Bacteremia originating in the oral cavity. A review

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Abstract

In patients at risk because of heart disease, bacteremias induced by invasive dental treatments have been reported as a cause of bacterial endocarditis (BE) - a serious disorder that continues to involve a high mortality. As a result, different scientific societies have supported recommendations for the administration of antibiotics prior to invasive dental treatments, in order to neutralize bacteremia. In this context, the recommendations of the American Heart Association (AHA) are the most widely used in our setting. Advances in our knowledge of the etiopathogenesis of bacterial endocarditis have placed increasingly less importance on invasive dental treatments as a causal factor (the AHA again reduced the number of cases in which antibiotic prophylaxis is recommended, on occasion of its latest guidelines update in 2007) - with increasingly greater importance being placed on factors associated with hygiene and oral health.

The present study offers a critical review of the relationship between dental treatment, bacteremia and bacterial endocarditis.

Key words: *Bacteremia, endocarditis, dental treatment, prophylaxis.*

Introduction

The presence of germs in the bloodstream is referred to as bacteremia. Blood cultures are used to identify bacteria in blood. The identification of certain virulent germs in blood (Neisseria meningitidis, Streptococcus pneumoniae, Salmonella typhi) is of diagnostic value in application to certain diseases. The difficulty arises when the microorganism detected in blood is a usual colonizer of the skin or mucosal membranes, and moreover does not prove positive on a continuous basis in blood cultures. Thus, in a patient with clinical manifestations of disease (e.g., bacterial endocarditis (BE)), successive blood cultures must be made, with an evaluation of other signs and symptoms in order to establish a precise diagnosis. Although dental professionals must be familiarized with the manifestations of such diseases, it is more relevant for them to know whether their dental activity is able to induce bacteremias, and to establish the degree in which such bacteremia can cause pathology in their patients. The present study provides a review of these aspects.

The germs in the oral cavity

The oral cavity is intensely colonized by bacteria. The maximum concentration is found in bacterial plaque, where it is estimated that there are between 10^{11} and 10^{12} microorganisms per gram of wet weight - though there

are also abundant bacteria on the back of the tongue and in the cheek and palatal mucosa (1). Up to 200 different bacterial species have been isolated from a single oral cavity in the course of time, though the usual residents number about 20. Although there are differences among the different oral ecosystems, globally the most abundant microorganisms are Streptococci of the viridans group (mitis, sanguis, salivarius, etc.) (2).

Any breach in the oral mucosal barrier places the internal body environment in contact with a highly contaminated ecosystem - resulting in the penetration of microorganisms into the bloodstream. It is then possible to identify the germs in the blood through blood cultures. Although it has been suggested that such bacteremia may be the cause of a number of processes (distant abscesses, kidney damage, failed joint prostheses, etc.), the disease with which bacteremia traditionally has been associated is bacterial endocarditis (BE) - an infection of the endocardium that produces general or systemic symptoms of infection, embolic phenomena and endocardial vegetations (Figures 1 and 2). Although patient fatalities associated with such alterations have decreased significantly, the mortality rate remains in the range of 5-11%. The germs most often related with BE are Streptococcus viridans and Staphylococcus aureus (21% and 23%, respectively, in absolute terms) (3) -though other microorganisms capable of causing BE have also been isolated from the oral cavity (enterococci, diphteroides, Coxiella, fungi, etc.). It comes as no surprise that some medical textbooks affirm that "in the classical form of endocarditis affecting native valve tissue, the most common antecedent is dental manipulation without the pertinent antibiotic prophylaxis, thus resulting in bacteremia due to Staphylococcus viridans…" (4).

It is essential for dental professionals to know whether bacteremia associated with the provided dental treatment is really capable of causing BE, if the risk is general for all patients and, if so, what measures can be taken to avoid such complications.

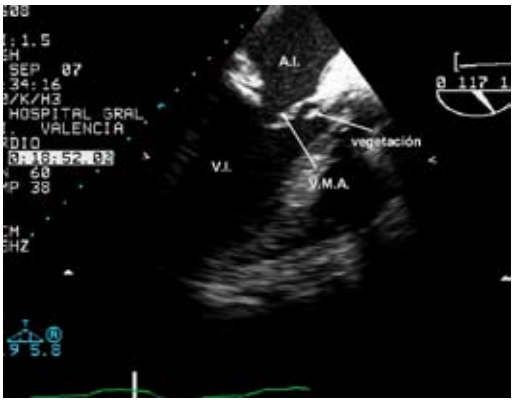

Fig. 1. Ultrasound view of vegetation in aortic valve. V.I: left ventricle. A.I.: left atrium. V.M.A.: open mitral valve.

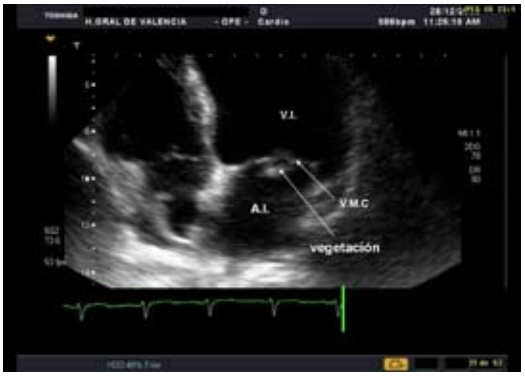

Fig. 2. Ultrasound view of vegetation in mitral valve. V.I: left ventricle. A.I.: left atrium. V.M.C.: closed mitral valve.

Dental treatment and bacteremia

Dental extraction is undoubtedly the oral surgical procedure where most research into bacteremia has been made ever since the relationship between both phenomena was established in the mid-twentieth century - though dental extraction is not the only example (5,6) (Table 1). The frequency of bacteremia is estimated to be between 39-100%, and Streptococcus viridans is the bacterium most often identified in the majority of studies (7,8), both in determinations made in the immediate postoperative period and after a certain period of time (minutes). A characteristic of such bacteremia is its transient nature, since the microorganisms are cleared from the bloodstream within a few minutes - though recently Tomas et al. have reported bacteremia in 20% of patients one hour after completing the surgical procedure (tooth extraction under general anesthesia) (8).

Studies have been made to determine whether oral hygiene and health are related to the degree of bacteremia detected after oral surgical operations. The results have been contradictory, for although some authors have recorded an increased prevalence of bacteremia with poorer oral health, other investigators have reported no differences (9). Some authors have even obtained opposite results, with higher bacteremia percentages at some point during the study (sampling after 15 minutes and at one hour) in subjects without spontaneous gingival bleeding (8).

Oral dynamics versus dental treatment as a cause of bacteremia

Transient bacteremia is produced not only as a result of dental manipulation. Daily life activities such as eating, chewing gum, brushing the teeth or using toothpicks also induce bacteremia detectable by means of blood cultures in a variable percentage of subjects (10).

In a study carried out by Carrol in 1980, it was seen that patients who used dental floss on a daily basis showed no

Table 1. Prevalence of bacteremia associated with dental treatments.

Dental treatment	Prevalence	Source
Endodontics	30% 11% (with PCR) 31-54% (only anaerobes)	*(Savarrio L, 2005)* *(Debelian Gj, 1998)*
Nasotracheal intubation	12.3%	*(Oncag O, 2005)*
Local anesthesia	16% oral infiltration; 97% intraligamentous	*(Roberts Gj, 1998)*
Prior to dental manipulation	2.5% 9.3% (general anesthesia) 23% 19% 0% 8% (general anesthesia)	*(Erverdi N, 2001)* *(Roberts GJ, 2000)* *Lucas VS, 2002)* *(Lucas VS, 2007)* *(Rosa E, 2005; Schlein RA, 1991)* *(Roberts GJ, 1998)*
Extraction	88% (50% one minute after incision, 44% immediately after extraction) 96.2% after 30 sec., 20% after one hour 89-94% 43-54%	*(Rajasuo A, 2004)* *(Tomas I, 2007)* *(Lockhart PB, 1996)* *(Roberts GJ, 1998)*
Suture removal	5%	*(King RG, 1998)*
Orthodontics Removal brackets Removal palatal Haas expander Tooth brushing with orthodontic treatment Fitting brackets	2.5% 26% 50% 25% 7.5% 32.1%	*(Erverdi N, 2001)* *(Lucas VS, 2007)* *(Rosa E, 2005)* *(Schlein RA, 1991)* *(Erverdi N, 2001)* *(Roberts GJ, 1997)*
Periodontal probing	40% (patients with periodontitis) 10% (patients with gingivitis)	*(Daly CG, 2001)*
Tartar removal	24.5%	*(Roberts, 1997)*

bacteremia following its use. However, when these same patients stopped flossing for 1-4 days, bacteremia was detected in 86% of cases after reintroducing the habit.

The fact that daily life activities such as these can induce significant bacteremia seriously questions the idea that dental manipulation is the most relevant cause of endocarditis - unless the intensity of bacteremia is significantly greater in dental extractions, and thus results in an increased risk of developing BE. However, the intensity of bacteremia produced by dental treatment (extraction) is similar to that induced by the aforementioned activities of daily living (less than 1000 colony forming units (CFU)/ml) (11).

According to a survey conducted in Spain in 1997, involving 1351 individuals, 26.5% had visited the dentist in the previous 6 months, 12.1% in the previous 6 months to one year, 24.4% in the previous 1-2 years, and 35.4% had not seen the dentist in over two years (12). The reason for the last dental visit, among the 1029 subjects that had visited the dentist at some time, was a dental checkup or cleaning in 26.9% of the cases, tooth extraction in 24.4%, and endodontic treatment in 3.2% (only the activities considered to constitute a risk of bacteremia are reported). Based on these data, and assuming that extraction and tartar removal produce similar bacteremia rates (between 39-100%)(5,6), it can be estimated that 5.6-14.4% of the population presented transient bacteremia as a result of dental intervention in the 6 months prior to the study; that 2.6-6.6% of the population developed bacteremia between 6 months and one year before the study; and that 5.2-13.3% of the population presented bacteremia 1-2 years before consultation. Based on the data from the same study, and accepting that tooth brushing produces bacteremia in 20-68% of cases, it was seen that brushing during a 6-month period caused between 108 and 367 bacteremia episodes in 31.3% of the population, 72-245 episodes in 29.5%, and 36-122 episodes of bacteremia in 22.7% of the study population. In regard to chewing, and assuming that the latter produces bacteremia in 7-51% of the cases and that 100% of the population eats at least two meals a day, it can be estimated that the number of bacteremia episodes as a consequence of chewing ranges from 25-275 over a period of 6 months.

On the other hand, it must be added that in studies of bacteremia, between 0-23% of the subjects show posi-

tive bacteremia before any kind of oral manipulation (13,14). As pointed out by Tomas et al. (8), most positive cultures detected from the blood sample prior to dental manipulation could correspond to bacteremia secondary to nasotracheal intubation (Table 1). However, there are also studies that detect baseline bacteremia in patients not subjected to general anesthesia, and who obviously have undergone no prior manipulation other than vein puncture (14,15). We have found no study in the literature centered on such presumed spontaneous bacteremia or on their causal relation to bacterial endocarditis (BE).

In this section it can be concluded that not only tooth extractions but also many other dental techniques and even daily life activities can produce bacteremia. Indeed, any activity producing a breach in the oral mucosal barrier and allowing contact between the oral environment and the bloodstream can lead to bacteremia.

Bacteremia induced by dental treatment and bacterial endocarditis

Having reached this point, it is very important for the dental professional to know the pathogenic potential of such bacteremia episodes of oral origin.

As has been commented above, the identification in blood and in the oral cavity of the same germs, and the fact that Streptococcus viridans is the cause of about 50% of all cases of native cardiac valve BE, gave support to the idea that dental manipulation - and specifically extraction - is one of the main causes of BE. Some texts even continue to consider such manipulation to be the main cause of the disease (4). however, this idea is not deeply questioned. Krcmery et al. (16) reviewed 339 cases of BE seen between the years 1991 and 2001. Of these cases, 29.2% were caused by staphylococci and 15% by streptococci. A history of dental surgery was noted in 13.2% of the patients, thus constituting the second most important risk factor after rheumatic fever (24.2%). The authors also noted that a history of dental surgery was much less frequent in the group of patients seen between 1997-2001 than in those seen between 1991-1997 (20% versus 5%). Hricak et al. (17) also identified a decrease in dental surgery as a risk factor in a series of 606 patients with BE seen in the period between 1984 and 2006.

Lascasin, in a case-control series involving 171 patients with BE, found no association between overall oral procedures and an increased risk of BE. Root rasping procedures and root canal treatments did show a certain increase in the risk of BE, though statistical significance was not reached (p=0.065).

In our setting, Castillo et al. recorded no antecedents of dental treatment in a group of 49 patients with BE in the absence of predisposing heart disease seen between 1987 and 1997 (18). A relevant aspect documented by Wilson et al. is that many of the studies in which a relationship is established between oral procedures and BE consider a period of up to 6 months between both events. Considering that the incubation period of the disease is no more than 15 days in 85% of all patients, it is very likely that many of the cases of BE attributed to dental treatment are actually unrelated to the latter (11).

In a recent study, Duval et al. estimated the risk of BE in patients with predisposing cardiac factors to be one in every 46,000 procedures carried out without antibiotic prophylaxis. More specifically, the authors estimate the risk of BE to be one case in every 10,700 procedures without prophylaxis in patients with a valve prosthesis, and one case in every 54,300 procedures in patients with predisposing factors on native valve tissue. The investigators estimated that 37 of the 1370 cases of BE (2.7%) diagnosed in France during one year were possibly related to invasive treatments without antibiotic protection, which reach percentages of up to 62% (19).

Somewhat lesser risk levels were reported by Pallasch, who on the assumption that dental treatments are responsible for 1% of all cases of BE, estimated the risk in the general population to be one case of BE for every 14 million dental procedures. In patients at risk, the estimate was one case of BE for every 114,000 procedures in individuals with heart valve prostheses, and one case in every 95.00 procedures in patients with previous BE (20). Thus, the available information suggests that the risk of causing BE as a consequence of dental procedures is low.

Antibiotic prophylaxis in dental treatments

Once the risk has been identified, the next step is to determine whether it can be avoided, and in what way.

According to Ito, the first reference to the association between oral bacteria and BE was published in 1908 (Horder T. Infective endocarditis. Q J Med 11:319-23). In 1935, Okell and Elliot published in The Lancet that bacteremia appears after tooth extraction (61% of cases in their series), and that positive blood cultures are observed in 11% of patients with deficient oral hygiene. On the basis that most of the germs found in blood after tooth extraction correspond to Streptococcus viridans, and that the latter together with staphylococci are responsible for most cases of BE, many scientific societies established recommendations for antibiotic prophylaxis with a view to neutralizing the deleterious effects of transient bacteremia (e.g., the American Heart Association (AHA), the Japanese Circulation Society, the British Society for Antimicrobial Chemotherapy, the Agence Française de Securité Sanitaire des Produits de Santé, etc.). The most widely accepted of these recommendations in our setting are the guidelines of the AHA, which since 1955 (the year in which its first recommendations were published) has edited 9 updates in the light of new knowledge in the field. The latest update of the AHA guidelines took place in 2007 (11). Table 2 details the cardiac disorders in which prophylaxis is advised, while Table 3 specifies the timing,

Table 2. Heart disorders associated with an increased risk of endocarditis, and for which prophylaxis is recommended prior to dental treatments.

Heart valve prostheses. Prior infectious endocarditis. Congenital heart disease (CHD)*. Untreated cyanotic CHD, including shunts and palliative ducts. Congenital heart defect fully repaired with material or prosthesis, involving surgery or catheter, in the 6 previous months §. CHD, repaired but with residual defects in or adjacent to the material or prosthesis (thus inhibiting epithelization). Heart transplant patients that develop valve disease.
*Prophylaxis is only recommended in the following three situations. Not recommended for any other form of CHD. § Prophylaxis is recommended because re-epithelization of the prosthetic material takes place in the 6 months following placement.

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Table 3. Antibiotic treatment regimens for the prevention of bacterial endocarditis in dental procedures.

Antibiotic regimens for dental procedures			
Patient condition	**Drug**	**Single dose 30-60 minutes before dental treatment**	
		Adults	Children
Oral route	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin or cefazolin or ceftriaxone	2 g IM* or IV† 1 g IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin via oral route	Cephalexin‡§ or Clindamycin or azithromycin or clarithromycin	2 g 600 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg
Allergic to penicillins or ampicillin via oral route, and unable to take oral medication	Cefazolin or ceftriaxone or clindamycin	1 g IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV

* IM: Intramuscular
† IV: Intravenous
‡ Or other first or second generation cephalosporin at equivalent doses for children and adults
§ The cephalosporins are not to be used in patients with a history of anaphylaxis, angioedema or urticaria with penicillins or ampicillin

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dose and type of antibiotic recommended, depending on the clinical situation of the patient. In addition to patients with heart disease, some authors recommend antibiotic prophylaxis in inflammatory joint diseases, immunosuppression, type 1 diabetes, certain situations involving joint prostheses (less than two years since implantation, and a history of prior prosthetic infection), denutrition, hemophilia, transplants, uncontrolled diseases (liver and kidney failure), and splenectomized patients (21).

The current tendency is to recommend antibiotic prophylaxis in increasingly fewer patients. The previous recommendations of the AHA (1997) contemplated prophylaxis for moderate risk categories for BE (mitral valve prolapse, hypertrophic myocardiopathy, acquired valve dysfunction - rheumatic fever - and non-cyanotic congenital cardiac malformations). The current recommendations do not include these processes as tributary to prophylaxis. Modifications have also been introduced in the dental procedures requiring prophylaxis. Thus, prophylaxis is now advised in all procedures involving manipulation of the gingival tissue or periapical region, or perforation of the oral mucosa. Prophylaxis is not recommended in anesthetic infiltrations through uninfected tissues, the placement of orthodontic brackets, the exfoliation of primary teeth, and bleeding secondary to trauma of the oral mucosa and lips, among others.

Another tendency that has become consolidated in the successive recommendations is the reduction of the duration of prophylaxis. Thus, from the 5 days and up to 21 antibiotic doses of the first recommendations, we have dropped to a single dose administered between 30 and 60 minutes before the intervention - amoxicillin being the main drug advised in the different prophylactic protocols.

Controversy regarding the prevention of BE with antibiotics in dental treatments

Many authors call for reflection upon the usefulness and safety of these prophylactic measures. Although they may prove very useful in a given individual, the cost / benefit analysis is not favorable to antibiotic prophylaxis when taking into account that even if 100% efficacy is assumed when administered correctly, the number of cases of BE that could be avoided in the course of a year is very limited (22).

However, the effectiveness of prophylaxis by no means reaches 100%. Diz et al. studied percentage bacteremia in patients subjected to tooth extraction under general anesthesia with and without antibiotic prophylaxis, and recorded bacteremia initially and after 30 seconds, 15 minutes and one hour. The initial prevalence of bacteremia was 96% for the control group, 46% for amoxicillin, 85% for clindamycin and 57% for moxifloxacin - the values dropping to 20%, 4%, 22% and 7% after one hour (23).

Lockhart et al. obtained similar results on examining bacteremia in children subjected to dental treatments under general anesthesia. In effect, bacteremia was observed in 84% of the patients not administered prophylaxis and in 33% of those given amoxicillin (24).

Another point of controversy is the possibility that the massive use of antibiotics for prophylactic purposes may be contributing to the increase in bacterial resistances. Groppo et al. studied antibiotic resistance among the staphylococci and streptococci of saliva and skin in patients at high risk of BE. They found 53.3% of the staphylococci and 16.7% of the streptococci to be resistant to amoxicillin; 23.3% of the streptococci were resistant to azithromycin and clarithromycin; and 26.7% to clindamycin (25). Smith et al. likewise documented relevant levels of antibiotic resistance in Streptococcus viridans isolated from blood cultures. In this sense, 27% of Streptococcus oralis proved resistant to penicillin, and 6% to clindamycin. The corresponding resistance figures for Streptococcus mitis were 11% and 3%, respectively (26).

We have found no publications exploring the true risk of fatal adverse reactions with use of the antibiotics recommended by the AHA, and the latter points out that during the 50-year history of its guidelines, no fatal cases of anaphylaxis secondary to antibiotic prophylaxis have been documented. However, the possible adverse effects of antibiotics must be taken into account, since some studies have reported approximately 2.9% of all adverse drug reactions to be a result of amoxicillin use - including skin reactions (82%), gastrointestinal alterations (7%), liver problems (1%) and hematological complications (1%)(27). Thus, the greater the indiscriminate use of antibiotics, the greater the probability that the risk of adverse reactions may exceed the risk of bacterial endocarditis.

Current trends in bacterial endocarditis prophylaxis among dental professionals

As has been commented, during 50 years dental professionals have attempted to theoretically prevent BE through prophylactic antibiotic use when providing oral surgical treatments in patients at risk. This attitude has gradually changed over time, however. In recent years, the provision of optimum oral health in patients at risk of developing BE has centered attention as a decisive factor for preventing the disease. Slots points out that periodontal pathology causes transient bacteremia, and that certain diseases such as BE, aspiration pneumonia, disseminated candidiasis, septicemia, etc., can be associated to such oral microorganisms (28). Ayadi et al. reported buccodental lesions to be the probable cause in 59.5% of all patients with BE, and considered the latter to be more closely related to deficient oral hygiene than to incorrect dental treatments (29). The many publications identifying an association between periodontal disease and other oral alterations on one hand, and ischemic heart disease (acute myocardial infarction) on the other (30), as well as the finding of oral bacteria in atheroma plaques - particularly in patients with active

periodontal disease (31), support a possible relationship between oral disease and cardiac disorders (including BE). However, in the same way as with antibiotic prophylaxis in dental treatments, we lack the necessary scientific evidence to firmly conclude that transient bacteremia caused by routine activities is responsible for most cases of BE, or that good oral health would avoid or reduce the risk of endocarditis. Most authors point to the need for randomized, multicenter clinical trials to examine this hypothesis more in depth.

To summarize, the American Heart Association (AHA) recognizes that the effectiveness of its recommendations is not clear, and defines them as corresponding to class IIb (i.e., a variety of opinions exist, or there is conflict in the evidence on the usefulness or efficacy of the recommendations - their usefulness / efficacy ratio being deficiently established by the existing evidence / opinion), with B level evidence (the data are derived from a single randomized trial or from non-randomized studies). In effect, there is no evidence of the efficacy of BE prophylaxis with penicillins; the clinical benefit of such prophylaxis has not been shown to outweigh the costs and risks; and there is a lack of scientific support of the quality of the recommendations regarding prophylaxis made by the different scientific societies. Despite the above, however, we coincide with Carmona et al. (32) that it seems prudent, at least from the medical-legal perspective, to administer antibiotic prophylaxis to those patients with prior bacterial endocarditis or with heart valve prostheses. In sum, we feel it advisable to follow the indications of the AHA regarding the prophylaxis of BE, providing the patient with the necessary information on the associated risks and benefits, and obtaining informed consent in each case.

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