawn up by other societies. Those guidelines provide a description of the susceptible patient, the at-risk dental procedures, the influence of the anaesthetic technique applied in dental treatment, the antibiotic prophylaxis protocols (antibiotics of choice, dose and route of administration) and the use of antiseptic prophylaxis.

2. Development of antimicrobial prophylaxis protocols for infective endocarditis secondary to dental procedures: 1930 to 1955

In the early 1930s, Brown and Abrahamson [20,21] were 2 of the pioneers of the application of IE prophylaxis before performing certain dental manipulations in patients with valvular heart disease. Those investigators recommended the prophylactic use of autogenous vaccines. In 1938, Feldman and Trace [22] suggested cleaning and scraping the teeth before any manipulation in order to reduce contamination of the operative field; they performed only 1 or 2 dental extractions per session, and followed this by curettage and irrigation of the periodontal pockets with antiseptics. A year later, Elliott [23] proposed perialveolar cauterization of the gingiva as a prophylactic measure after dental extraction; this technique not only sterilized the sulcus but also sealed the gingival capillaries, preventing the entry of microorganisms into the bloodstream. The practice of dental extractions under local anaesthesia with epinephrine by the infiltration technique was also recommended, as some authors had shown that this type of anaesthetic applied in this way created a barrier, preventing vascular invasion by the bacterial inoculum [14,22]. Fish and Maclean [24] recommended that teeth be filled with cotton soaked in a paste of zinc oxide and oil of cloves and that this should be renewed every few days; those authors also recommended the administration of a dose of prontosil (azosulfamide) before a dental extraction, in addition to cauterization of the gingiva. However, Bender and Pressman [17] soon declared themselves contrary to the use of cauterization to prevent post-dental extraction bacteraemia, arguing that the teeth extracted in all the published series in which this technique was used were single rooted and a maximum of only 2 teeth were extracted in each session. According to those authors, cauterization of multirooted teeth damaged the adjacent periodontal tissues [17].

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The first guideline for antibiotic prophylaxis for IE associated with dental manipulations in patients with valvular heart disease were soon developed and were based on the use of certain sulfonamides [25,26]. In 1939, Long and Bliss [27] published a book titled *The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds*, in which they recommended the prophylactic administration of sulfanilamide to patients with rheumatic heart disease before performing dental extractions. In 1941, Kolmer and Tuft [28] drew up the most complete prophylactic guidelines published up to that time; those authors did not favour "massive dental extractions" and recommended not extracting more than 2 teeth in a single session; they also recommended the use of an autogenous streptococcal vaccine obtained from culture of the apical area of the first tooth extracted, which was to be administered before extraction of the following tooth. On the matter of antibiotic prophylaxis, those investigators proposed a regimen based on the use of 15 grains of sulfapyridine every 6 hours, starting 2 days before the manipulation and continuing for 2 or 3 days afterwards; they also endorsed the protocol for the prolonged administration of sulfonamides −previously proposed by Thomas et al [25]−for patients with acute rheumatic fever; that protocol consisted of the administration of 10 grains of sulfanilamide twice a day for a period that ran from November to June [28]. In 1941, Spink [29] indicated that sulfanilamide had to be administered between 8 and 12 hours before the dental manipulation in order to achieve a serum concentration of 7 mg/100 ml at the time of the manipulation. A year later, Budnitz et al [30] proposed a prophylactic protocol that consisted of an initial dose of 1 g of sulfapyridine followed by 0.5 g every 4 hours for 6 to 7 days, performing the dental extraction on the third or fourth day.

In 1943, Northrop and Crowley [31] were the first authors to evaluate the effect of the antibiotic sulfathiazole on the prevalence of post-dental extraction bacteraemia; their study group was formed of 73 patients who received 1 g of sulfathiazole every 4 hours, starting at 4 pm the day before the dental treatment and finishing at 12 noon the day of the procedure, 1 to 2 hours before the dental extraction. Blood samples were collected to perform the corresponding cultures at baseline and at 10 seconds and 10 minutes after the manipulation. All the baseline blood cultures and all those collected at 10 minutes after the dental extraction were negative, both in the controls and in individuals receiving antibiotic prophylaxis; however, at 10 seconds after the dental extraction, 13% of controls presented detectable bacteraemia compared to 4% of those who received antibiotic therapy (with blood levels of sulfathiazole of at least 3 mg/100 ml). These authors therefore concluded that a serum concentration of sulfathiazole of 4-5 mg/100 ml was effective for the prevention of post-dental extraction bacteraemia [31]. A year later, in the *Journal of Oral Surgery*, the same authors published another study based on the administration of a single dose of 5 g of sulfathiazole 3 hours before the dental manipulation, observing a reduction in the percentage of post-dental extraction bacteraemia from 16% to 4% [32]. Hopkins [16] and Budnitz et al [30], in their respective studies of patients at risk of IE, administered sulfanilamide or sulfapyridine before dental extraction; in both series all the post-dental extraction blood cultures were negative. In 1945, Bender and Pressman [17], in a study of the prevalence of post-dental extraction bacteraemia, created 3 randomly assigned study groups: a control group, a sulfanilamide group (this group was administered 4 doses of 1.35 g of the drug the previous day and 2 g 4 hours before the manipulation) and a cauterisation group (cauterisation of the free gingival border and of the full depth of the pocket was

performed after the dental extraction). The mean serum levels of sulfanilamide were 7.5 mg/100 ml. In contrast to the results reported previously by other authors [16], the administration of sulfanilamide in this study did not reduce the prevalence of immediate post-dental extraction bacteraemia (83% in the control group *versus* 77% in the sulfanilamide group), although there was a detectable reduction in the number of positive blood cultures at 10 minutes after completion of the manipulation (33% in the control group *versus* 13% in the sulfanilamide group) and in the number of bacterial species isolated. Those authors indicated that the good results reported previously in the literature could be attributable to the absence of para-aminobenzoic acid (necessary to neutralise the sulfonamides) from the culture media used in some studies and based their findings mainly on the bacteriostatic action of this group of antibiotics [17].

In 1948, Hirsh et al [33] were the first authors to investigate the effect of penicillin on the prevalence of post-dental extraction bacteraemia. The study population was composed of a control group of 65 patients and a study group of 65 patients who received 600,000 IU of penicillin intramuscularly 3 to 4 hours before the dental extraction. Blood samples were collected immediately after the completion of surgery and at 10 and 30 minutes. Although the overall percentage of bacteraemia did not decline significantly (46% in controls *versus* 37% in the group that received penicillin), evaluation of only those cultures that were positive for streptococcal species showed a significant reduction in the prevalence of positive cultures in the group receiving prophylaxis compared to the control group (15% *versus* 34%), confirming that penicillin was effective in reducing the prevalence of streptococcal bacteraemia, although not bacteraemia caused by other microorganisms. Those authors speculated about 2 possible mechanisms of action of penicillin in the prevention of bacteraemia secondary to dental extractions: the first was that the penicillin present in the blood destroyed the microorganisms that reached the bloodstream, and the second that the antibiotic could inhibit bacterial growth in the oral cavity, thus reducing the size of the inoculum before vascular invasion occurred [33]. In another study on the efficacy of penicillin in the prevention of post-dental extraction bacteraemia published the same year, Glaser et al [34] administered 50,000 IU of penicillin intramuscularly every 2 hours for 24 hours prior to dental extraction, administering the final injection approximately 20 minutes before the manipulation. They then determined the sensitivity to penicillin of the microorganisms isolated from the blood cultures of patients who received the antibiotic therapy. In that study, prophylaxis with penicillin significantly reduced the prevalence of post-dental extraction bacteraemia (by 25%), as well as the number of bacteria isolated: there was a predominance of α-haemolytic streptococci in the control group (81% *versus* 29% in the group that received penicillin) and the majority of streptococci isolated in the penicillin group were non-haemolytic. However, none of the microorganisms isolated in the subjects who received prophylaxis were resistant to penicillin, confirming that this was not the cause of onset of the bacteraemia. Two very interesting findings of that study were that prophylaxis with penicillin was more effective in patients with periodontal disease and in those in whom only a single dental extraction was performed. Finally, those authors described a third mechanism of action of penicillin in the prevention of IE, the inhibition of bacterial growth after implantation of the microorganisms on the endocardium and before the resulting disease became clinically detectable [34]. Rhoads and Schram [35] evaluated the efficacy of

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penicillin and a new sulfonamide, 3,4-dimethyl-5-sulfanilamidoisoxazole (Gantrosan), for the prevention of post-dental extraction bacteraemia. Based on their optimal results, those authors were emphatic in their indication of the need to administer antibiotic therapy prior to performing dental extractions in patients with valvular heart disease [35].

The book on oral surgery published by Thoma in 1948 [36] was the first to include antibiotic prophylaxis prior to oral surgical procedures in patients with heart disease, although no specific regimen was described. In the first edition of Archer's classic book on oral surgery published in 1952 [37], a complex prophylactic regimen was described based on the administration of an injection of procaine penicillin G the day before oral surgery and an injection of crystalline penicillin G 30 minutes before the procedure, followed by an injection of procaine penicillin G once a day for 3 days and an injection of bicillin together with the final injection of procaine penicillin G. A very similar antibiotic prophylaxis regimen appeared in another book on oral surgery published by Mead in 1954 [38], but the penicillin was limited to 3 doses: one the day before, one 20 to 30 minutes before the manipulation and the final one the day after the intervention.

In 1955, the Committee on Prevention of Rheumatic Fever and IE of the AHA, which at that time was formed exclusively by 7 physicians, developed the first prophylactic protocol for use in patients with IE undergoing dental procedures [39]. This protocol was recommended in patients with congenital or rheumatic heart disease who were undergoing dental extractions or other manipulations that affected the gingival tissues. The AHA experts stated that the aim of prophylaxis was to make high concentrations of the antibiotic available at the time of the manipulation and to maintain the presence of the drug in the bloodstream for several days in order to eliminate any bacteria that had adhered to the heart valves during the bacteraemic episode. The method chosen was an intramuscular injection of a dose of 600,000 IU of aqueous penicillin and 600,000 IU of procaine penicillin dissolved in oil with 2% aluminium monostearate administered 30 minutes before the dental procedure. Alternatively (although less desirable), they proposed the oral administration of 250,000-500,000 IU of penicillin 30 minutes before each meal and before bedtime, starting 24 hours before the dental treatment and continuing for 5 days afterwards, and with an extra dose of 250,000 IU of penicillin immediately prior to the manipulation. For patients with a history of allergy to penicillin, the AHA recommended the use of other antibiotics such as oxytetracycline, chlortetracycline or erythromycin for 5 days, with administration starting the day before dental treatment [39].

3. Development of antimicrobial prophylaxis protocols for infective endocarditis secondary to dental procedures: 1960 to 2009

Since the AHA published its first protocol for the prevention of IE associated with dental procedures, numerous expert committees in different countries have drawn up different prophylactic regimens, many of which have subsequently been revised and modified based on subsequent epidemiological and clinical studies (prevalence of bacteraemia secondary to dental procedures, studies of the efficacy of antibiotic and antiseptic prophylaxis, pharmaco-

kinetics of antibiotic prophylaxis, antimicrobial sensitivity of isolates identified in post-dental manipulation blood cultures) and on animal experimentation [40].

The AHA has published 9 IE prophylaxis protocols, the latest revision being in 2007 [39,41-48]. The BSAC published its first antibiotic prophylaxis regimen for IE in 1982; this was revised and modified in 1986, 1990, 1992 and 2006 [49-53]. The European Society of Cardiology (ESC), together with the group of experts of the International Society of Chemotherapy published a European Consensus on IE prophylaxis in 1995 [54]. In 2004, the ESC and the British Cardiac Society (BCS), in association with the Royal College of Physicians (RCP) of London, drew up guidelines for the prevention of IE associated with dental procedures [55,56]. In 2008, the National Institute for Clinical Excellence (NICE) of the United Kingdom published clinical guidelines entitled "Prophylaxis against IE: antimicrobial prophylaxis against IE in adults and children undergoing interventional procedures" [57]. In that document, the NICE reviewed 4 clinical guidelines on the prevention of IE, including those published by the BSAC in 2006 and the AHA in 2007. The NICE also reviewed the available evidence on the principal issues of IE of oral origin and reported their conclusions. In 2009, the Task Force of the ESC published a new guideline on the prevention, diagnosis and treatment of IE [58].

3.1. Susceptible patients

In its 2 protocols published in the 1960s on the prevention of IE associated with dental procedures, the AHA defined subjects considered to be at risk of IE as those with rheumatic heart disease or congenital heart disease [41,42]. In the early seventies, the AHA emphasised that IE represented one of the most serious cardiac complications as it was associated with a high morbidity and mortality, though it recognised that it was impossible to predict which patients with cardiac abnormalities were susceptible to developing IE after interventions (including those performed in the dental setting) [43]. However, they added patients with a past history of IE, including those with no detectable cardiac abnormalities, to the list of patients considered to be at risk of IE. For the first time, the AHA indicated that patients who were candidates for cardiac surgery should undergo an exhaustive dental examination in order to perform all necessary treatments in the weeks prior to the operation, with the aim of reducing the risk of postoperative IE. After cardiac surgery, patients would remain indefinitely in the category labelled at risk of IE (particularly those with prosthetic valves) and would therefore be candidates for antibiotic prophylaxis. In the opinion of the AHA, patients with atrial septal secundum defects repaired surgically by direct suturing, without the need for a prosthetic patch, and patients who had undergone surgical repair of a patent ductus arteriosus were not at risk of IE; in the AHA's opinion, those patients would only need to receive antibiotic prophylaxis for dental treatment performed during the first 6 months after cardiac surgery [43].

Five years later, in its new guideline, the AHA pointed out that, despite advances in antimicrobial chemotherapy and cardiovascular surgery, IE continued to be associated with a significant morbidity and mortality [44]. For the first time, this Association listed those cardiac alterations considered to carry a risk of IE and in which the administration of antibiotic prophylaxis was indicated; the list included congenital heart disease, acquired valve disease (rheumatic fever), idiopathic hypertrophic subaortic stenosis, mitral valve prolapse with

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insufficiency and prosthetic valves, but not the presence of a secundum atrial septal defect. The AHA stated that mitral valve prolapse was associated with a relatively low incidence of IE and that the use of prophylaxis in these patients was therefore controversial. Antibiotic prophylaxis was not recommended for patients after coronary artery surgery, the insertion of pacemakers, those on renal dialysis with arteriovenous fistulae or hydrocephalic patients with ventriculoatrial shunts, although the it was added that "*It will be the physician or dentist who takes the final decision about whether the patient requires the administration of antibiotic prophylaxis*" [44].

In the first BSAC guideline on the prevention of IE secondary to dental procedures, patients considered to be at risk of IE included those with alterations of the endocardium due to congenital or acquired disease, those with valvular heart disease and those with prosthetic heart valves [49]. In 1984, the AHA stated that certain patients, such as those with prosthetic heart valves or surgically constructed systemic-pulmonary shunts, presented a higher risk of IE than patients with other heart conditions. This was the first guideline to include a discussion of the action to be taken in patients who were anticoagulated with heparin or dicoumarin derivatives, stating that the antibiotic prophylaxis should be administered intravenously or orally, and that intramuscular injections should be avoided because of the risk of causing haematomas [45].

In 1990, the AHA listed the heart conditions that did and did not require antibiotic prophylaxis [46]. On the subject of heart transplant patients, the AHA briefly commented that some experts considered these patients to be at risk of IE. In the case of patients with severe renal dysfunction, it was suggested that the second dose of antibiotic (gentamycin or vancomycin) proposed in some regimens should be omitted or modified [46]. Concerning the controversy over valve prolapse, in 1990, the BSAC gave its first opinion in favour of prophylaxis in mitral valve prolapse if the prolapse was associated with a systolic murmur [51].

The intense debate about IE prophylaxis that developed during the European Symposium held in Lyon in 1994 led an international group of experts to draw up a consensus protocol jointly with the Working Group on Valvular Heart Disease of the ESC [54]. The guideline was published in 1995 and it listed the heart conditions that required prophylaxis, establishing for the first time the conditions or diseases that were considered to carry a high risk of IE, such as prosthetic heart valves, cyanotic congenital heart disease and previous episodes of IE. The controversy concerning the administration of antibiotic prophylaxis in cases of mitral stenosis without valve incompetence was also discussed [54].

In 1997, the AHA adopted a more conservative attitude, admitting that the incidence of IE secondary to medico-surgical interventions in patients with cardiac abnormalities was low [47]. It was suggested that the indication for antibiotic prophylaxis should be conditioned by a number of factors such as the degree of risk of IE associated with the patient's specific cardiac abnormality, the probability that the procedure performed might cause bacteraemia, possible adverse reactions to the recommended antibiotics and the cost-benefit relationship of the prophylactic regimens. One of the important novelties introduced by the AHA was the differentiation between cardiac diseases with distinct levels of risk of developing IE (as had previously been done by the ESC in the European Consensus of 1995), and consideration of the associated morbidity and mortality (Table 1) [47].

PROPHYLAXIS RECOMMENDED	PROPHYLAXIS NOT RECOMMENDED
HIGH RISK OF IE	**LOW RISK OF IE**
-Valve prostheses	-Isolated secundum atrial septal defect
-Previous episodes of IE	-Surgically repaired structural heart defects (after 6 months)[c]
-Cyanotic congenital heart disease[a]	-Previous coronary artery bypass graft surgery
-Surgically constructed systemic-pulmonary shunts or conduits	-Physiological, functional or innocent heart murmurs[d]
MODERATE RISK OF IE	-History of Kawasaki's disease without valve dysfunction
-Structural heart defects[b]	-History of rheumatic fever without valve dysfunction
-Acquired valve disease (e.g. due to rheumatic disease)	-Cardiac pacemakers or defibrillators
-Hypertrophic obstructive cardiomyopathy	
-Mitral valve prolapse with regurgitation and/or thickened leaflets	

a- Including isolated ventricular defects, transposition of the great vessels and tetralogy of Fallot; b- Including ventricular septal defect, bicuspid aortic valve, primum atrial septal defects, patent ductus arteriosus and coarctation of the aorta; c- Including atrial and ventricular septal defects and patent ductus arteriosus; d- If the precise nature of the murmur is not known, specialist opinion should be sought.

Table 1. Classification of patients at risk of IE: AHA guideline (1997) [47].

The AHA also defined the profile of the patient with mitral valve prolapse in whom prophylaxis should be given as male, over 45 years of age, with mitral valve thickening and/or regurgitation. If the patient required emergency dental treatment and it was not known whether or not regurgitation secondary to the prolapse was present, the AHA recommended antibiotic prophylaxis. The AHA also stated that, whilst auscultation enabled innocent cardiac murmurs to be defined clearly in paediatric patients, their diagnosis in adults required complementary studies, such as echocardiography. Finally, the AHA reiterated that many professionals classified heart transplant recipients as having a moderate risk of IE indefinitely, as they were patients with a particular tendency to develop valve dysfunction (particularly during episodes of rejection) and because they were usually on immunosuppressants; these patients should therefore receive antibiotic prophylaxis [47].

In the guideline proposed by the ESC in 2004 [55], the classification of at-risk patients was similar to that published previously by the AHA in 1997 [47]. For the ESC, the classification represented a class I recommendation (when there is evidence and/or general agreement that a certain treatment or diagnostic approach is beneficial, useful or effective) with level C evidence (when there is expert consensus based on clinical trials or investigations). For the first time, the ESC added a number of so-called non-cardiac conditions in which antibiotic prophylaxis should be given: conditions that favour the development of nonbacterial thrombotic vegetations, those which compromise immune function and/or local non-immune defence mechanisms in the host and advanced age [55].

In 2004, the BSC and RCP indicated that the risk of developing IE varied according to the underlying cardiac abnormality and that, in the case of congenital heart disease, it depend-

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ed on the haemodynamic repercussions of the condition and whether surgical treatment was palliative or curative [56]. To reflect these differences in susceptibility to IE, the experts established 3 risk groups (Table 2). The principal differences to be found on comparison with the classifications of at-risk patients published previously by the AHA [47] and ESC [55] were that mitral valve prolapse with regurgitation and/or thickening of the leaflets was incorporated into the high-risk group and that prophylaxis was recommended up to 12 months after atrial septal defect/patent foramen ovale (ASD/PFO) catheter-based closure procedures and only for the first 6 months after heart and/or lung transplant [56]. The BSC and RCP also recommended that all patients at risk of IE should have a card with the following information: type of cardiac lesion, degree of risk of developing IE, history of penicillin allergy, the prophylactic regimen that should be administered, and name and telephone number of the cardiologist [56].

PROPHYLAXIS RECOMMENDED	PROPHYLAXIS NOT RECOMMENDED
HIGH RISK OF IE	**LOW RISK OF IE**
-Prosthetic heart valves	-Pulmonary stenosis
-Previous episodes of IE	-Surgically repaired structural heart defects[c]
-Cyanotic congenital heart disease	-Post Fontan or Mustard procedure with no residual murmur or defect
-Transposition of the great vessels	-Isolated *secundum* atrial septal defect[d]
-Tetralogy of Fallot	-Previous coronary artery bypass surgery
-Gerbode's defect	-Mitral valve prolapse without regurgitation
-Surgically constructed systemic-pulmonary shunts or conduits	-Innocent heart murmurs[e]
-Mitral valve prolapse with clinical repercussion[a]	-Cardiac pacemakers or defibrillators[f]
MODERATE RISK OF IE	-Coronary artery stent implantation
-Acquired valve disease (e.g. due to rheumatic heart disease)	-Heart and/or lung transplant[g]
-Aortic stenosis	
-Aortic regurgitation	
-Mitral regurgitation	
-Structural heart defects[b]	
-Hypertrophic obstructive cardiomyopathy	
-Subaortic membrane	

a- Presence of mitral valve regurgitation and/or thickening of the valves; b- Including ventricular septal defects, bicuspid aortic valve, primum atrial septal defects, patent ductus arteriosus, aortic root replacement, coarctation of the aorta, atrial septal aneurysm and patent foramen ovale; c- Including atrial septal defect, ventricular septal defect and patent ductus arteriosus; d- Antibiotic prophylaxis recommended up to 12 months after catheter closure of ASD/PFO; e- If the precise nature of the murmur is not known, the opinion of a cardiologist should be sought; in emergency situations, even if the possible repercussion of the murmur is not known, prophylaxis may be administered for certain dental procedures; f- With the exception of patients considered to have a moderate or high risk of IE, in whom antibiotic prophylaxis is recommended; g- Antibiotic prophylaxis is recommended for the first 6 months after surgery.

Table 2. Classification of patients at risk of IE: BCS and RCP (London) guideline (2004) [56].

In recent years, the updated guidelines published by the BSAC [53], the AHA [48], the NICE [57] and the ESC [58] have limited prophylaxis to high-risk patients, but the cardiac conditions included by each Expert Committee differ (Table 3). For example, according to the latest AHA guideline, IE prophylaxis for dental procedures should be recommended only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE. The conditions included in the list were prosthetic heart valves, previous IE, congenital heart disease (unrepaired defect, repaired defect with residual alterations and the first 6 months after complete repair of a defect) and heart transplant recipients who develop valve disease [48]. Although the AHA guideline recommended prophylaxis in heart transplant recipients who developed valve disease, the ESC stated that such a recommendation was not supported by strong evidence. In addition, although the risk of an adverse outcome was high when IE occurred in transplant patients, the probability of IE of oral origin was extremely low in these patients. Consequently, the ESC did not recommend prophylaxis in such situations [58]. The ESC recommended prophylaxis for cardiac conditions associated with the highest risk of IE (the list is similar to the one proposed by the AHA, except for heart transplant) based on a Class IIa recommendation (weight of evidence/opinion is in favour of usefulness/efficacy) and Level C evidence (consensus of opinion of the experts and/or small studies, retrospective studies, registries)[58]. The NICE also included other cardiac conditions at risk of IE, such as acquired valve disease with stenosis or regurgitation and hypertrophic cardiomyopathy [57].

In our opinion, this lack of consensus could provoke conflicting situations for clinicians at the time of identifying high-risk patients requiring antibiotic prophylaxis, and this could have medico-legal repercussions. However, if a clinician takes into account all the high-risk cardiac conditions defined each of the Expert Committees, there would be no omissions from the group of at-risk patients requiring antibiotic prophylaxis compared with previous IE prophylaxis protocols [59].

3.2. At-risk dental procedures

In 1960, the AHA stated that the dental procedures in which prophylaxis was indicated were dental extractions and gingival treatments, specifying that these procedures frequently caused transient bacteraemia and that the bacteraemia was more intense in patients with oral infections. They also admitted that certain normal activities such as toothbrushing and chewing gave rise to bacteraemia, although of lower intensity [41].

In 1972, a dentist, Dean Millard, was incorporated for the first time onto the AHA panel of experts; this led to recognition of the importance of a good oral health status in minimising the risk of developing IE of oral aetiology. The administration of antibiotic prophylaxis was recommended before performing any dental procedure associated with the potential for causing bacteraemia, the intensity of which depended on the magnitude of the procedure, the degree of the trauma to the gingival tissues and the presence of infection. Prophylaxis was therefore recommended for any dental procedure that caused gingival bleeding [43]. Five years later, the AHA recognised the impossibility of predicting which dental procedures could be responsible for causing IE. Antibiotic prophylaxis was recommended for treatments that can

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PROPHYLAXIS RECOMMENDED	
BSAC, 2006	**AHA, 2007/ESC, 2009**
-Previous episodes of IE	-Previous episodes of IE
-Prosthetic heart valve	-Prosthetic heart valve
-Surgically constructed systemic or pulmonary shunt or conduit	-Congenital heart disease (CHD)[a]
	Unrepaired cyanotic CHD, including palliative shunts and conduits
	First 6 months after complete repair of a congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention[b]
	Repaired congenital heart defect with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibits endothelialisation)
	-Heart transplant recipients who develop valve disease[c]
NICE, 2008	
-Previous episodes of IE	
-Prosthetic heart valve	
-Acquired valve disease with stenosis or regurgitation	
-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 ductus arteriosus, and closure devices that are judged to be endothelialised	
-Hypertrophic cardiomyopathy	

a- Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD; b- Prophylaxis is recommended because endothelialisation of prosthetic material can take up to 6 months after the procedure; c- Although the AHA guideline recommend prophylaxis in heart transplant recipients who develop valve disease, the ESC Task Force does not recommend prophylaxis in such situations.

Table 3. High-risk cardiac conditions requiring antibiotic prophylaxis for IE: guidelines of the BSAC (2006), the AHA (2007), the NICE of the United Kingdom (2008) and the ESC (2009) [48,53,57,58].

cause gingival bleeding, such as scaling, but not for procedures such as the adjustment of orthodontic appliances and the exfoliation of primary teeth [44].

In the first guideline for the prevention of IE published by the BSAC in 1982, antibiotic prophylaxis was recommended exclusively for dental extractions, scaling and root planing and periodontal surgery [49]. In 1986, the AHA confirmed that certain dental procedures such as dental extractions were associated with a higher frequency of significant bacteraemia than other treatments [50]. In 1990, the AHA reported that bacteraemia secondary to dental procedures did not persist for more than 15 minutes after completion of the procedure. However, their Committee reiterated the importance of maintaining an optimal oral health status in patients considered to be at risk of IE. On this matter, dentists were encouraged to minimise gingival inflammation. Curiously, the AHA also discussed the need to control the fit of dental prostheses in edentulous patients as there was a possibility of developing

bacteraemia because of mucosal ulceration due to poorly fitting prostheses [46]. For its part, the BSAC, in 1992, pronounced for the first time against the use of intraligamental local anaesthesia in patients considered to be at risk of IE [52].

In 1995, the ESC declared that dental treatment constituted the principle risk factor for IE and that all procedures should therefore be performed under antibiotic prophylaxis, with the exception of superficial fillings and supragingival prosthetic preparations. However, the ESC recognised that although at-risk dental procedures led to a high prevalence of bacteraemia, this was not predictive of the risk of developing IE. In this context, the duration of the procedure could represent a possible conditioning factor [54].

In its guideline published in 1997, the AHA listed the dental procedures that required antibiotic prophylaxis and those in which this was not necessary (Table 4) [47].

PROPHYLAXIS RECOMMENDED	PROPHYLAXIS NOT RECOMMENDED
-Dental extractions	-Restorative dentistry (operative and prosthodontic) with or without retraction cord
-Periodontal procedures[a]	-Non-intraligamental anaesthetic injections
-Placement of implants and reimplantation of avulsed teeth	-Intracanal post placement and build-up
-Endodontal instrumentation or periapical surgery	-Placement of a rubber dam
-Placement of subgingival antibiotic fibres or strips	-Removal of sutures
-Initial placement of orthodontic bands	-Placement of removable prosthetic or orthodontic appliances
-Intraligamental anaesthetic injections	-Intra-oral impressions
-Cleaning of teeth or implants[b]	-Fluoride treatments
	-Intra-oral radiographs
	-Orthodontic appliance adjustment
	-Exfoliation of primary teeth

a- Including surgery, root planing and scaling, probing and maintenance; b- When bleeding is anticipated.

Table 4. Dental procedures and antibiotic prophylaxis in patients with a high or moderate risk of IE: AHA guideline (1997) [47].

In general, as in previous protocols, antibiotic prophylaxis was recommended for dental procedures associated with gingival bleeding but it was not recommended for restorative dental procedures (with or without gingival retraction), the placement of a rubber dam or the removal of sutures. Although the possibility of developing bacteraemia secondary to traumatic ulcers caused by poorly fitting prostheses had previously been included, the AHA no longer recommended prophylaxis in edentulous patients during the fitting of complete prostheses [47].

In 2004, in agreement with previous guidelines [47,52,54], the ESC once again recommended antibiotic prophylaxis for "*dental treatments that caused gingival or mucosal trauma*" [55]. In contrast, the BCS and the RCP modified certain aspects concerning bacteraemia of oral origin [56]. First, they excluded the concept of "*procedures that cause bleeding*" as a criterion for the

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indication for antibiotic prophylaxis in patients at risk of IE; they also re-evaluated the definition of "*significant bacteraemia*" which, according to their new interpretation, was defined as "*bacteraemia secondary to a dental procedure that was statistically significant with respect to the bacteraemia present under basal conditions (prior to any manipulation)*". Considering these new provisions, the indication for prophylaxis included not only surgical procedures such as dental extractions or mucoperiosteal flaps but also other less traumatic procedures such as the placement of a rubber dam, matrices, wedges or retraction cords (Table 5) [56]. Although that Committee recognised the existence of bacteraemia secondary to activities considered to be physiological (such as toothbrushing), it also recognised the impossibility of administering prophylaxis for such practices due to the high risk of potentiating the development of bacterial resistance [56].

In 2006, the BSAC summarized the indications for antibiotic prophylaxis for high-risk patients stating that it should be given for "*all dental procedures involving dento-gingival manipulation or endodontics*" [53]. According to the latest AHA and ESC guidelines, prophylaxis was recommended for all dental procedures that involved manipulation of gingival tissues or the periapical region of teeth or perforation of the oral mucosa. This included procedures such as biopsies, suture removal and placement of orthodontics bands, but it did not include routine anaesthetic injections through non-infected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, placement of orthodontic brackets, or adjustment of orthodontic appliances [48,58]. The dental procedures with the highest risk of IE and for which prophylaxis was recommended were associated with a Class IIa recommendation (weight of evidence/opinion is in favour of usefulness/efficacy) and Level C evidence (consensus of opinion of the experts and/or small studies, retrospective studies, registries) [58]. There are other events for which prophylaxis was not recommended, such as shedding of deciduous teeth and trauma to the lips or oral mucosa [48].

In the latest guidelines published by the BSAC, the AHA, the NICE of the United Kingdom, and the ESC, the emphasis for the cause of IE shifted from procedure-related bacteraemia to cumulative bacteraemia due to everyday oral activities [48,53,57,58]. The NICE considered that it was biologically implausible that a dental procedure would lead to a greater risk of IE than regular toothbrushing. On the other hand, even some expert committee guidelines concurred with the premise "*Maintenance of optimal oral hygiene and periodontal health may reduce the incidence of bacteraemia of oral origin and, in the context of a dental procedure, is more important than prophylactic antibiotics to reduce the risk of IE*" [48,58].

The NICE has adopted a drastic stance in this respect, issuing the statement that "*antibiotic prophylaxis for IE is not recommended in individuals undergoing dental procedures*" [58]. Recently, following the introduction in March 2008 of a clinical guideline from NICE recommending the cessation of antibiotic prophylaxis in the United Kingdom, Thornhill et al [60] quantified the change in the prescription of antibiotic prophylaxis to patients at risk of IE undergoing invasive dental procedures and looked for any concurrent change in the incidence of IE. Despite a 78.6% reduction in the prescription of antibiotic prophylaxis after the introduction of the NICE guideline, that study detected no large increase in the incidence of cases of IE or of IE-related deaths over the following 2 years. Those authors concluded that ongoing data monitoring was

TYPE OF PROCEDURE	PROPHYLAXIS RECOMMENDED	PROPHYLAXIS NOT RECOMMENDED
ORAL SURGERY	-Extraction of a single tooth -Extraction of multiple teeth -Mucoperiosteal flap for access to a tooth or lesion -Dental implants (as for mucoperiosteal flap)	-Incision and drainage of an abscess -Biopsy -Insertion of implants (transmucosal approach) -Exfoliation of primary teeth -Suture removal -Removal of surgical packs
PERIODONTICS	-Periodontal surgery -Gingivectomy -Root curettagea -Root planing (similar to curettage) -Placement of antibiotics in the gingival sulcusb -Rubber cup polishing -Oral irrigation with water	-Air polishing
ENDODONTICS	-Root canal instrumentation beyond the apex -Reimplantation of avulsed teeth[c]	-Root canal instrumentation (within the root canal) -Pulpotomy of primary molars -Pulpotomy of permanent molars[d]
ORTHODONTICS	-Placement of interproximal separators -Exposure of unerupted teeth	-Band placement and cementation -Band removal -Adjustment of fixed appliances -Taking alginate impressions
CONSERVATIVE DENTISTRY	-Placement of a rubber dam -Matrix band and wood wedge placement -Placement of a retraction cord	-Slow and fast drilling (without a rubber dam)
PREVENTIVE DENTISTRY		-Fossa and fissure sealing -Fluoride application
ANAESTHETIC TECHNIQUES	-Local intraligamental	-Local infiltrative -Local nerve block -General with oral intubation -General with nasal intubation -General with laryngeal mask
EXPLORATION TECHNIQUES	-Periodontal probing	-Dental examination with mirror and probe
DIAGNOSTIC TECHNIQUES	-Sialography	-Intra-oral radiographs -Extra-oral radiographs

a- Both supra and subgingival, with manual instrumentation or ultrasound; b- Although there are no studies on this subject, this procedure is very similar to the placement of a retraction cord; c- Antibiotic prophylaxis may be administered up to 2 hours after dental reimplantation; d- Although there are no studies on this subject, this procedure is very similar to pulpotomy of primary molars.

Table 5. Dental procedures and antibiotic prophylaxis in patients with a high or moderate risk of IE: BCS and RCP (London) guideline (2004) [56].

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needed to confirm this observation supporting the NICE guideline and that further clinical trials should be performed to determine if antibiotic prophylaxis still has a role in protecting some patients at particularly high risk [60].

3.3. Anaesthetic technique

In 1960, the AHA recommended the administration of antibiotic prophylaxis for any surgical intervention (including those in the orofacial area) performed under general anaesthesia in patients considered to be at risk of IE [41]. However, in subsequent protocols published by the AHA, no specific observations were made with regard to the type of anaesthesia used [42-48].

The BSAC, on the other hand, specified for the first time in 1982 that when dental treatment was performed under general anaesthesia, special prophylactic protocols should be applied, also considering that "*If patients due to undergo a general anaesthesia have prosthetic heart valves and/or are allergic to penicillin and/or have received prolonged treatment with penicillin and/or have had* previous episodes of IE, their dental problems should be treated in a hospital environment" [49]. The BSAC has maintained that opinion in its protocols on IE prevention published in 1986, 1990 and 1992 [50-52]. In 1995, the ESC also included the anaesthetic technique among the factors to be taken into account when choosing the prophylactic regimen [54]. In the guideline published by the BCS and RCP in 2004, specific prophylaxis regimens were included for dental procedures performed under general anaesthesia [56].

In agreement with the AHA, the latest protocols of the BSAC and ESC on IE prevention recommend antibiotic prophylaxis irrespective of whether the dental procedure is performed under general or local anaesthesia [53,58].

3.4. Antibiotics of choice, dose and route of administration

In 1960, the AHA pronounced in favour of administering antibiotic prophylaxis from between 24 and 48 hours before the dental procedure, even in the absence of intraoral infections, in order to reduce the intensity of the post-manipulation bacteraemia [41]. However, in view of the problem of bacterial resistance, it was also suggested that prophylaxis could be administered immediately before the procedure. According to the AHA, the choice of one or other regimen depended on the professional, who should evaluate the probability of infection in order to decide when the prescription of antibiotics was indicated. In contrast to the guideline published in 1955 [39], the exclusively oral protocols were excluded in favour of intramuscular administration, although penicillin continued to be the antibiotic of choice; the prophylactic regimen consisted of several injections of penicillin from 2 days before up to 2 days after the session of dental treatment. A combined intramuscular-oral prophylactic regimen was also elaborated. For patients with a history of penicillin allergy, the AHA was the first to recommended erythromycin at doses of 250 mg orally 4 times a day (for adults and older children); in small children, the dose of erythromycin was of 20 mg/kg body-weight per day, divided into 3 or 4 doses, not exceeding a total dose of 1 g per day [41].

In 1965, the AHA stated that antibiotic prophylaxis should only be administered immediately before the dental procedure and on the subsequent days; this recommendation was based on

the argument that penicillin did not sterilise the apical foci, and that its excessive use led to the selection of a resistant oral flora. The AHA also reduced the parenteral regimen to a single injection of several penicillins. In those cases in which the complete collaboration of the patient could be anticipated, an exclusively oral regimen of several doses of penicillin was proposed. Erythromycin was recommended for patients allergic to penicillin [42].

In 1972, the AHA modified its recommendations to include an increase in the initial doses of penicillin and erythromycin administered orally and the use of erythromycin in patients on prolonged treatments with penicillin, as penicillin-resistant *Streptococcus viridans* could predominate in their oral flora [43]. Five years later, the AHA suggested increasing the initial dose of the antibiotic even further in order to reach higher serum concentrations at the moment at which the microorganism entered the bloodstream [44]. However, they favoured the parenteral regimen, particularly in patients considered to be at high risk of IE. Two regimens were recommended: regimen A, based on the use of penicillin (erythromycin was recommended in patients allergic to penicillin) for parenteral-oral or exclusively oral administration, and regimen B, which combined penicillin and streptomycin (vancomycin and erythromycin for patients allergic to penicillin) for parenteral-oral administration. This latter protocol was reserved for patients with prosthetic heart valves, although patients with a good oral health status could receive the oral prophylaxis regimen for certain non-surgical dental procedures [44].

The BSAC, in its first guideline, suggested a single prophylactic regimen of a single dose of amoxicillin before the dental procedure for all patients considered to be at risk of IE (including patients with prosthetic heart valves) [49]. The BSAC substituted penicillin V, previously recommended by the AHA [44], with amoxicillin due to its more favourable pharmacokinetic and pharmacodynamic characteristics. Erythromycin stearate was the antibiotic of choice in patients allergic to penicillin but because this macrolide has lower activity than amoxicillin against some oral streptococci and showed a lower absorption after a single oral dose, they proposed a second dose 6 hours after completing the dental procedure. One quarter of the adult dose was recommended in children under 5 years of age and a half dose in those of 5 to 10 years of age [49]. In contrast to the AHA [44], the BSAC proposed a combined intramuscular-oral regimen in patients undergoing dental treatment under general anaesthesia. Special prophylactic regimens were proposed for patients being treated in the hospital environment; these regimens were based on the association of amoxicillin and gentamycin or, in patients unable to receive penicillin, a combination of vancomycin and gentamycin; the following doses were used in children under 10 years of age: amoxicillin, half the adult dose; gentamycin, 2 mg/kg body-weight; and vancomycin, 20 mg/kg body-weight [49].

In its protocol published in 1984, the AHA reduced the dose of the antibiotic after completion of the dental treatment, recommending the administration of penicillin V before the dental procedure and a second dose 6 hours after the first. In those patients in whom the oral route was not available, intramuscular penicillin G was proposed before the procedure and 6 hours later [45]. The AHA also showed a clear preference for the parenteral route in patients at high risk of IE and drew up a special regimen for these patients consisting of intramuscular or intravenous ampicillin and gentamycin, together with a second dose of penicillin V orally;

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intravenous vancomycin was recommended for patients allergic to penicillin, eliminating the second dose of erythromycin [45].

In 1986, the BSAC suggested that vancomycin should be given by slow intravenous infusion over 60 minutes (instead of the previously recommended 30 minutes) to minimise adverse reactions such as episodes of hypotension caused by histamine release (red-man syndrome) [50]. As an alternative to the parenteral regimen proposed earlier, the BSAC proposed 2 oral regimens for patients without prosthetic heart valves undergoing dental treatment under general anaesthesia. The first was based on the administration of amoxicillin before anaesthetic induction followed by a second dose in the immediate postoperative period; the second regimen consisted of the combination of amoxicillin and probenecid administered before anaesthesia [50]. For the first time, the BSAC differentiated between patients with prosthetic heart valves and other patients considered to be at risk of IE, as the AHA [45] had done in its 1984 guideline, proposing specific oral prophylactic regimens for such patients undergoing dental treatment under local anaesthesia [50].

Differing from the BSAC guideline [50], the 1990 AHA guideline continued to favour regimens based on 2 doses. Of particular note amongst the novelties introduced in this protocol was the incorporation of amoxicillin as the antibiotic of choice for all groups at risk of IE [46], an approach that had been adopted by the BSAC in 1982 [49]. According to the AHA, amoxicillin, ampicillin and penicillin showed similar efficacy against α-haemolytic streptococci *in vitro* but amoxicillin reached higher serum concentrations due to its better gastrointestinal absorption. However, they also defended the use of penicillin V as a suitable alternative for prophylaxis in dental procedures. Erythromycin, in its ethylsuccinate or stearate salt preparations, continued to be the antibiotic of choice in patients allergic to penicillin, being administered 2 hours before the procedure to ensure high serum concentrations. For the first time, the AHA recommended the administration of clindamycin in patients intolerant to penicillin and erythromycin [46]. For patients unable to take oral medication, the AHA drew up a number of regimens for parenteral administration as alternatives to the standard protocol, proposing ampicillin (in patients not allergic to penicillin) and clindamycin (in penicillin-allergic patients) as the antibiotics of choice [46]. In contrast to the previous protocols [45], the AHA recommended the administration of the standard regimen to patients with prosthetic heart valves and other patients considered to be at high risk of IE (patients with a past history of IE and those with surgically constructed systemic-pulmonary shunts). However, recognising that some professionals preferred parenteral prophylaxis, they also drew up a special parenteral regimen for this type of patient [46].

The prophylactic protocol recommended by the BSAC in 1990 included a new option [51]. Due to the high prevalence of undesirable gastrointestinal effects caused by erythromycin, and based on the guideline published in 1984 by the Swiss Expert Committee for the prevention of IE [61], the BSAC proposed the administration of a single oral dose of 600 mg of clindamycin 1 hour before the procedure as an alternative in patients with penicillin allergy; the dose of clindamycin in children under 10 years of age was of 6 mg/kg body-weight [51]. In 1992, the BSAC definitively replaced erythromycin with clindamycin in patients allergic to penicillin, modifying the initial dose in children to 300 mg in those between 5 and 10 years of age and to 150 mg in those under 5 years [52]. Due to the high prevalence of adverse effects associated

with vancomycin and its prolonged duration of administration (around 100 minutes), the BSAC drew up 2 alternative regimens for penicillin-allergic patients with a high risk of IE who were being treated in the hospital environment. One was based on the intravenous combination of teicoplanin and gentamycin (in children under 14 years of age the doses were teicoplanin, 6 mg /kg body-weight, and gentamycin, 2 mg/kg body-weight); and the other consisted of an intravenous infusion of clindamycin with a second dose 6 hours after the first. Finally, in patients undergoing dental treatment under general anaesthesia, the BSAC specified that prophylaxis with amoxicillin should be administered intravenously instead of intramuscularly, particularly in children [52].

In 1995, the ESC performed a critical review of the prophylaxis protocols drawn up by the different national committees, noting clear differences between countries, although all included a simple or standard regimen and another more complex regimen for use in special circumstances [54]. In general, the standard guidelines consisted of the oral administration of a single dose of antibiotic which, in the majority of countries, was amoxicillin. Some societies recommended the administration of a second dose, particularly in patients considered to be at high risk of IE. In patients allergic to the beta-lactams, the antibiotic of choice was clindamycin at doses between 300 mg and 600 mg, although some countries, for example, Holland and France, recommended other antibiotics such as erythromycin or pristinamycin [54]. The more complex regimens were based on the synergistic and prolonged effect provided by several doses of different antibiotics with the aim of increasing the safety margin in special situations. In an analysis performed by the ESC, it was found that the majority of protocols recommended ampicillin or amoxicillin by intravenous infusion followed by a second oral dose 6 hours later; there were only minor differences with respect to the doses used. Although some countries did not use the aminoglycosides, these were recommended in other countries in patients considered to be at high risk of IE. The most frequently used antibiotic of choice in patients allergic to penicillin was vancomycin by intravenous infusion; for some scientific societies, teicoplanin and clindamycin were possible antimicrobial alternatives [54]. According to the ESC, the choice of the most suitable prophylactic regimen should be based on the following considerations: the heart condition defined as carrying a risk of IE; the type, magnitude and duration of the dental procedure; and the type of anaesthesia used (local or general). The ESC therefore considered the possibility of individualising the antibiotic prophylaxis regimen in certain situations [54]. The oral regimen proposed by the ESC consisted of the administration of amoxicillin or clindamycin (in penicillin-allergic patients), whilst the combination of amoxicillin or ampicillin with gentamycin and a second dose of amoxicillin orally 6 hours later was recommended in the parenteral regimen. In patients allergic to penicillin, the association of vancomycin and gentamycin was recommended, administering a second dose of vancomycin by intravenous infusion 12 hours after the first dose [54].

The prophylactic protocol recommended by the AHA in 1997 is shown in Table 6 [47]. It is based on a single dose of amoxicillin administered orally 1 hour before the procedure. In this protocol, the dose of amoxicillin was reduced from 3 g to 2 g after confirming that this latter dose provided adequate serum levels of the drug over several hours and caused fewer adverse gastrointestinal effects. Accepting an approach that had been adopted by other societies several years earlier [49-52], the AHA recognised that the administration of a second dose of antibiotic was unnecessary, since the serum levels of the drug exceeded the minimum inhibitory concentra-

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tions of many oral *Streptococcus* spp. and the antimicrobial activity of amoxicillin was prolonged (6 to 14 hours). In patients allergic to penicillin, the antibiotics of choice were clindamycin, cephalosporins (cefalexin or cefadroxil) or macrolides (azithromycin or clarithromycin), although the AHA specified that the cephalosporins should be avoided in patients with type 1 hypersensitivity to penicillin [47]. In patients unable to take oral medication or with problems of gastrointestinal absorption (independently of the IE risk category), the AHA drew up a regimen based on the use of intramuscular or intravenous ampicillin 30 minutes before the procedure. In penicillin-allergic patients in whom parenteral administration of the antibiotic was required, the recommended antibiotic was clindamycin phosphate and, in those patients not presenting type 1 hypersensitivity, was cefazolin. Although erythromycin was abandoned because of its gastrointestinal complications and its particular pharmacokinetic characteristics, the AHA indicated that "*Dentists who are used to prescribing this antibiotic successfully for prophylaxis may continue to use it*" [47].

STANDARD REGIMEN (ORAL)	
NOT ALLERGIC TO PENICILLIN	
ADULTS	CHILDREN
2 g of amoxicillin 1 h before tmt	50 mg/kg body-weight of amoxicillin 1 h before tmt
ALLERGIC TO PENICILLIN	
ADULTS	CHILDREN
A) 600 mg of clindamycin 1 h before tmt	A) 20 mg/kg body-weight of clindamycin 1 h before tmt
B) 2 g of cefalexin or cefadroxil 1 h before tmt[a]	B) 50 mg/kg body-weight of cefalexin or cefadroxil 1 h before tmt[a]
C) 500 mg of azithromycin or clarithromycin 1 h before tmt	C) 15 mg/kg body-weight of azithromycin or clarithromycin 1 h before tmt
PARENTERAL REGIMEN[b]	
NOT ALLERGIC TO PENICILLIN	
ADULTS	CHILDREN
2 g of ampicillin (IM or IV) 30 min before tmt	50 mg/kg body-weight of ampicillin (IM or IV) 30 min before tmt
ALLERGIC TO PENICILLIN	
ADULTS	CHILDREN
A) 600 mg of clindamycin (IV) 30 min before tmt	A) 20 mg/kg body-weight of clindamycin (IV) 30 min before tmt
B) 1 g of cefazolin (IM or IV) 30 min before tmt	B) 25 mg/kg body-weight of cefazolin (IM or IV) 30 min before tmt

tmt= treatment; min= minutes; h= hours; IM= intramuscular; IV=intravenous; mg= milligrams; g= grams; kg= kilograms.

a- The cephalosporins must not be administered to subjects with immediate hypersensitivity reactions to penicillin (urticaria, angioedema or anaphylaxis); b- This protocol is to be applied in patients unable to take the medication orally; the total dose in children should not exceed the adult dose.

Table 6. IE prophylaxis protocol for dental procedures: recommendation of the AHA (1997) [47].

In 2004, the ESC published a guideline on IE prophylaxis which were very similar to the 1997 guideline of the AHA [47], except that the use of cephalosporins in patients allergic to penicillin was excluded [55].

In the prophylaxis protocol for IE secondary to dental procedures drawn up by the BSC and RCP (London) in 2004, prophylaxis was reserved for patients with heart diseases included in the categories of high and moderate risk of IE, and the prophylactic regimens varied according to the type of anaesthesia used [56]. Oral prophylaxis regimens were to be administered in procedures performed under local anaesthesia and parenteral regimens for those performed under general anaesthesia (Tables 7 and 8) [56]. In contrast to the 1997 guideline of the AHA [47], the BCS and RCP also provided a special prophylactic regimen for patients with prosthetic heart valves and/or previous episodes of IE (Table 9) [56].

The most recent IE prophylaxis protocols published by the BSAC [53], the AHA [48] and the ESC [58] are very similar and are summarized in Tables 10 and 11. The most recent prophylactic protocol published by the AHA continues to recommend amoxicillin as the antibiotic of choice for oral prophylaxis. For individuals who are allergic to penicillins, the use of cephalexin or another first-generation oral cephalosporin, clindamycin, azithromycin or clarithromycin is recommended [48]. Because of possible cross-reactions, a cephalosporin must not be administered to patients with a history of anaphylaxis, angioedema or urticaria after treatment with any form of penicillin, including ampicillin or amoxicillin. Patients who are unable to tolerate an oral antibiotic may be treated with intramuscular or intravenous ampicillin, ceftriaxone or cefazolin. For penicillin-allergic patients who are unable to tolerate an oral agent, prophylaxis is recommended with parenteral cefazolin, ceftriaxone or clindamycin [48]. According to the ESC, the main aim of antibiotic prophylaxis in patients at risk of IE is to target the oral streptococci. The impact of increasing resistance of these pathogens on the efficacy of antibiotic prophylaxis is unclear. Fluoroquinolones and glycopeptides are not recommended because their efficacy has not been established and because of the potential induction of resistance [58].

It has been estimated that the number of cases of IE that result from dental interventions is very small. The AHA has therefore concluded that only an extremely small number of cases of IE will be prevented by antibiotic prophylaxis for dental procedures even if such prophylactic regimens are 100% effective [48]. According to the ESC, this observation leads to 2 conclusions: (i) IE prophylaxis can at best only protect a small proportion of patients; and (ii) the bacteraemia that causes IE in the majority of patients appears to derive from another source [58]. Finally, the AHA stated the need for prospective placebo-controlled studies of antibiotic prophylaxis for IE to evaluate its efficacy in IE prevention [48].

Reviewing the effect of antibiotic prophylaxis on the intensity and duration of bacteraemia following dental procedures, the NICE recently concluded that "*Antibiotic prophylaxis does not eliminate bacteraemia following dental procedures but some studies show that it does reduce the frequency of detection of post-procedure bacteraemia*" [57]. This conclusion was reached after analysis of a number of studies on the efficacy of antibiotic prophylaxis for the prevention of post-dental manipulation bacteraemia; those studies presented methodological

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differences with respect to the type of antibiotic used and the time and route of administration. These important differences make a comparison of the results between the different series inappropriate [59].

STANDARD REGIMEN (ORAL)	
NOT ALLERGIC TO PENICILLIN	
ADULTS 3 g of amoxicillin 1 h before tmt	CHILDREN OVER 10 YEARS OF AGE Adult dose CHILDREN BETWEEN 5 AND 10 YEARS OF AGE 1.5 g of amoxicillin 1 h before tmt CHILDREN UNDER 5 YEARS OF AGE 750 mg of amoxicillin 1 h before tmt
ALLERGIC TO PENICILLIN[a]	
ADULTS 600 mg of clindamycin 1 h before tmt	CHILDREN OVER 10 YEARS OF AGE Adult dose CHILDREN BETWEEN 5 AND 10 YEARS OF AGE 300 mg of clindamycin 1 h before tmt CHILDREN UNDER 5 YEARS OF AGE 150 mg of clindamycin 1 h before tmt
UNABLE TO TAKE ORAL MEDICATION[b]	
ADULTS 500 mg of azithromycin 1 h before tmt	CHILDREN OVER 10 YEARS OF AGE Adult dose CHILDREN BETWEEN 5 AND 10 YEARS OF AGE 300 mg of azithromycin 1 h before tmt CHILDREN UNDER 5 YEARS OF AGE 200 mg of azithromycin 1 h before tmt

h= hours; tmt= treatment; mg= milligrams; g= grams.

a- This protocol should also be used in patients who have received penicillin or another beta-lactam on more than 1 occasion in the previous month; b- In Great Britain, clindamycin is not available in oral suspension.

Table 7. IE prophylaxis protocol for dental procedures performed under local anaesthesia: recommendation of the BCS and RCP (London) (2004) [56].

PARENTERAL REGIMEN	
NOT ALLERGIC TO PENICILLIN	
ADULTS	CHILDREN OVER 10 YEARS OF AGE
2 g of amoxicillin or ampicillin (IV) during anaesthetic induction	Adult dose
	CHILDREN BETWEEN 5 AND 10 YEARS OF AGE
	500 mg of amoxicillin or ampicillin (IV) during anaesthetic induction
	CHILDREN UNDER 5 YEARS OF AGE
	250 mg of amoxicillin or ampicillin (IV) during anaesthetic induction
ALLERGIC TO PENICILLIN[a]	
ADULTS	CHILDREN OVER 10 YEARS OF AGE
300 mg of clindamycin (IV over 10 min) during anaesthetic induction	Adult dose
	CHILDREN BETWEEN 5 AND 10 YEARS OF AGE
150 mg of clindamycin (oral or IV) 6 h after the first dose	150 mg of clindamycin (IV over 10 min) during anaesthetic induction
	CHILDREN UNDER 5 YEARS OF AGE
	75 mg of clindamycin (IV over 10 min) during anaesthetic induction

min= minutes; h= hours; IV= intravenous; mg= milligrams; g= grams; kg= kilograms.

a-This protocol should also be used in patients who have received penicillin or another beta-lactam on more than 1 occasion in the previous month.

Table 8. IE prophylaxis protocol for dental procedures under general anaesthesia: recommendation of the BCS and RCP (London) (2004) [56].

PARENTERAL REGIMEN	
NOT ALLERGIC TO PENICILLIN	
ADULTS	CHILDREN OVER 10 YEARS OF AGE
2 g of amoxicillin + 1.5 mg/kg body-weight of gentamycin (IV) 30 min before tmt	Adult dose
	CHILDREN UNDER 10 YEARS OF AGE
1 g of amoxicillin (oral or IV) 6 h after the first dose	1 g of amoxicillin + 1.5 mg/kg body-weight of gentamycin (IV) 30 min before tmt
	Amoxicillin (oral) 6 h after the first dose
ALLERGIC TO PENICILLIN[a]	
ADULTS	CHILDREN OVER 10 YEARS OF AGE
1 g of vancomycin (IV over 2 h) + 1.5 mg/kg body-weight of gentamycin (IV) before tmt	Adult dose
	CHILDREN UNDER 10 YEARS OF AGE
	20 mg/kg body-weight of vancomycin (IV over 2 h) + 1.5 mg/kg body-weight of gentamycin (IV) before tmt

min= minutes; h= hours; tmt= treatment; IV= intravenous; mg= milligrams; g= grams; kg= kilograms.

a- This protocol should also be used in patients who have received penicillin or another beta-lactam on more than 1 occasion in the previous month.

Table 9. Parenteral IE prophylaxis protocol for patients with prosthetic heart valves and/or previous episodes of IE undergoing dental procedures under local or general anaesthesia: recommendations of the BCS and RCP (London) (2004) [56].

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More than half of the studies published on antibiotic prophylaxis and post-dental extraction bacteraemia have investigated the efficacy of the penicillins. The results obtained in the majority of those studies confirmed the efficacy of these antibiotics in prevention, as bacteraemia did not develop in a significant number of patients (compared with the results obtained in patients not receiving antibiotic prophylaxis) [62,63]. However, there are fewer studies on the effect of the prophylactic administration of other antibiotics (clindamycin, azithromycin and cephalosporins) recommended for the prevention of post-dental extraction bacteraemia, and their results have not established whether these antibiotics are effective [62].

	STANDARD REGIMEN (ORAL)	
BSAC, 2006	**NOT ALLERGIC TO PENICILLIN**: 3 g of amoxicillin 1 h before tmt	
	ALLERGIC TO PENICILLIN: 600 mg of clindamycin 1 h before tmt	
	UNABLE TO TAKE ORAL MEDICATION[a] : 500 mg of azithromycin 1 h before tmt	
AHA, 2007	**NOT ALLERGIC TO PENICILLIN**:	2 g of amoxicillin 1 h before tmt
	ALLERGIC TO PENICILLIN:	2 g of cephalexin 1 h before tmt[b]
		600 mg of clindamycin 1 h before tmt
		500 mg of azithromycin or clarithromycin 1 h before tmt
ESC, 2009	**NOT ALLERGIC TO PENICILLIN**: 2 g of amoxicillin 30 min-1 h before tmt	
	ALLERGIC TO PENICILLIN: 600 mg of clindamycin 30 min-1 h before tmt	

tmt= treatment; min= minutes; h= hours; mg= milligrams; g= grams.

a- In Great Britain, clindamycin is not available in oral suspension; b- Cephalosporins must not be administered to subjects with immediate hypersensitivity reactions to penicillin (urticaria, angioedema or anaphylaxis).

Table 10. IE prophylaxis protocols (oral regimens) for dental procedures: recommendations of the BSAC (2006), the AHA (2007) and the ESC (2009) [48,53,58].

For children, the BSAC recommended amoxicillin (≥10 years, adult dose; ≥5-<10 years, 1.5 g; <5 years, 750 mg), clindamycin (≥10 years, adult dose; ≥5-<10 years, 300 mg; <5 years, 150 mg) or azithromycin (≥10 years, adult dose; ≥5-<10 years, 300 mg; <5 years, 200 mg). For children, the AHA recommended amoxicillin (50 mg/kg body-weight), clindamycin (20 mg/kg body-weight), cefalexin (50 mg/kg body-weight), or azithromycin or clarithromycin (15 mg/kg body-weight). For children, the ESC recommended amoxicillin (50 mg/kg body-weight) or clindamycin (20 mg/kg body-weight).

For children, the AHA and ESC recommended ampicillin or amoxicillin (50 mg/kg body-weight), clindamycin (20 mg/kg body-weight), or cephalexin, cefazolin or ceftriaxone (50 mg/kg body-weight).

For children, the BSAC recommended amoxicillin (≥10 years, 1 g; ≥5-<10 years, 500 mg; <5 years, 250 mg) or clindamycin (≥10 years, 300 mg; ≥5-<10 years, 150 mg; <5 years, 75 mg).

A second conclusion reached by the NICE was that "*It is not possible to determine the effect of antibiotic prophylaxis on the duration of bacteraemia*". Probably influenced by the idea that

	PARENTERAL REGIMEN	
BSAC, 2006	**NOT ALLERGIC TO PENICILLIN**: 1 g of amoxicillin (IV) just before tmt or at induction of anaesthesia **ALLERGIC TO PENICILLIN**: 300 mg of clindamycin (IV)[a] just before tmt or at induction of anaesthesia	
AHA, 2007	**NOT ALLERGIC TO PENICILLIN**:	2 g of ampicillin (IM or IV) 30 min before tmt
	ALLERGIC TO PENICILLIN:	1 g of cefazolin or ceftriaxone (IM or IV) 30 min before tmt[c] 600 mg of clindamycin (IM or IV) 30 min before tmt
ESC, 2009	**NOT ALLERGIC TO PENICILLIN**:	2 g of ampicillin (IV) 30 min-1 h before tmt
	ALLERGIC TO PENICILLIN:	2 g of cephalexin (IV) 30 min-1 h before tmt 1 g of cefazolin or ceftriaxone (IM or IV) 30 min before tmt[c] 600 mg of clindamycin (IV) 30 min-1 h before tmt

tmt= treatment; min= minutes; h= hours; IM= intramuscular; IV= intravenous; mg= milligrams; g= grams.

a- Given over at least 10 min; b- Given over 2 hours; c- Cephalosporins must not be administered to subjects with immediate hypersensitivity reactions to penicillin (urticaria, angioedema or anaphylaxis).

Table 11. IE prophylaxis protocols (parenteral regimens) for dental procedures: recommendations of the BSAC (2006), the AHA (2007) and the ESC (2009) [48,53,58].

bacteraemia secondary to dental procedures is of a transitory nature, few studies have been published on the effect of antibiotic prophylaxis on the duration of post-dental extraction bacteraemia [40]. On this question, the results of our research group have shown that the prophylactic administration of oral amoxicillin (2 g) significantly reduces the prevalence of bacteraemia at 15 minutes and 1 hour after completing dental extractions under general anaesthesia [62]. The conclusions reached by the NICE on the lack of efficacy of antibiotic prophylaxis for the prevention of bacteraemia following dental procedures are based on a small volume of published scientific evidence [59]. Further research should therefore be performed on the recommended antibiotics regimens for IE prophylaxis, analysing the influence of the choice of antibiotic and the time and route of administration, and also on new antibiotic protocols [40].

Antibiotic administration does carry a small risk of anaphylaxis [58]. However, no case of fatal anaphylaxis has been reported in the literature after the oral administration of amoxicillin for IE prophylaxis [63]. Widespread and often inappropriate use of antibiotics may result in the emergence of resistant microorganisms [58], but the extent to which antibiotic use for IE prophylaxis could be implicated in the general problem of resistance is unknown [64].

3.5. Antiseptics

In 1977, the AHA suggested for the first time performing disinfection of the gingival sulcus as a complement to antibiotic prophylaxis, although they recommended caution in the use of oral

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irrigators in patients considered to be at risk of IE, particularly in the presence of deficient oral hygiene habits [44]. This approach was also adopted by the BSAC en 1982 [49], when it recommended the application of antiseptics at the gingival margins in addition to the prophylactic administration of antibiotics prior to dental manipulations.

In 1990, the AHA recommended the application of chlorhexidine or other antiseptics (povidone iodine or a combination of iodine and glycerine) for 3 to 5 minutes around the tooth—a proposal also supported by the BSAC at that time [51]—before performing dental extractions in patients considered to be at high risk of IE and/or with deficient oral hygiene [46]. Two years later, the BSAC specified the form of presentation and the concentration of chlorhexidine to be used before starting a dental procedure: 1% gel at the gingival margin or 0.2% mouthwash for 5 minutes [52].

In the European Consensus of 1995, the application of antiseptics was once again recommended as a complementary measure in addition to antibiotic prophylaxis [54]. In its 1997 recommendations, the AHA recognised the need to use antiseptic mouthwashes (chlorhexidine or povidone iodine) prior to a dental manipulation, although they did not favour their application using gingival irrigators and recommended against the continual use of antiseptics in order to avoid the selection of resistant microorganisms [47]. Paradoxically, in their protocols on the prevention of IE secondary to dental manipulations published in 2004, the ESC and the BCS jointly with the RCP made no reference to the use of antiseptics before starting a manipulation [55,56].

In 2006, the BSAC recommended that, when possible, and in addition to the antibiotic prophylaxis, a pre-operative mouthrinse with 0.2% chlorhexidine gluconate should be performed, holding the antiseptic in the mouth for 1 minute [53]. In contrast, in its latest IE guideline, the Expert Committee of the AHA did not recommend the use of antiseptic prophylaxis before at-risk dental procedures [48].

With regard to the effect of chlorhexidine prophylaxis on the intensity and duration of bacteraemia following dental procedures, the NICE concluded that "*Chlorhexidine used as an oral rinse does not significantly reduce the level of bacteraemia following dental procedures*" [57]. This conclusion was reached after analysis of certain studies on the efficacy of chlorhexidine prophylaxis for the prevention of post-dental manipulation bacteraemia; those studies presented methodological differences with respect to the dental procedure performed, the concentration of chlorhexidine used, and the technique for applying the antiseptic solution (mouthwash and/or irrigation). These important differences make a comparison of the results between the different series inappropriate [59].

Very few studies have been published on the efficacy of mouth rinsing with 0.2% chlorhexidine (recommended by the BSAC in 2006) for the prevention of post-dental extraction bacteraemia [65]. Our research group demonstrated that initial rinsing with 0.2% chlorhexidine significantly reduced the duration of post-dental extraction bacteraemia [66,67]. These results allow us to speculate that the efficacy of antibiotic prophylaxis could be improved by the simultaneous application of chlorhexidine prophylaxis, although there is no scientific evidence to support this hypothesis.

The conclusions reached by the NICE on the lack of efficacy of antiseptic prophylaxis for the prevention of bacteraemia following dental procedures are based on a small volume of published scientific evidence [59]. At the present time, the controversies concerning the risk of developing IE of oral origin, the clinical repercussions of bacteraemia of oral origin, the efficacy of antibiotic prophylaxis and the risk-benefit and cost-benefit relationships of antibiotic prophylaxis could justify the reappraisal of the need for antibiotic prophylaxis for the prevention of IE currently being undertaken by the scientific community. Further research should be encouraged to confirm the efficacy of the recommended chlorhexidine regimens and to investigate new antiseptic protocols [59].

4. Conclusions

Over the past 50 years, prophylactic regimens for the prevention of IE secondary to dental procedures have been modified but remain consensus based. The indication for prophylaxis is now limited to patients with the highest risk of IE undergoing the highest risk dental procedures. The most recent prophylactic protocols published by the BSAC, the AHA and the ESC continue to recommend amoxicillin as the antibiotic of choice for oral prophylaxis. For individuals who are allergic to penicillins, the use of clindamycin, cephalexin or another first-generation oral cephalosporin, azithromycin or clarithromycin is recommended. However, the NICE has adopted a drastic stance in this respect, recommending the cessation of antibiotic prophylaxis for IE in individuals undergoing dental procedures in the United Kingdom. Further research should be encouraged to determine the impact of this recommendation of the NICE guideline.

All Expert Committees on IE prevention agree on the premise that "Good oral hygiene and regular dental checkups are of particular importance for the prevention of IE of oral origin".

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