Antimicrobial prophylaxis in oral surgery and dental procedures

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Received: 1-9-2006
Accepted: 31-11-2006

Maestre-Vera JR, Gómez-Lus Centelles ML. Antimicrobial prophylaxis in oral surgery and dental procedures. Med Oral Patol Oral Cir Bucal 2007;12:E44-52.

Indexed in:
-Index Medicus / MEDLINE / PubMed
-EMBASE, Excerpta Medica
-SCOPUS
-Indice Médico Español
-IBECS

ABSTRACT

Transient bacteraemia is a known risk factor following oral surgery and invasive dental procedures in patients with altered immune system response and those with a susceptible site of infection (patients with heart valve prostheses or recent joint replacements, etc.) The most commonly isolated aerobic bacteria in postoperative bacteraemia are *Streptococcus Viridans*. However, other periodontal pathogenic anaerobic bacteria are found in up to 64% in blood cultures (mixed bacteria or anaerobic bacteria alone). Dental pathogenic bacteria do not appear to be covered by standard amoxicillin or clindamycin prophylactic regimens. This is partly due to the fact that these anaerobic bacteria often produce beta lactamase and also in view of results of antimicrobial sensitivity tests observed in recent studies.

A personal history of exposure to dental pathogenic bacteria may have an impact on the patient's global health, not only because of classical local or systemic infectious complications, but also because dental pathogenic bacteria have been found in atheromatous plaques in coronary and carotid arteries. This finding, along with epidemiological data, suggests that such bacteria may contribute to the progression of vascular arteriosclerotic lesions and the occurrence of cardiovascular and/or cerebrovascular accidents, although the pathogenic mechanisms involved are not yet well known. Taking these facts into consideration, and in view of antimicrobial sensitivity data available at present, we believe that the use of amoxicillin/clavulanic acid is the most appropriate option for prophylaxis of all infectious risks associated with bacteraemia of oral origin, due to its broader cover of dental pathogenic bacteria and its pharmacokinetic profile.

Key words: *Prophylaxis, amoxicillin/clavulanic acid, oral surgery, dental procedures*

RESUMEN

Tras la cirugía oral y los procedimientos odontológicos invasivos, la bacteriemia transitoria es un factor de riesgo conocido para los pacientes que sufren alteraciones del sistema inmune y para aquellos que presentan focalidad susceptible (pacientes con prótesis valvulares cardiacas o prótesis articulares recientes, entre otros). Los *Streptococcus* viridans son las bacterias aerobias aisladas con mayor frecuencia en las bacteriemias postquirúrgicas orales; no obstante otras bacterias odontopatógenas anaerobias se encuentran por hemocultivo hasta en el 64% de los casos (tratándose en estos casos de bacteriemias mixtas o exclusivamente anaerobias). Las bacterias odontopatógenas no parecen bien cubiertas con el régimen profiláctico estándar de amoxicilina o clindamicina, debido, entre otras causas, a la frecuente produc-

ción de betalactamasas por dichas bacterias anaerobias y a los resultados de las pruebas de sensibilidad antimicrobiana observados en estudios recientes.
La historia personal de exposición a bacterias odontopatógenas puede repercutir en la salud global del individuo, no sólo por las complicaciones infecciosas clásicas: locales o sistémicas, sino por el hecho de haber sido encontradas bacterias odontopatógenas en placas de ateroma de arterias coronarias y carótidas; sugiriendose con este hallazgo, y por los datos epidemiológicos, que puedan contribuir (por mecanismos patogénicos aún no bien conocidos) a la progresión de lesiones vasculares arterioescleróticas y a la aparición de accidentes cardiovasculares y/o cerebrovasculares. Tomando en consideración estos hechos y los datos de sensibilidad antimicrobiana disponibles, el empleo de amoxicilina/clavulánico nos parece la opción más adecuada como profilaxis de todos los riesgos infecciosos asociados con la bacteriemia de origen oral, por su mayor cobertura frente a las bacterias odontopatógenas y su mejor perfil farmacocinético.

Palabras clave: *Profilaxis, amoxicilina/clavulánico, cirugía oral, procedimientos odontológicos.*

1. ORAL MICROBIOTA AND DENTAL PATHOGENIC FLORA

The mouth is one of the areas of our body with the greatest microbial population and variety. Different ecosystems can be found in the mouth, where over 200 different aerobic and anaerobic bacterial species live. (1) Oral bacteria (dental or commensal pathogens) and their products (toxins) may move from this primary location to other neighbouring or distant locations. Invasive dental procedures and oral surgery favour bacterial dissemination, especially into the bloodstream, causing transient bacteraemia.

Transient bacteraemia is unavoidable, but its severity (bacterial load), duration (time in which bacteria remain in the bloodstream), type of bacteria in the blood (aerobic, anaerobic or mixed) and the patient's predisposition (underlying diseases, susceptible site of infection, etc.), all play a significant role in the onset of possible complications.

Bacteraemia, initially considering mono-microbial bacteraemia, is caused by contamination/infection of the normal oral and dental pathogenic microbiota during the surgical procedure. Since the thirties, we have known that 75% of patients with caries, gingivitis and periodontitis will have positive *Streptococcus* blood cultures following dental procedures, in comparison with 30% in healthy subjects. (2, 3) Predominant organisms are *Streptococcus* from the *viridans* group (4), *Staphylococcus spp* and, in 4-7% of cases, gram-negative HACEK bacilli (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, *Kingella*), several of which are considered as dental pathogens. (5) We should not neglect the existence of mixed (aerobic/anaerobic) bacteraemia, or anaerobic bacteraemia alone (*Eubacterium*, *Peptostreptococcus*, *Propionibacterium*, *Lactobacillus*), which are detected in a significantly high percentage of cases when an appropriate microbiological method is used (oxygen-free blood cultures for anaerobic recovery). (6-8)

2. BACTERAEMIA AND ITS RISKS

The following questions arise when discussing bacteraemia:

• **How and when does it occur?** The frequency of bacteraemia varies significantly from one study to another, ranging from 0 to 88% depending on procedures analysed. Thus, it has been observed more frequently in invasive oral procedures with a higher level of bleeding, such as tooth extractions and periodontal surgery. (3-9) However, transient bacteraemia has also been observed following tooth brushing, chewing and cleaning with dental floss, although there is probably a lower bacterial load and shorter-lived bacteraemia in these cases, with less consequences for the patient than those that arise following invasive procedures.

• **What is the inoculum or bacterial load?** The number of bacteria in the blood is unknown, since a laborious microbiological analysis (quantitative blood cultures) is required to assess this. However, we can presume that the bacterial load is greater and probably more persistent in invasive processes and in patients who present periodontal inflammation.

• **What type of bacteria is involved?** Aerobic and anaerobic. Lockhart PB et al (9) observed bacteraemia in 84% of children undergoing dental procedures and identified 29 different species of micro-organisms in blood cultures performed. Rajasuo A et al (7) observed transient bacteraemia in 88% of patients undergoing tooth extraction (50% within the first minute following incision), 74% of which were anaerobic bacteria (*Prevotella, Eubacterium* and *Peptostreptococcus*). Otten et al (8) observed bacteraemia following tooth extraction in 74% of patients studied, 64.2% of which were mixed bacteria (aerobic/anaerobic), isolating *S. viridans* in 50% of cases. However, in 35.8% of these cases anaerobic bacteria alone were found. What effects might these anaerobic bacteria have on a susceptible patient? We will return to this subject later.

• **How long does the bacteraemia last?** Bacteraemia peaks during the first two minutes following tooth extraction or invasive dental procedure, and falls in time. However, oral bacteria have been found on blood culture after 1 to 45 minute periods, following tooth extraction. (9)

• **What future awaits these bacteria in the bloodstream**? In theory a healthy immune system is capable of eradicating bacteria from the blood stream in just a few minutes. However, dental pathogenic bacteria have been found in atheromatous plaques in carotid and coronary arteries, and therefore there is some degree of uncertainty regarding their possible pathogenic role, either directly, or indirectly (through inflammation) in cardiovascular disease. (10,11)

• **Are there susceptible sites in patients?** Yes/no. Short, medium and long-term risks vary according to these circumstances. Patients who are more susceptible to infections following bacteraemia are those who have endocardial risks, bone prostheses and joint replacements. (12) But in what other circumstances does bacteraemia imply a risk? Has the patient got incipient, silent vascular arteriosclerotic lesions in carotid or coronary arteries? Are these lesions susceptible sites for the growth of bacterial colonies resulting from dental pathogenic bacteria in the bloodstream? What pathogenic role might oral bacteria play in cardiovascular disease? Recent studies using PCR techniques on samples obtained from carotid endarterectomy have detected periodontal pathogenic bacteria in atheromatous plaques in severely damaged vessel walls. (13, 14) Furthermore, other authors have related periodontal inflammation with thickening of carotid artery walls. (10) In vitro studies have observed that *Streptococcus viridans* and dental pathogenic bacteria such as *P. gingivalis,* are capable of inducing platelet aggregation and hypercoagulability. (15,16) Song H et al (17) observed that haemagglutinin (HagB), present in the gram-negative anaerobic bacteria *P. gingivalis*, plays a significant role in the capacity of this periodontal pathogenic bacteria to adhere to human coronary artery endothelial cells. Li L et al (18) investigated the effect of repeated intravenous inoculation of *P. gingivalis* in an animal model. Their results indicate that this dental pathogenic bacterium is capable of accelerating the progression of atheromatous plaques. Coinciding with these results, Brodala N et al (19) proceeded to administer repeated intravenous injections of *P. gingivalis* in experimentation animals (pigs) and then analysed their carotid and coronary arteries. The authors observed that recurrent bacteraemia induced arteriosclerotic lesions in normocholesterolaemic animals and increased lesions in hypercholesteraemic animals. *P. gingivalis* was detected using PCR in 94% of the arteries of the inoculated animals, but not in the control group. In the light of these results, is there a causal relationship between these bacteria and the evolution of atheromatous plaques, in the formation of thrombi in pre-existing arterial plaques, or in bringing on cardiovascular accidents in human beings? Is this all an insignificant, coincidental finding? Or are we missing something?

• **Are there any other underlying circumstances that predispose a patient to suffering an infectious complication following bacteraemia?** The following patients are particularly susceptible to suffering local and systemic infections: immunocompromised patients, cancer patients, patients with congenital or acquired immunodepression (e.g. lupus erythematosus), patients with drug-induced immunodepression (steroid therapy, chemotherapy), recent recipients of transplants, grafts or other causes, patients with infectious immunodepression (acquired immunodeficiency syndrome), patients with metabolic disorders (diabetes), splenectomies, and with kidney or liver failure. (12, 20, 21)

• **Can bacteraemia be avoided?** No, but its negative impact on patients' health can be reduced. Lockhart PB et al (9) studied the impact of amoxicillin prophylaxis on the incidence, nature and duration of bacteraemia in 100 children undergoing tooth extraction and other dental procedures. They observed that the incidence of bacteraemia (detectable on blood culture) was lower in the group that received prophylaxis (33% incidence) in comparison with the placebo group (84%). They also observed that in the placebo group the bacteraemia lasted longer (in some cases up to 30 or 45 minutes after tooth extraction), whereas in the group that received prophylaxis, no bacteraemia was found after 15 minutes following the intervention. Anaerobic bacteria were the most persistent bacteria in the blood. Would it be a good idea to consider early eradication of bacteraemia, especially in patients who are more susceptible to suffering infectious complications?

• **What negative repercussions does bacteraemia have on a patient on a short and medium term?** In patients with a susceptible site of infection, such as those who have a mitral valve prosthesis and are to undergo oral surgery, bacteria in the bloodstream could colonise the valve and/or perivalvular tissue, causing infective endocarditis weeks or months after surgery. (5,12,22) To reduce the risk of infection, patients with a susceptible site of infection (with cardiopathy, recent joint replacements, etc.) who are to undergo any invasive oral procedure, should be given systemic pre-operative antimicrobial prophylaxis. (12, 22,23)

• **Are there any prophylaxis regimens that are used to prevent infective endocarditis?** Although action protocols have been widely diffused in scientific journals, in the academic and professional media, there is a serious concern regarding the lack of information and application of prophylaxis regimens amongst health professionals. Thus, Tomás I et al (24) conducted a survey amongst 400 Spanish dentists selected at random in 2004, and observed that 45% of dentists did not recommend any prophylactic regimen in patients at risk (valve prosthesis carriers) prior to surgery. Of the dentists who recommended prophylaxis, 30% did so correctly for patients who were not allergic to beta lactamics and 28.3% did so correctly for those who were allergic to penicillin. The authors were concerned by these results. Clearly, there is still much ground to be covered.

• **What long-term repercussion might there be from exposure to dental pathogenic bacteria?** The micro-organisms and their products (toxins) that are present in the mouth can reach any part of the body through the blood. Geerts SO et al (25) observed that endotoxaemia could be induced simply by chewing, and the risk was greater in patients with periodontal disease. Forner L et al (26) observed that there was a higher level of bacteraemia following scaling in patients with periodontitis than in that observed in patients with gingivitis and in healthy subjects. Epidemiological data suggest that the infection that is present in the periodontal tissues may spread into the bloodstream and contribute towards arteriosclerotic progression. Different authors who have conducted studies using rigorous methodologies have found that there is an association between periodontitis and cardiovascular disease, regardless of other factors. (11) However, not all studies have established this positive association. (27) The discrepancy continues, since the pathogenic mechanism is unknown and the causal relationship remains unclear. However, it is possible that a patient's exposure to dental pathogenic bacteria contributes towards the onset of cardiovascular and cerebrovascular accidents, at least as a risk factor. If this situation is confirmed, how should we approach bacteraemia of oral origin in medical practice and dentistry? In periodontal disease, it can be observed that the host shows a systemic inflammatory response, with elevation of C-reactive protein and other reactants during the acute phase, and this may contribute, in part, to these patients' higher risk of cardiovascular disease. On the same line, some authors have observed that periodontal treatment with antimicrobials reduces C-reactive protein and tumour necrosis factor (TNF-alpha) levels, which may be beneficial for patients, since high levels of these factors may be associated with an increased risk of developing arteriosclerosis in patients with periodontitis. (28) Would it be wise to give systemic antibiotics to eradicate dental pathogenic bacteria in patients who are particularly susceptible? Should antibiotics also be administered as prophylaxis to prevent cardiovascular and cerebrovascular accidents in selected patients? What global benefits would be obtained? Which antibiotics would be the best to cover aerobic and anaerobic dental pathogen bacterial flora? What role do dentists and maxillofacial surgeons play in public health and health prevention issues that are apparently far removed from their own professional practice? What implications might there be in conserving good mouth and dental health in a person's overall well-being, now and in the future? These questions and others arise when discussing this subject, and while they are being answered, mistakes are being accounted for and the truth is being revealed, we would like to make a few comments about the suitability of antibiotic prophylaxis in oral surgery.

3. ANTIBIOTIC PROPHYLAXIS IN ORAL SURGERY

Traditionally prophylaxis has been defined as pre- and peri-operative administration of antibiotics in order to prevent local and/or systemic post-operative infection. In Altemeier's classification, oral surgery is often graded as class II (clean-contaminated surgery), with a rate of local infection of 5 to 15% without antibiotics and <7% with antibiotics. (20)

In oral surgical prophylaxis, the target microbiota differs depending whether the intention is to prevent **local complications** (phlegmon, abscess) or **distant infections** (endocardial infections, bone prostheses, joint replacements) in risk patients who require prophylaxis because of their underlying condition. In order to prevent local infection, target microbiota is usually polymicrobial because many species tend to be isolated in pairs (*Bacteroides* sp. and *Fusobacterium*; *Peptostreptococcus* sp. and *Prevotella* sp.; *Prevotella* sp. and *Eubacterium* sp.), with a marked aerobic/anaerobic component (29), and to a much lesser extent microaerophilous component, since these infections originate from the possible surgical contamination/infection from the normal microbiota of the mouth and saliva, and from dental pathogens in the periodontal disease, which has a very high prevalence in the general population (it is estimated that about 50% of adults have gingivitis and 30% have periodontitis). (30)

Systemic infections that should be prevented in patients with underlying disease are caused by bacteraemia, especially following invasive procedures. (12)

4. ANTIMICROBIAL SPECTRUM

The choice of the antimicrobial spectrum used for prophylaxis should take the following into consideration: bacteria that are normally present in the mouth (potential pathogens such as *Streptococcus Viridans*), aerobic and anaerobic bacteria detected in bacteraemia of mouth-dental origin, bacteria involved in odontogenous infection, and all bacteria involved in local and systemic complications. Three types of bacteria should be considered, in view of their clinical significance:

1. Periodontal pathogens that cannot be cultured or are difficult to isolate, e.g. Treponemas such as *T. denticola* (and other spirochaeta), which are sensitive to penicillin and present aetiopathogenic specificity for severe periodontitis.
2. Anaerobic gram-negative bacteria such as *Prevotella spp and Fusobacterium spp* (these are the most prevalent anaerobic bacteria in dental infections such as periodontitis, pericoronaritis, periodontal and periapical abscesses). Approximately 50% of these bacteria produce inactivant enzymes (ß-lactamases). Some of them are also detected in mixed bacteraemia.
3. Aerobic gram-positive bacteria such as *Streptococcus viridans*, responsible for post-operative bacteraemia in oral procedures and distant complications such as endocarditis.

5. CAN INFECTIOUS COMPLICATIONS BE AVOIDED BY USING AMOXICILLIN OR CLINDAMYCIN PROPHYLAXIS?

Dental pathogenic bacteria do not show homogeneous sensitivity to antibiotics. When selecting an antibiotic, we need to refer to the largest, most recent and most reliable studies, amongst the little research that has been conducted in this field. As mentioned earlier, local infections are usually polymicrobial and mixed, and they involve bacteria from the three above groups. Distant complications, such as infective endocarditis, are usually mono-microbial, and usually involve gram-positive bacteria such as *S. viridans*. When choosing an antibiotic for prophylactic or therapeutic use in dental procedures or oral surgery, the aim should be for the antibiotic spectrum of action to cover all three types of dental pathogenic bacteria mentioned above. (12) In fact, assuming that standard antibiotic prophylaxis is amoxicillin or clindamycin, it does not appear that these requirements are met for different reasons, in view of the sensitivity presented by dental pathogenic micro-organisms as observed in recent studies. (31, 32) In our experience, although amoxicillin efficiently covers the spectrum of aerobic bacteria such as *Streptococcus viridans,* it would not be appropriate to use it to cover other anaerobic bacteria or beta lactamase producing dental pathogens (approximately 50% of anaerobic gram-negative bacteria isolated in the mouth produce beta lactamase). With regard to clindamycin, 10% of aerobic gram-positive bacteria (oral *Streptococcus)* are resistant to clindamycin, and 21% of anaerobic bacteria that we have isolated in cases of adult periodontitis are also resistant to this antibiotic. (31)

6. ANTIMICROBIAL OPTIONS FOR PROPHYLACTIC OR THERAPEUTIC PURPOSES

ß-lactamics: Penicillin G (parenteral), or phenoxymethylpenicillin (oral), continues to be one of the drugs of choice in dentistry and oral surgery because the majority of oral aerobic and anaerobic bacteria are sensitive to it. However, there are an increasing number of oral anaerobic bacteria that produce inactivant enzymes (ß-lactamases), making them resistant to penicillin, and leading to treatment failure. (33, 34) Recently, we conducted a study to analyse 261 aerobic and anaerobic bacteria isolated in 48 adult patients with periodontitis (31). We observed that 54.1% of bacteria of the *Prevotella* genus, 38.9% bacteria of the *Fusobacterium* genus, and 30% of the *Capnocytophaga* genus, produced ß-lactamase. For this reason, ß-lactamics that are capable of resisting the action of these enzymes, such as the amoxicillin + clavulanic acid association, have become the antibiotic of choice for oral infections. In our study, 100% of the dental pathogenic strains (both aerobic and anaerobic) that were isolated in patients with periodontitis were sensitive to the amoxicillin + clavulanic acid association. 100% of *Streptococcus viridans* were also sensitive to aminopenicillins. (31)

Van Winkelhoff et al (35) reviewed subgingival bacterial microbiota susceptibility in adult patients with periodontitis in the Netherlands and Spain. They found significant differences between the levels of microbiota resistance in the two populations. A high level of resistance was found to penicillin, amoxicillin, clindamycin and particularly tetracycline amongst the Spanish patients. In our experience, 22% of *Streptococcus viridans* and *Prevotella spp*, were resistant to tetracycline. (31)

Metronidazole: In a recent study, Brescó et al (32) observed high resistance (50.5%) in bacteria isolated in patients with pericoronaritis and periapical lesions. We already know that aerobic gram-positive cocci such as *S. viridans* are usually resistant to this antimicrobial agent. In our series (31), 6% of bacteria of the *Prevotella* genus were also resistant.

Macrolides: Macrolides are not considered as first line drugs in the treatment of dental infections. (36) Anaerobic dental pathogenic bacteria are resistant, and up to 47.7% of streptococci isolated in our series were resistant to azithromycin. (31) Data from other studies indicate that in *S. viridans*, the high resistance to Macrolides (erythromycin and clarythromycin) is often associated with a high resistance to tetracycline and clindamycin. (37) In Spain, Tomás I et al (38) demonstrated high prevalence of oral iatrogenic bacteraemia caused by streptococci resistant to erythromycin (40.8%) and clindamycin (21%), and the majority of bacteria isolated were sensitive to aminopenicillins.

Clindamycin: Traditionally it has always been thought that very low concentrations of this antibiotic inhibit anaerobic bacteria growth. However, in our experience, up to 21.1% of *Prevotella* bacteria (the most commonly isolated anaerobic bacteria in the aforementioned study on adult periodontitis) (31) were resistant to clindamycin. Amongst the aerobic gram positive bacteria, it was observed that 10% of *S. viridans* bacteria were resistant to clindamycin. (31)

7. EFFECTIVE/INEFFECTIVE COVER OF THE TARGET ORAL MICROBIOTA. CONSEQUENCES

Pharmacodynamic cover is understood as the value of "the relation between serum pharmacokinetic parameters and in vitro susceptibility", thus predicting efficacy in terms of a) the dose percentage interval at which levels that exceed the MIC (minimum inhibitory concentration for in vitro bacterial growth), must be over 40-50% for ß-lactamics, macrolides and lincosamides, and b) the relation of the area under the curve of serum levels /CMI that must be over 25 for azalides (azythromycin). According to studies conducted on amoxicillin + clavulanic acid (39), spiramycin and metronidazole (49), antibiotic concentrations in gingival fluid are similar to or higher than serum levels. According to studies that have applied the concepts of pharmacokinetics and pharmacodynamics in dentistry, and analysed different antibiotics used for the five most prevalent bacteria isolated (but not all bacteria involved) in dental infections (V*iridans group streptococci*, *Peptostreptococcus* sp., *Prevotella inter-*

media, *Porphyromonas gingivalis* and *Fusobacterium nucleatum*) (41), the only antibiotics that meet pharmacodynamic requirements are amoxicillin + clavulanic acid, at a dose of 875/125 mg / 8hrs, its new formulation of 2000/125 mg / 12 hrs, and clindamycin 300 mg / 6-8hrs. However, clindamycin does not cover the following genera appropriately: *Staphylococcus*, *Streptococcus* and *Peptostreptococcus*, because they present a notable level of resistance. (20) metronidazole, macrolides and spiramycin do not cover all gram positives (*Streptococcus* and *Peptostreptococcus*) and the latter two antibiotics do not cover *Fusobacterium* either. (41)

8. ANTIBIOTIC PROPHYLAXIS

8. 1. Which infectious complications need to be prevented?

There are four types of infections that need to be prevented:

a) local infections and their consequences (phlegmon, abscess, tooth loss, loss of implants and prostheses).

b) generalised systemic or local infections in patients with altered immune system response.

c) systemic infections with a focal point of infection caused by a focal underlying condition in a patient who is susceptible to infection (endocardial alterations, bone prostheses and joint replacements).

d) vascular colonisations that induce lesions in susceptible patients.

8. 2. Which patients and conditions require prophylaxis?

Non-invasive dental procedures do not normally require prophylaxis. In a healthy subject, the need for prophylaxis is based solely on the risk that the procedure entails (21); there is a high risk inherent to transplants, reimplants, grafts, tumour surgery and bone surgery (as in the case of orthopaedic and trauma surgery), as well as in periapical surgery, dental inclusions and possibly in root canal retreatment, where there may be previous infection. (20,21)

In patients at risk of systemic or local infection due to altered immune system response, antibiotic prophylaxis is indicated in intraligamental local anaesthesia, endodontic prosthetic care, curettage, drilling, tooth loss, transplants/reimplants, periapical surgery, periodontal surgery, bone surgery, frenectomy, salivary gland biopsy and dental-facial orthopaedics, because they are all invasive procedures. (12)

In patients with risk factors for focal infection following bacteraemia (endocarditis, prosthetic infection), prophylaxis is always indicated for invasive procedures performed in these patients. (12) The French Agency for Health Product Health Safety advises against or contraindicates dental-facial surgery, bone surgery, periodontal and periapical surgery, including root canal retreatment, root amputation, and reimplants in these patients, except under very specific circumstances, because there is such a high risk of infection. (20,21)

8.3. Which is the most appropriate prophylactic regimen for preventing the risk of bacteraemia?

As mentioned earlier, systemic infectious complications are usually mono-microbial and occur as a result of bacteria passing directly into the bloodstream and then spreading in the blood. Bacteraemia that occurs following an invasive oral procedure can significantly increase in the presence of periodontal disease. (42) This is due to the permeability of the epithelium that surrounds the tooth-tissue interface at a level of the prostaglandins in the local circulation that increase the number of leukocytes, and also because of fibrinogen levels, slowing down the circulation in both cases, and thus favouring the movement of bacteria into the bloodstream. (42) Thus, in animal models, endocarditis following bacteraemia occurred in 48% of rats with periodontal disease versus 6% in healthy rats. (43) In humans, the rate of bacteraemia following invasive oral procedures varies according to cases, but different studies have reported rates of 51-88%. (4, 7-9)

Distant infectious complications (systemic), are associated with aerobic bacteria, and oral *viridans* group streptococci in particular. They occur in patients with a susceptible site or with underlying disease. Thus, following dental procedures, bacteraemia caused by *Streptococcus* has been detected in 75% of patients with periodontal disease and up to 30% of patients without the latter disease. (2,3) Bacteraemia caused by dental procedures is significantly associated with infective endocarditis. It is estimated that 14-20% of infective endocarditis cases are of an oral origin. (4, 44)

What can be said of anaerobic bacteria detected on blood culture following dental procedures and oral surgery? What pathogenic role might long-term complications play, especially in patients with silent vascular lesions? Would prophylactic administration of amoxicillin or clindamycin be effective in avoiding these complications? What other antibiotics could cover the spectrum of dental pathogens in our setting?

Rajasuo A et al (7) observed bacteraemia in 88% of patients who underwent tooth extraction, and 74% of these cases were caused by anaerobic bacteria (*Prevotella, Eubacterium* and *Peptostreptococcus*). Otten et al (8) observed bacteraemia following tooth extraction in 74% of patients studied, and 35.8% of these were anaerobic bacteria alone.

In view of all of this, if the objective of prophylaxis is to prevent all possible complications derived from bacteraemia, it seems clear that the ideal cover is achieved through high doses of amoxicillin/clavulanic acid, because of the significantly frequent production of ß-lactamase in *Prevotella, Fusobacterium* and *Capnocytophaga* (31) and because of high resistance to tetracyclines (37) and azalides (azithromycin). (31). A problem may arise in patients who are allergic to ß-lactamics, where the choice of clindamycin appears to be the most logical, since *S. viridans* resistance is much higher in tetracyclines and macrolides, and macrolides are not active against *Prevotella*. Since bacteraemia is transient and short-lived, prophylaxis should be administered 30 to 60 minutes before the dental procedure. A single dose is sufficient.

8.4. Specific prophylaxis for infective endocarditis

As we have already seen, the incidence of transient bacteraemia has been widely studied, and stands at 60% and

88% following tooth extraction and periodontal surgery, respectively. (9, 22, 45) However, the pathogenic role of anaerobic periodontal pathogens and/or of the HACEK group in causing infective endocarditis is a completely different question (12), while the presence of certain species in blood, fundamentally viridans group streptococci, has a much greater specific weight in this condition than in the overall incidence of bacteraemia. (45) This is why it has always been believed that streptococci should be the target in preventing infective endocarditis, and if the latter occurs, it normally does so within two weeks of the dental procedure (22, 23) in risk patients. Antibiotic prophylaxis does not only act by killing bacteria, but also by inhibiting bacterial adherence. (46)

The risk can be calculated by multiplying harm by the probability of suffering such harm. In the case of infective endocarditis the risk is based on the catastrophic results it causes instead of its frequency, that varies from 1/115,500 patients (47) to 1.5/100 in the case of patients with valve prostheses. (22)

The risk depends on pre-existing cardiac factors and on the dental procedure. Logically, the risk of streptococcal viridans bacteraemia is greater in certain invasive procedures such as those that involve the gingival sacs and in all oral surgery (high-risk procedures). With regard to the endocarditis site, pre-existing cardiac disorders may be high-risk (valve prostheses, previous endocarditis, congenital cyanotic heart disease, or pulmonary shunts), or low-risk (mitral valve prolapse or regurgitation, aortic stenosis or regurgitation, tricuspid or pulmonary valve defects, ventricular septal defects, degenerative valve disease in the elderly).

Prophylaxis is indicated in high-risk dental procedures in patients with pre-existing high-risk heart disorders. It is also recommendable, at the dentist's discretion, in high-risk dental procedures in patients with pre-existing low-risk heart disorders, and in low-risk dental procedures in patients with pre-existing high-risk heart disorders. (12)

The standard recommended regimen (23) includes high doses of amoxicillin in children and adults alike, 1 hour prior to the dental procedure. The prophylactic regimen in adults should include 2g of oral amoxicillin. (22) If findings in (mixed and solely anaerobic) bacteraemia of oral origin are heeded together with sensitivity data on dental pathogenic bacteria, we would suggest prophylactic administration of amoxicillin + clavulanic acid (2000/125), in order to afford the best cover against all potentially pathogenic bacteria that reach the bloodstream. This would ensure simultaneous eradication of aerobic and anaerobic bacteria that are susceptible of causing complications, and of secondary colonisation of dental pathogenic bacteria in vascular lesions.

Prophylaxis should be administered as a single dose except in cases where the procedure takes more than 2 hours, in which case another dose should be administered. Clindamycin or clarythromycin is recommended in patients who are allergic to ß-lactamics. (22) As mentioned earlier with regard to prevention of bacteraemia, macrolides and azalides do not appear to be appropriate in Spain because of the high rate of resistance shown by viridans group streptococci. Furthermore, patients with congenital heart disease are usually carriers of resistant micro-organisms, and this may cause prophylactic failure if the most appropriate antibiotic is not chosen. (48)

8.5. Specific prophylaxis against local infection

With regard to indications for prophylaxis against local infection, in the case of both healthy subjects and patients with altered immune system response as described earlier, the prophylactic regimen should cover the habitual microbiota as well as periodontic pathogens in view of the high prevalence of periodontitis in the population. Bearing in mind the resistance phenotypes discussed earlier (including ß-lactamase production on the part of the habitual anaerobic microbiota and of certain dental pathogens), and the pharmacodynamic cover required, it appears to be advisable to use high doses of amoxicillin together with a ß-lactamase inhibitor, such as clavulanic acid.

In certain circumstances, there is a problem in distinguishing between the term "prophylaxis" and the term "preventive treatment" regarding infection arising from surgery. In the study conducted in Spain, it was demonstrated that complications following third molar extraction included infective disease, and not just inflammatory disease, since significant differences were found in the frequency of infectious complications between groups receiving amoxicillin/clavulanic acid 2000/125mg as treatment (5 days), pre-operative prophylaxis (single dose) and placebo (2.7%, 5.3% and 16% respectively). (49) The rate of infectious complications was higher in the case of osteotomy or longer surgery, and in these cases treatment was clearly more effective than prophylaxis or placebo. (49) Only amoxicillin/clavulanic acid at a suitable dose and interval covers treatment requirements, followed by clindamycin, which starts to present problems in the case of streptococci, peptostreptococci and anaerobic gram-negative dental pathogenic bacteria.

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