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## Pathogenesis of Endocarditis – Bacteraemia of Oral Origin

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### 1. Introduction

Bacteraemia is defined as the presence of bacteria in the blood. A feature that is unique to the oral bacterial biofilm, particularly the subgingival plaque biofilm, is its close proximity to a highly vascularised milieu. Any disruption of the natural integrity between the biofilm and the subgingival epithelium, which is at most about 10 cell layers thick, could lead to a bacteraemic state (Parahitiyawa et al., 2009). 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 cases of infective endocarditis (IE); certain dental procedures may therefore carry a significant risk (Carmona et al., 2002). However, this statement has come under question, its detractors argue 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 as yet little evidence of genetic similarity between bacteria isolated from the heart valves, the bloodstream, and the oral cavity of patients with IE (Pallasch, 2003; Seymour et al., 2000).

Apart from its possible role in the onset of episodes of IE, bacteraemia of oral origin has attracted particular interest in the past two decades due to its possible involvement in the progression of atherosclerosis and its consequent implication in the development of ischaemic disease; however, the mechanism of action has not yet been fully elucidated (Beck et al., 1996; DeStefano et al., 1993; Olsen, 2008). A number of recently published clinical studies have demonstrated an association between periodontal disease and cardiovascular disease (Dietrich et al., 2008; Monteiro et al., 2009; Stein et al., 2009), and oral bacteria have been detected in atherosclerotic plaques, heart valves and aortic aneurysms (Gaetti-Jardim et al., 2009; Nakano et al., 2009; Pucar et al., 2007).

This chapter first provides a historical perspective of IE of oral origin. The models of the onset of IE of oral origin and the diagnostic methods for the detection and identification of oral bacteraemia are then discussed. This is followed by a critical review of bacteraemia secondary to dental procedures, focusing on prevalence, duration, magnitude and bacterial diversity, also analyzing factors that could favour the onset of bacteraemia. For this purpose, dental procedures have been divided into surgical and non-surgical, as invasive procedures are more likely to carry a higher risk. As the periodontal space is considered to be the principal portal of entry of bacteria into the bloodstream (Fig. 1), an independent analysis is

performed of the dental procedures involving this anatomical region (periodontal procedures). Several authors have demonstrated that certain activities of daily living, such as chewing or toothbrushing, can also cause bacteraemia of oral origin; the importance of this observation is that these activities can significantly increase the number of episodes of bacteraemia compared to those produced exclusively by dental treatments. It has thus appeared appropriate to include a section on bacteraemia after everyday oral activities, including the concept known as "cumulative exposure", which encompasses this interesting aspect of bacteraemia of oral origin. The chapter concludes with a discussion of how current scientific evidence in the field of oral bacteraemia has influenced clinical practice guidelines on prophylaxis for IE of oral origin.

## 2. Historical perspective on infective endocarditis of oral origin

A focal infection is "a localised or generalised infection caused by the dissemination of microorganisms or toxic products from a focus of infection" (Easlick, 1951). The idea that many systemic infections could originate from infections of the oral cavity and that conservative dental treatment could favour this process took on special importance at the beginning of the 20<sup>th</sup> century. In 1900, William Hunter wrote: "Gold fillings, crowns and bridges built on and about diseased tooth roots form a veritable mausoleum over a mass of sepsis to which there is no parallel in the whole realm of medicine or surgery..." (Hunter, 1900).

Frank Billings was a key person in elaborating the concept and later dissemination of the theory of focal infection (Billings, 1916). He suggested that there was a possible relationship between the focus of infection, positive blood cultures and cardiac disease (Billings, 1909). Furthermore, this theory explained the origin of many acute systemic diseases and of a number of chronic diseases such as arthritis and nephritis (Billings, 1912). The microbiologist Edward Rosenow was Billings' most outstanding pupil, and his experiments on animal models permitted new theories to be elaborated which supported the importance of focal infection, including "bacterial transmutation" and "elective localisation" (Rosenow, 1914).

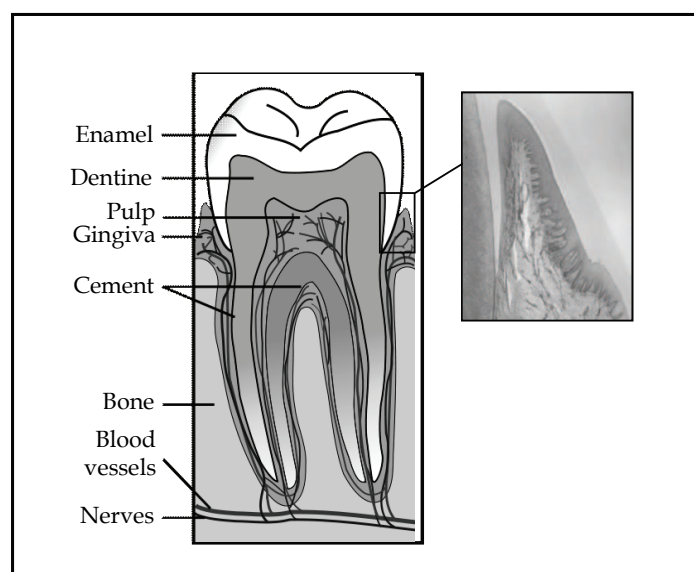


Fig. 1. Dental anatomy and histology of the critical area through which oral bacteria enter the bloodstream

After a period of popularity of the theory of focal infection, leading to the application of so-called “therapeutic edentulism” to many patients, the first detractors to this theory appeared in the 1930s (Holman, 1928). Reimann & Havens strenuously criticised Rosenow’s experiments on the basis that, in many cases, the infectious agents had not been identified and that the patient’s systemic disease did not reliably improve after dental extraction or tonsillectomy (Reimann & Havens, 1940).

However, in the forties and fifties there was a resurgence of the theory of focal infection, based mainly on the appearance in the medical literature of many cases of IE of oral origin (Bernstein, 1932; Brown, 1932; Geiger, 1942) and on epidemiological studies which revealed that the practice of dental extractions represented an important cause of IE (Kelson & White, 1945; Northrop & Crowley, 1943).

Okell & Elliott were the first authors to report bacteraemia after performing dental extractions; in a study of 138 patients undergoing such procedures, they detected bacteraemia due to *Streptococcus* species in 64% of cases (Okell & Elliott, 1935). A year later, Burket & Burn inoculated pigmented *Serratia marcescens* into the gingival sulcus of 90 patients before performing a dental extraction, isolating this bacterium in 20% of post-manipulation blood cultures. These results confirmed that microorganisms from the oral cavity could enter the bloodstream when performing a dental extraction (Burket & Burn, 1937). Between the mid 1930s and early 1950s numerous studies were published on the prevalence of post-extraction bacteraemia, reporting frequencies between 2% and 83% (Bender & Pressman, 1945; Hopkins, 1939; Palmer & Kempf, 1939; Rhoads et al., 1950; Robinson et al., 1950).

With respect to other oral activities, Richards performed a curious experiment in 1932 based on demonstrating whether “massage of a focus of infection” (located in joints, tonsils, gums, prostate or boils) caused the passage of bacteria into the bloodstream. In the case of the gums, the author selected 17 patients with gingivitis or the presence of periapical infection (confirmed by x-ray study) and massaged the gums or “moved” the teeth for 10 minutes; post-massage bacteraemia was detected in 3 cases (18%) (Richards, 1932). In 1941, Murray & Moosnick published an interesting study consisting of the extraction of blood cultures from patients with oral infections (active caries and/or periodontal disease) after chewing paraffin for 30 minutes. The blood cultures were positive for *Streptococcus* species in 185 (55%) of the 336 participants in this experiment (Murray & Moosnick, 1941).

In the early 1930s attention started to be paid to the need for IE prophylaxis in patients with valvular heart disease undergoing certain dental manipulations. Abrahamson & Brown, two of the pioneers of this idea, recommended the prophylactic use of autogenous vaccines (Abrahamson, 1931; Brown, 1932). In 1938, Feldman & Trace suggested cleaning and scraping the teeth prior to the manipulation in order to reduce contamination of the operating field, performing only 1 or 2 dental extractions per session, following the procedure with curettage and antiseptic irrigation of the periodontal pockets (Feldman & Trace, 1938). A year later, Elliott proposed perialveolar cauterization of the gingiva after dental extraction as a prophylactic measure, as this technique not only sterilized the sulcus but also sealed the gingival capillaries, thus preventing the passage of microorganisms into the bloodstream (Elliott, 1939). The practice of dental extractions under local infiltration anaesthesia with epinephrine was also recommended, as some authors had shown that this type of anaesthesia and this mode of administration acted as a barrier, preventing vascular invasion by the bacterial inoculum (Burket & Burn, 1937; Feldman & Trace, 1938). Fish &

Maclean recommended that the teeth of patients with IE be filled with cotton-wool soaked in a paste of zinc oxide and oil of cloves and that this was renewed every few days; those authors also recommended the administration of a dose of "prontosil" (azosulfamide) prior to dental extraction, in addition to cauterization of the gingiva (Fish & Maclean, 1936).

The first guidelines 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 different sulfonamides (Hupp, 1993; Thomas et al., 1941). In 1948, Hirsh et al. were the first authors to investigate the effect of penicillin on the prevalence of post-extraction bacteraemia. The study group was composed of 65 control patients and 65 study patients, the latter group receiving 600,000 IU of penicillin intramuscularly 3 to 4 hours before the dental extraction; blood samples were taken 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 those who received penicillin), the prevalence of streptococcal species in the positive blood cultures was significantly lower in patients who received prophylaxis compared with controls (15% *versus* 34%), confirming that penicillin was effective in reducing the prevalence of streptococcal bacteraemia, although not bacteraemia caused by other microorganisms (Hirsh et al., 1948).

In 1955, the American Heart Association (AHA), which at that time was formed by only seven physicians, developed its first protocol for IE prophylaxis before dental procedures. That protocol was recommended in patients with congenital or rheumatic heart disease who were undergoing dental extractions or other manipulations affecting the gingival tissues. Those experts considered that the fundamental principle of prophylaxis was to make high concentrations of antibiotic available in the bloodstream at the time of the manipulation and to maintain those levels for several days in order to eliminate the bacteria that had adhered to the heart valves during the bacteraemic episode. Their method of choice was based on the intramuscular injection of aqueous penicillin, 600,000 IU, and procaine penicillin, 600,000 IU, dissolved in oil with 2% aluminum monostearate and administered 30 minutes before the dental procedure. Alternatively (although less desirable), they proposed the oral administration of 250,000 IU to 500,000 IU of penicillin 30 minutes before each meal and before bedtime, starting 24 hours before the dental treatment and continuing for five days, with the administration of an extra dose of 250,000 IU of penicillin immediately before the procedure. For patients with a history of allergy to penicillin, the AHA recommended the use of other antibiotics such as oxytetracycline, chlortetracycline or erythromycin for five days starting the day before dental treatment (American Heart Association [AHA], 1955).

Later, several international committees, made up mainly of cardiologists, specialists in infectious diseases and pharmacologists, drew up alternative prophylactic regimens for IE in the context of dental procedures, describing the profile of the "susceptible patient" and the "at-risk" dental procedures. Those protocols have generated controversy and a degree of confusion.

### **3. Models of the development of infective endocarditis of oral origin**

The classical model of the development of IE of oral origin is that the lesions occur in areas of damaged valvular endothelium, with accumulation of fibrin and platelet deposits constituting a so-called nonbacterial thrombotic endocarditis. This vegetation is sterile until

invaded by oral microorganisms as a consequence of bacteraemia, with the subsequent onset of IE (Drangsholt, 1998) (Fig. 2).

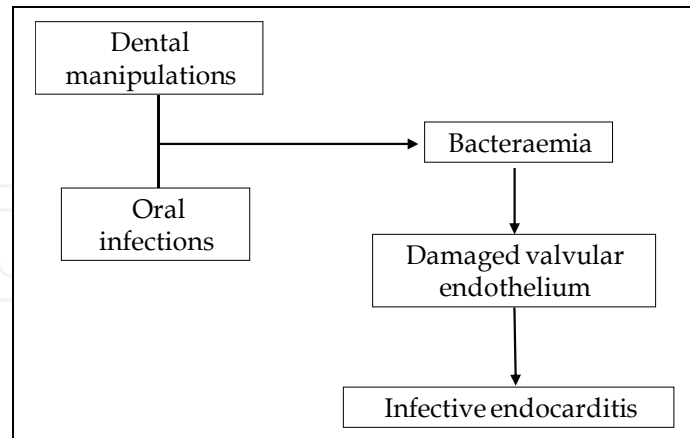


Fig. 2. Classical model of the development of infective endocarditis of oral origin

Several authors have demonstrated that bacteraemia of oral origin can play a significant role in the onset of atherosclerosis (Beck et al., 1996; DeStefano et al., 1993) and, based on these considerations, Drangsholt suggested that bacteraemia of oral origin, instead of directly inducing the onset of IE, could favour the initial thickening of the cardiac valves due to atherosclerosis, making them more susceptible to bacterial adherence and subsequent colonisation. He therefore proposed a new model for the pathogenesis of IE of oral origin, in which initially several episodes of bacteraemia would affect the endothelial surface of the cardiac valves over a long period of time, until finally a bacteraemic episode with a duration of days or weeks led to bacterial adherence and colonisation of the affected valve, culminating in an established cardiac infection (Drangsholt, 1998) (Fig. 3).

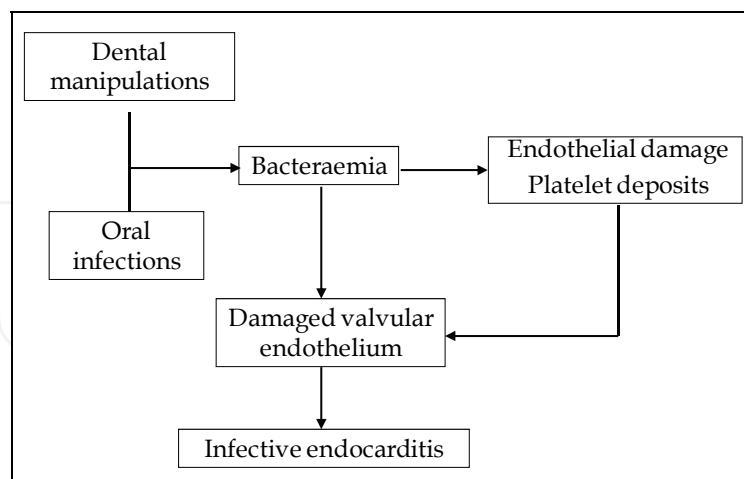


Fig. 3. A more recent model for the development of infective endocarditis of oral origin

Rather than an acute infectious disorder, this model describes IE of oral origin as a chronic disease with a long latency period and a number of well-defined stages. However, there is little evidence to support this model and few studies have been performed in experimental animals on the long-term effect of low-intensity bacteraemia of oral origin on the endothelial surface of the heart valves (Cohen et al., 2004).

#### 4. Diagnostic methods for the detection and identification of bacteraemia of oral origin

There are several procedures for the microbiological analysis of blood cultures taken after dental procedures (Loza Fernández de Bobadilla et al., 2003; Romero et al., 1993). Early studies used quantitative methods that enabled the number of bacteria per millilitre of blood cultured to be determined; this technique was based on extending the blood sample on nutrient agar and then incubating (Elliott & Dunbar, 1968). However, it is recognized that this method is complex and requires expert staff, that it must be done at the time bacteraemia is suspected and the blood drawn and that it is not effective for the isolation of anaerobic bacteria (Romero et al., 1993).

In more recent papers on bacteraemia of oral origin, other authors used a lysis-centrifugation technique (Heimdahl et al., 1990), which is based on the collection and centrifugation of blood in a "Vacutainer system" tube with saponins that break down blood cells, followed by cultivation of the resulting pellet directly on the culture plates (Loza Fernández de Bobadilla et al., 2003; Romero et al., 1993). A variant of this technique is called lysis-filtration, in which, after the initial lysis stage, the blood is filtered and it is the filters that are cultivated directly on the culture plates (Hall et al., 1993). These two techniques enable semi-quantitative estimation to be performed by counting the colonies isolated, although it has been suggested that manipulation of the sample could increase the possibility of contamination (Loza Fernández de Bobadilla et al., 2003; Romero et al., 1993).

Qualitative methods have been used in many studies. In this method, blood is cultured in bottles with liquid or biphasic media (Roberts et al., 1997; Roberts et al., 1998b; Tomás et al., 2007). The culture medium must be examined each day to detect signs of bacterial growth. Although the conventional method involves daily visual inspection of the bottles, automated reading systems now exist based on the detection of the CO<sub>2</sub> produced by bacterial growth using radiometric or fluorimetric techniques, infrared spectroscopy, changes in pH, etc. (Loza Fernández de Bobadilla et al., 2003; Romero et al., 1993).

In 2002, Lucas et al. compared two techniques, lysis-filtration and the BACTEC system, for the analysis of post-dental extraction blood cultures in children. The results revealed that the BACTEC system is a quicker and more efficient method for the detection of both aerobic and anaerobic bacteria, particularly *Staphylococcus* spp. and some species of *Streptococcus*, and that it is able to detect extremely low levels of bacteraemia (Lucas et al., 2002a). Although the lysis-filtration technique allows the intensity of bacteraemia to be estimated, it requires immediate processing, whereas processing with the BACTEC system may be delayed up to 48 hours without affecting the bacterial detection rate (Chapin & Lauderdale, 1996). Nevertheless, after reviewing the literature on bacteraemia of oral origin, significant differences were detected between studies in relation not only to the microbiological technique applied, but also to the transport and culture media, atmosphere and incubation times used, as well as the characteristics of the phenotypic identification of the isolates (Diz et al., 2011; Tomás et al., 2011). All these factors could affect bacterial isolation and identification, particularly of fastidious oral bacteria. Some authors have therefore stated that "it is likely that oral bacteria recovered from blood by culture are probably only part of those present there" (Olsen, 2008). As a result, recently developed methods for the specific detection and identification of microorganisms, particularly polymerase chain reaction

(PCR) techniques, have brought renewed interest to this field, as shown by the studies performed by a number of authors (Kinane et al., 2005; Lockhart et al., 2008; Roberts et al., 2006; Savarrio et al., 2005; Sonbol et al., 2009).

In 2005, Savarrio et al., studying blood cultures taken during root canal treatment, found a lower prevalence of bacteraemia when using PCR analysis than they detected using conventional culture techniques (17% versus 30%) (Savarrio et al., 2005). However, Kinane et al., comparing conventional culture methods and PCR analysis, detected the following prevalences of bacteraemia: after ultrasonic scaling (13% by conventional culture and 23% by PCR), periodontal probing (20% and 16%, respectively) and toothbrushing (3% and 13%, respectively) (Kinane et al., 2005). Recently, Castillo et al. assessed the presence of subgingival pathogens (*Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, *Eikenella corrodens*, *Campylobacter rectus* and *Prevotella intermedia*) in peripheral blood samples from patients with periodontitis before and after scaling and root planing; their analysis was based on anaerobic culture and nested PCR. Specific bacterial DNA was detected in 14% of patients before the therapeutic intervention and in 19% after scaling and root planing. Although blood culture rendered higher detection rates immediately after the periodontal intervention, the prevalence fell significantly at subsequent sampling times, whereas detection by nested PCR was more uniform over the sampling period. Those authors therefore concluded that the use of these molecular-based techniques may improve the accuracy of results obtained by blood culture (Castillo et al., 2011).

In 2008, Bahrani-Mougeot et al. compared two different methods for the identification of oral bacteria from blood samples after dental extractions: biochemical analysis and sequence analysis of the 16S ribosomal RNA gene. Of the 58 bacteria isolated in their series, only 17% were identified as the same species by both methods, 55% belonged to the same genus but different species and 28% showed no correlation at all. Those authors stated that DNA sequencing resulted in more accurate identification of a more diverse population of bacteria in bacteraemia following dental extractions (Bahrani-Mougeot et al., 2008). On the other hand, the sensitivity of real-time, quantitative PCR techniques to quantify bacteraemia following dental manipulations has been limited up to now. In a paper published by Lockhart et al., the sensitivity of the method was 25 colony-forming units (CFU) per polymerase chain reaction, which corresponds to  $10^3$  to  $10^4$  CFU per millilitre of blood, all samples being below this detection threshold (Lockhart et al., 2008). Nevertheless, it has recently been demonstrated that real-time PCR with pyrosequencing can accurately identify microorganisms directly from positive blood culture bottles with the same sensitivity as culture-based methods (the two techniques were concordant for 97.8% of the bacteria) (Jordan et al., 2009).

The genetic relatedness between isolates from oral cavity and bloodstream samples may be analyzed by PCR techniques. Pérez-Chaparro et al., using a pulsed-field gel electrophoresis technique, recently confirmed the coexistence of the same bacterial clone in samples from the subgingival plaque and from peripheral blood in 16% of patients with bacteraemia following scaling and root planing (Pérez-Chaparro et al., 2008).

Hence, it is imperative that these molecular sequence-based approaches be validated and used in prospective trials to achieve a better understanding of the bacterial characteristics associated with oral bacteraemia.



## 5. Bacteraemia of oral origin

Numerous authors have studied the development of bacteraemia of oral origin, although the differences detected in the methodology used and in the characteristics of the study groups make it difficult to compare results from different series.

### 5.1 Baseline bacteraemia

A number of pioneers of the research into the field of bacteraemia of oral origin assumed that there was no bacteraemia at baseline (prior to any dental manipulation) and they therefore performed no pre-manipulation determinations in their studies (Giglio et al., 1992; Lockhart, 1996). However, in 2004, the British Society of Cardiology and the Royal College of Physicians of London were emphatic on this matter: "Those studies of bacteraemia of oral origin that do not incorporate into their methodology a blood sample taken at baseline should not be considered evaluable" (British Society of Cardiology [BSC] & the Royal College of Physicians [RCP] of London, 2004).

Approximately 70% of the papers on bacteraemia following dental procedures include analysis of a baseline blood culture (Diz et al., 2011). In most of those studies the authors found that there was no bacteraemia rate before the intervention (Heimdahl et al., 1990; Okabe et al., 1995), although some authors reported positive blood cultures in 7% to 11% of cases (Roberts et al., 1998b; Savarrio et al., 2005). In 2005, Kinane et al., using PCR analysis, detected a baseline bacteraemia of 9% (Kinane et al., 2005). Roberts's group from the University of London deserves special mention; this group has repeatedly detected a higher prevalence of baseline bacteraemia in children (varying between 19% and 57%) (Lucas et al., 2002b; Lucas et al., 2007), although their results have not been confirmed by other authors studying paediatric patients. Surprisingly, Fine et al. recently detected a baseline bacteraemia (intensity of 1-2 CFU/ml) in half of adults with mild to moderate gingivitis (Fine et al., 2010). From a review of the literature, we have found that baseline bacteraemia is of very low intensity (median of the majority of series published to date, 0.33 CFU/ml). Although Lucas et al., in another paediatric case series, observed that baseline bacteraemia was mainly staphylococcal in nature (Lucas et al., 2002b; Lucas et al., 2007), Castillo et al., applying PCR analysis, recently detected *Prevotella gingivalis* in all patients with bacteraemia prior to scaling and root planing (Castillo et al., 2011).

To determine the prevalence of bacteraemia of oral origin it is essential to clarify its definition. Up to a few years ago, the detection of a positive post-dental manipulation blood culture was considered to indicate bacteraemia of oral origin. However, in 2004, the BSC and the RCP of London established a new concept of bacteraemia of oral origin defined as "that bacteraemia that is statistically significant with respect to the bacteraemia present at baseline" (BSC & RCP, 2004).

### 5.2 Bacteraemia following surgical and non-surgical procedures

#### 5.2.1 Prevalence

In 1945, Bender & Pressman (Bender & Pressman, 1945) stated that the practice of dental extractions led to the entry of bacteria into the bloodstream due to the rupture of blood vessels in the gingival sulcus and the pumping effect induced by the manipulation. Over 70% of the literature on bacteraemia following oral surgery focuses on dental extraction as a

procedure at risk of producing bacteraemia, probably because of the high frequency of this procedure and the associated bleeding (Diz et al., 2011).

An important aspect is the time at which the blood sample is collected. Roberts et al., in a study of 229 children undergoing dental extractions, determined the prevalence of bacteraemia at different times after completing the procedure (10, 60, 120, 180 and 600 seconds). They demonstrated that the optimum time for drawing the blood sample was 30 seconds after completion of the dental manipulation (Roberts et al., 1992). However, the time of collection of the post-manipulation blood sample varies between studies, ranging from “during” the procedure to 5 minutes after the completing treatment (Baltch et al., 1982; Josefsson et al., 1985; Okabe et al., 1995).

<b>SURGICAL PROCEDURES</b>	<b>PREVALENCE OF BACTERAEEMIA Median<sup>1</sup> (range)</b>
Dental extractions	Children: 52% (30%-76%) Adults: 76% (58%-100%)
Extraction of third molars	49% (10%-62%)
Maxillofacial surgical techniques	18% (0%-58%)
Removal of osteosynthesis plates	8% (0%-20%)
Incision and drainage of abscesses	12% <sup>‡</sup>
Removal of oral sutures	10% (5%-16%)
Placement of dental implants	7% <sup>2</sup>
<b>NON-SURGICAL PROCEDURES</b>	<b>PREVALENCE OF BACTERAEEMIA Median<sup>1</sup> (range)</b>
Conservative procedures	22% (4%-66%)
Orthodontic procedures	22% (7%-57%)
Endodontic procedures	15% (0%-42%)
Local anaesthetic techniques	73% (16%-97%)

<sup>1</sup>Median of the majority of series published to date.

<sup>2</sup>The absence of a prevalence range is due to there being only one paper on this subject in the literature reviewed.

Table 1. Prevalence of bacteraemia following surgical and non-surgical dental manipulations

A review of the literature revealed a prevalence of positive post-extraction blood cultures that varied between 30% and 76% in children and between 58% and 100% in adults.

Surprisingly, these percentages are significantly higher than those obtained after the extraction of impacted or partially erupted third molars (10%-62%) and after more aggressive maxillofacial surgical techniques (0%-58%) (Diz et al., 2011). Recently, Piñeiro et al. showed that even implant placement via a mucoperiosteal flap does not carry a significant risk of producing bacteraemia compared with the baseline percentage (the prevalence was 6.7% at 30 seconds and 3.3% at 15 minutes *versus* 2% at baseline) (Piñeiro et al., 2010) (Table 1). A possible explanation for these results is that the periodontal space is not invaded in these other surgical procedures, a factor which would suggest that this space represents the critical region from which oral bacteria enter the bloodstream (Parahitiyawa et al., 2009).

When evaluating non-surgical dental interventions (Table 1), the prevalence of bacteraemia was similar after conservative dental procedures (4%-66%) and after other orthodontic procedures (7%-57%), and was lower after performing root canal treatment (0%-42%) (Diz et al., 2011). In 1997, Roberts et al. were the first authors to study the prevalence of bacteraemia secondary to 13 different dental manipulations in 735 children undergoing dental treatment under general anaesthesia. Those authors found that matrix band insertion with a wooden wedge and the placement of a rubber dam led to a significant increase in the percentage of positive blood cultures compared to baseline conditions (32% and 29% *versus* 9%). However, low- and high-speed drilling led to positive blood cultures in a very small percentage of cases (4% and 13%, respectively) (Roberts et al., 1997). These findings were corroborated in subsequent studies conducted by the same research group (Roberts et al., 2000). According to Roberts et al., placement of a matrix band with a wooden wedge or placement of a rubber dam produces to changes in local pressures which could facilitate the passage of bacteria from the dental plaque to the gingival tissues (Roberts et al., 1997). In contrast, high- or low-speed drilling did not lead to a high prevalence of post-manipulation bacteraemia, questioning the initial hypothesis that these manoeuvres could break up bacterial plaque into small fragments which could easily penetrate the gingival spaces (Roberts et al., 2000).

In 2002, Lucas et al. used the lysis-filtration technique to analyze bacteraemia after different orthodontic procedures in a series of 142 children. Contrary to previous results (Erverdi et al., 1999; McLaughlin et al., 1996), those authors showed that the manipulation which caused the highest percentage of positive blood cultures was band cementation (44%), followed by the placement of interproximal separators (36%), the taking of alginate impressions (31%) and, finally, changing the archwire (19%). Curiously, despite the high percentage of positive blood cultures detected, the prevalence was not significantly higher than the baseline bacteraemia, which varied between 23% and 36%, so the post-manipulation bacteraemic episodes in that series should theoretically be considered as non-significant bacteraemia (Lucas et al., 2002b).

One of the first studies on the prevalence of bacteraemia secondary to endodontic procedures was performed by Bender et al. in 1960. Those authors stated that manipulation of the root canal involved a small, confined operating field with a significantly lower number of capillaries and blood vessels than are exposed when performing dental extractions or periodontal techniques; in addition, the operating field is usually isolated, avoiding contact with the saliva. These characteristics of endodontic treatment could explain the low prevalence of post-manipulation bacteraemia detected in the different series (Bender et al., 1960).

Regarding methods of local anaesthetic infiltration, Roberts et al. investigated the prevalence of bacteraemia after infiltrative, intraligamental and modified intraligamental techniques in children. The results showed that all three of the anaesthetic techniques caused to the passage of bacteria into the bloodstream, though there was a higher risk of bacteraemia with intraligamental injection (97% of cases) than with the modified intraligamental (50%) or infiltrative techniques (16%) (Roberts et al., 1998a). It has been suggested that bacteria which colonise the surfaces of the teeth at the border of the gingival sulcus are dragged into the sulcus by the tip of the needle and from there enter the blood vessels due to the high pressures generated by the intraligamental anaesthetic technique (Roberts, 1999). On the other hand, Lockhart suggested that injection of a local anaesthetic containing epinephrine could restrict the passage of bacteria into the circulatory system by reducing local blood flow (Lockhart, 1996).

A review of the literature has shown that, except for dental extraction and intraligamental anaesthesia, there are no significant differences in the prevalence of bacteraemia when performing surgical or non-surgical procedures (Diz et al., 2011) thus confirming that visible bleeding is not predictive of bacteraemia secondary to dental manipulations (BSC & RCP, 2004; Roberts, 1999). According to Roberts et al., invasion of the bloodstream by the bacterial inoculum is probably a consequence of the creation of a negative pressure which would lead to an aspiration effect of the bacteria towards the interior of the blood vessels. This pressure would form part of an intermittent positive and negative pressure cycle occurring during any dentogingival manipulation, with the exception of local anaesthetic techniques (which only induce high positive pressures at the time of injection). Microscopic changes occur in the gingival capillaries due to these pressure changes, facilitating bacterial access (Roberts, 1999).

### 5.2.2 Duration

Using dental extraction as the reference surgical procedure (due to the lack of published data on other surgical manipulations), it has been found that the prevalence of bacteraemia was 39% to 80% in the first 15 minutes after the manipulation, 10% to 40% at 30 to 45 minutes and 5% to 28% at 1 hour (Diz et al., 2011). In a study published by Roberts et al., in 2006 conducted on a group of 500 children undergoing dental extractions, the authors observed that the risk of a positive blood culture after performing an extraction was no longer statistically significant after 15 minutes (Roberts et al., 2006). These findings confirm the premise established by the AHA in the 1960s, that “bacteraemias of oral origin are transient and usually last no more than 15 minutes after completion of the dental manipulation” (AHA, 1960). Under physiological conditions, these bacteria are transferred from the bloodstream into tissues and are rapidly cleared by the reticuloendothelial system.

With regard to the duration of bacteraemia caused by non-surgical dental interventions, the majority of studies evaluated this aspect in the context of endodontic procedures, detecting positive blood cultures in 0% to 17% of patients in the first 10 minutes and 13% at 45 minutes after completion of root canal treatment (Diz et al., 2011). On the basis of the literature reviewed, it appears that the duration of bacteraemia following surgical and non-surgical dental treatments is related to the nature of the procedure and is prolonged after a dental extraction.

### 5.2.3 Intensity and bacterial diversity

It has been stated that bacteraemia secondary to dental procedures is usually of low intensity and contrasts with the high bacterial load used to induce IE in experimental animals (between  $10^6$  and  $10^7$  CFU/ml) (Carmona et al., 2002). The magnitude of bacteraemia caused by a surgical dental procedure varies between 0 and 300 CFU/ml (median of the majority of series published to date, 1.7 CFU/ml). Paradoxically, after relatively non-aggressive manoeuvres, such as an intraligamental injection or placement of a rubber dam, some authors detected bacteraemias in the range  $10^3$ - $10^5$  CFU/ml (Roberts et al., 1998b; Roberts et al., 2000). However, in general it has been demonstrated that non-surgical dental treatments provoke bacteraemias of very low intensity (median of the majority of series published to date, 0.5 CFU/ml). Accordingly, taking into account the magnitude of bacteraemia at baseline (median of the majority series published to date, 0.33 CFU/ml), many of these episodes should be considered as non-significant bacteraemia (Lucas et al., 2002b; Lucas et al., 2007; Roberts et al., 2000; Sonbol et al., 2009). Nevertheless, conventional microbiological cultures could be providing us with inaccurate information on the true magnitude of the bacteraemia; this aspect may be improved in a near future through the use of quantitative PCR techniques.

Analysis of the literature shows that the bacteria most frequently isolated from blood cultures obtained after surgical dental interventions in adults (mainly dental extractions) were obligate anaerobic bacteria (50%), *Streptococcus* spp. (30%) and *Staphylococcus* spp. (5%) (Diz et al., 2011); however, Lockhart et al., applying PCR techniques, recently detected a high percentage of streptococcal isolates responsible for post-extraction bacteraemia (Lockhart et al., 2008). No data are available from large series on non-surgical interventions (Diz et al., 2011). In children, there was a predominance of *Streptococcus* spp. (55%) in the positive blood cultures taken after both surgical and non-surgical dental procedures; these were followed in frequency by *Staphylococcus* spp. (15%) and, at a much lower frequency, obligate anaerobic bacteria (1%-7%) (Diz et al., 2011). In recent paediatric case series in which patients underwent dental extractions or conservative dental procedures and bacteraemia was evaluated using PCR techniques, the predominant bacterial species identified in the positive post-manipulation blood cultures was *Streptococcus* spp. (Roberts et al., 2006; Sonbol et al., 2009).

### 5.2.4 Contributing factors

Most of the studies published on bacteraemia following surgical (mainly dental extractions) and non-surgical dental manipulations evaluated the influence of different factors on the development of bacteraemia of oral origin.

A number of paediatric case series published in the 1970s reported a frequency of post-extraction bacteraemia of 30% (Speck et al., 1976), significantly lower than the figures reported for adults (Shanson et al., 1978). Some authors suggested that the differences were due primarily to the small volume of blood drawn from younger patients (Robinson et al., 1950). In the past decade, despite the increased sensitivity of blood culture techniques, the prevalence of post-extraction bacteraemia detected in children is still lower than that reported in adults (Heimdahl et al., 1990; Roberts et al., 1998b). In 2009, Lockhart et al., using a logistic regression model, found that the prevalence of bacteraemia following dental extractions increased significantly with age (Lockhart et al. 2009).

Very few authors have analysed the influence of gender on the prevalence of oral bacteraemia. Okabe et al. reported no statistically significant gender-related differences in the prevalence of bacteraemia following dental extractions (Okabe et al., 1995). However, Tomás et al. detected a significantly higher prevalence of post-extraction bacteraemia at 15 minutes in females (with a higher value also observed at one hour), though no significant differences were observed in the oral health status between females and males (Tomás et al., 2007). It has been suggested that gender could affect the prevalence of certain septic episodes, although a higher susceptibility of one or other gender continues to be a subject of debate (Eachempati et al., 1999; Offner et al., 1999). Many experiments performed in animals have demonstrated that the immune response to bacteraemia could differ between males and females (Yanke et al., 2000) due to the immune modulating properties of the sex hormones on certain cells of the immune system on which specific receptors for these hormones have been identified (Angele et al., 2000).

Many authors have investigated whether the aggressiveness of different dental procedures could affect the prevalence of bacteraemia, although the results have been inconclusive. Elliott & Durban and Peterson & Peacock observed that the extraction of primary teeth caused bacteraemia in a considerable percentage of cases (32% and 36%, respectively), although in both series this was lower than the rate detected after the extraction of permanent teeth (64% and 61%, respectively) (Elliott & Durban, 1968; Peterson & Peacock, 1976). However, these findings have not been confirmed in more recent studies (Onçag et al., 2006). In agreement with the results of previous studies (Bender et al., 1963; Robinson et al., 1950), Okabe et al. found that the frequency of positive blood cultures increased significantly with the number of teeth extracted (65% in cases of one to five extractions compared with 100% in patients with more than 15 extractions) (Okabe et al., 1995). Subsequently, Roberts et al. also detected a higher percentage of bacteraemia (>50%) in children after multiple extractions compared with a single extraction (39%) (Roberts et al., 1997). In contrast, Coulter et al., in a series in children, observed that the number of teeth extracted did not influence the prevalence or intensity of post-extraction bacteraemia (Coulter et al., 1990), and Heimdahl et al. and Lockhart detected bacteraemia in almost 100% of adults after performing a single dental extraction (Heimdahl et al., 1990; Lockhart, 1996). In the series published by Tomás et al., the number of teeth extracted did not influence the prevalence of bacteraemia at 30 seconds, 15 minutes or one hour post-extraction (Tomás et al., 2007).

Some authors demonstrated an association between the severity of haemorrhage secondary to the surgical manipulation and the appearance of bacteraemia (more than 90% of patients with a blood loss exceeding 50 ml developed bacteraemia compared to 67% when the blood loss was less than 10 ml) (Okabe et al., 1995). In contrast, Takai et al. found that the prevalence of bacteraemia associated with various oral and maxillofacial surgical procedures was not affected by blood loss during surgery (Takai et al., 2005). Okabe et al. studied the effect of the duration of surgery and found that when the operation exceeded 100 minutes the frequency of post-extraction bacteraemia was 96% compared to 67% when the surgery was of shorter duration (Okabe et al., 1995); however, other authors have reported conflicting results (Josefsson et al., 1985).

With respect to minor surgical manipulations, Giglio et al. observed that the risk of bacteraemia associated with the removal of sutures was directly related to the number of

sutures removed, as positive blood cultures were only obtained from patients in whom five or more sutures were removed (Giglio et al., 1992).

In non-surgical dental procedures, Bender et al. demonstrated that although vitality of the pulp did not affect the prevalence of bacteraemia following endodontic procedures, the percentage of positive blood cultures varied with the depth of the instrumentation. When instrumentation was performed within the limits of the root canal, bacteria did not necessarily reach the general circulation, but with trans-apical instrumentation the bacteria were introduced directly into the interior of the vascular structures (Bender et al., 1960). Debelian et al., despite recognising the statistical limitations of the small size of their sample, reported no significant differences in the prevalence of post-endodontic bacteraemia according to the degree of periapical invasion or the size of the periapical lesion (Debelian et al., 1995).

Few studies have been published on the influence of the anaesthetic modality (local *versus* general anaesthesia) on the development of bacteraemia of oral origin, and the results are not consistent (Baltch et al., 1982; Keosian et al., 1956; Takai et al., 2005). In a paper published in 1956, a higher percentage of positive post-extraction blood cultures was detected after surgery under local anaesthesia than under general anaesthesia (26% *versus* 13%) (Keosian et al., 1956). In 2005, Takai et al. reported a similar prevalence of post-manipulation bacteraemia in patients undergoing extractions under general anaesthesia and under local anaesthesia (57.7% and 58.1%, respectively) (Takai et al., 2005). In contrast, Barbosa et al. found that the prevalence and duration of bacteraemia following dental extractions was higher in patients treated under general anaesthesia than in those treated under local anaesthesia (at 30 seconds, 89% *versus* 53%; at 15 minutes, 64% *versus* 24%; and at one hour, 21% *versus* 4%), suggesting that the practice of dental treatment under general anaesthesia could be a risk factor for bacteraemia. Those authors considered three hypotheses associated with general anaesthesia to explain the results obtained in their series: the appearance of bacteraemia secondary to the manoeuvres of nasotracheal intubation, the transitory changes in blood flow and in the immune response caused by the anaesthetic agents, and other factors such as the administration of contaminated anaesthetic agents (Barbosa et al., 2010).

With regard to oral health status, it appears that the number of teeth present in the mouth, their state of decay, and the existence of periapical abscesses do not alter the risk of post-intervention bacteraemia (Brennan et al., 2007; Coulter et al., 1990; Roberts et al., 1998b; Takai et al., 2005; Tomás et al., 2007). Some paediatric case series have reported significant differences in gingival inflammation scores between children with post-extraction bacteraemia and those with negative blood cultures (Roberts et al., 1998b). In addition, Roberts et al. suggested that the health of gingival tissues not only conditioned the prevalence of post-extraction bacteraemia but also probably its intensity by influencing the size of the bacterial inoculum (Roberts et al., 1998b). However, the majority of the authors consider that the state of gingival and periodontal health is not a determining factor in either surgical or non-surgical interventions (Burden et al., 2004; Lockhart et al., 2009; Lucas et al., 2002b; Roberts et al., 2000; Takai et al., 2005; Tomás et al., 2007), although it has been observed that the prevalence of post-extraction bacteraemia increased in the presence of an acute infectious process affecting the teeth (Okabe et al., 1995; Takai et al., 2005). For example, Takai et al. reported a significant increase in the prevalence of bacteraemia after

the extraction of teeth with some type of infection (periodontal or periapical infection or pericoronitis) compared to the prevalence detected after the extraction of uninfected teeth (68% *versus* 23%) (Takai et al., 2005).

### 5.3 Bacteremia following periodontal procedures

#### 5.3.1 Prevalence

The special interest of periodontal procedures is that they involve manipulation of the critical area through which oral bacteria enter the bloodstream (Fig. 1). Table 2 shows the prevalence of bacteraemia after different periodontal procedures.

The literature shows that surgical periodontal treatments (the most invasive procedures in terms of aggressiveness due to the need for dissection of a mucoperiosteal flap) are associated with a prevalence of bacteraemia of 39% to 60%. Approximately half of the published articles on bacteraemia following periodontal procedures focus on scaling as a procedure at risk of producing bacteraemia, with a reported prevalence that ranged from 8% to 77%. Similar figures have been reported after dental cleaning procedures (15%-60%). Less invasive manoeuvres, such as subgingival irrigation or periodontal probing (which is the introduction of a probe into the periodontal space for diagnostic purposes), can provoke bacteraemia in 0% to 30% and 10% to 40% of cases, respectively (Diz et al., 2011).

In 1973, Lineberger & De Marco studied the prevalence of bacteraemia associated with different periodontal manipulations (gingivectomy, flap surgery and/or osteoplasty) in 20 patients with chronic periodontitis, differentiating between those who had undergone previous periodontal treatment (scaling and routine dental prophylaxis) and those who had not. Although the size of the sample means that the results must be viewed with caution, they detected positive post-periodontal-surgery blood cultures in 50% of patients (Lineberger & De Marco, 1973). In studies in children undergoing dental treatment under general anaesthesia, Roberts et al. found that, after raising a mucoperiosteal flap, bacteraemia was detected in 39% to 43% of cases (Roberts et al., 1997; Roberts et al., 1998b).

Witzenberger et al. observed that 55% of patients with periodontitis developed bacteraemia after scaling and root planing (Witzenberger et al., 1982). Recently Lafaurie et al. and Maestre et al., in studies of adult patients with periodontitis, detected bacteria in the blood in 74% and 76%, respectively, of patients immediately after scaling and root planing (Lafaurie et al., 2007; Maestre et al., 2008). Other authors have shown that almost 30% of children develop bacteraemia secondary to professional cleaning with a rubber cup (De Leo et al., 1974; Roberts et al., 1997). Lucas & Roberts, in a paediatric case series, compared the prevalence of bacteraemia after scaling and after rubber-cup cleaning, finding no statistically significant difference in the number of positive blood samples in the groups studied (40% and 25%, respectively) (Lucas & Roberts, 2000).

In 1997 the AHA advised against the application of antiseptics using gingival irrigators (Dajani et al., 1997), probably assuming that the practice of subgingival irrigation could favour the passage of oral bacteria into the bloodstream. However, few papers have been published on this subject and their results are contradictory. Witzenberger et al. and Lofthus et al. studied bacteraemia secondary to subgingival irrigation in patients with periodontal pockets with a depth equal to or greater than 4 mm and macroscopic bleeding. Witzenberger et al. did not detect any positive post-manipulation blood cultures whereas



Lofthus et al. reported a bacteraemia rate of 30% (6 of 20 patients) at 2 minutes after irrigation (Lofthus et al., 1991; Witzemberger et al., 1982). Daly et al. observed bacteraemia after periodontal probing in 43% of subjects with untreated periodontal disease (Daly et al., 1997), while Kinane et al. recently detected positive post-probing blood cultures in 18% of volunteers with untreated periodontal disease, a prevalence similar to that detected by the same authors after ultrasonic scaling. Those authors suggested that detectable bacteraemia induced by periodontal procedures may be less intense than previously reported. Adult patients with periodontitis could represent a unique patient base whose immune systems are highly primed to cope with periodontal bacteria, such that when bacteraemia is induced it is quickly and efficiently cleared by the patient's reticuloendothelial system (Kinane et al., 2005). Roberts et al. performed a dental examination based on the removal of bacterial plaque close to the gingival margin (without performing probing of the sulcus) in 53 children, detecting positive post-manipulation blood cultures in 17% of cases (Roberts et al., 1997).

In the literature reviewed, there were no significant differences in the prevalence of bacteraemia when performing surgical or non-surgical (mainly scaling and dental cleaning procedures) periodontal interventions; this would indicate that visible bleeding is not a predictive factor for bacteraemia secondary to dental manipulations (Roberts, 1999).

PERIODONTAL PROCEDURES	PREVALENCE OF BACTERAEMIA Median <sup>1</sup> (range)
Periodontal surgery	42% (39%-60%)
Scaling	40% (8%-77%)
Professional cleaning	27% (15%-60%)
Subgingival irrigation	15% (0%-30%) <sup>2</sup>
Periodontal probing	18% (10%-40%)

<sup>1</sup>Median of the majority of series published to date.

<sup>2</sup>Mean has been expressed due to the small number of series published to date

Table 2. Prevalence of bacteraemia following different periodontal procedures

### 5.3.2 Duration

There are very few references in the literature that have evaluated the duration of bacteraemia following periodontal treatment. In early series, bacteraemic episodes persisted for at least 30 minutes in more than a third of patients undergoing ultrasound scaling (Baltch et al., 1982). Recently, Forner et al. detected bacteraemia in 13% of patients at 10 minutes after performing scaling and in 5% at 30 minutes (Forner et al., 2006). In contrast, Lafaurie et al., after performing scaling and root planing, detected positive blood cultures in 38% at 15 minutes and in 19% at 30 minutes after completion of the periodontal manipulation (Lafaurie et al., 2007).

### 5.3.3 Intensity and bacterial diversity

Although the authors of some studies in adults have reported that the bacteria most frequently isolated were *Streptococcus* spp., followed by obligate anaerobic bacteria (Daly et al., 1997; Forner et al., 2006), other authors have identified a predominance of obligate anaerobic bacteria in post-scaling bacteraemia, particularly periodontopathogenic bacteria such as *Porphyromonas gingivalis*, *Micromonas micros*, *Aggregatibacter actinomycetemcomitans*, *Prevotella* spp. and *Fusobacterium nucleatum* (Castillo et al., 2011; Lafaurie et al., 2007; Maestre et al., 2008). In a study of children undergoing various periodontal manipulations, the bacteria identified in positive post-manipulation blood cultures were mainly streptococci and staphylococci (Lucas & Roberts, 2000).

### 5.3.4 Contributing factors

The studies reviewed on bacteraemia following periodontal procedures showed considerable heterogeneity in methodological issues such as periodontal diagnosis, and the small sample size in some of the studies may have affected the statistical significance of the results obtained. Lineberger & De Marco determined the prevalence of bacteraemia associated with different periodontal surgical manipulations in patients with chronic periodontitis, observing no influence of age or sex on the results (Lineberger & De Marco, 1973). Equally, in other series, it has been demonstrated that the magnitude of post-scaling bacteraemia was not affected by age, gender, smoking or the duration of scaling (Forner et al., 2008).

Forner et al. showed that the prevalence and magnitude of bacteraemia after scaling was significantly higher in patients with periodontitis than in patients with gingivitis or healthy controls (Forner et al., 2008). Daly et al. studied the prevalence of positive blood cultures after periodontal probing in adults with untreated periodontitis and compared the results with those obtained in patients with chronic gingivitis. Patients with periodontal disease presented nearly a six-fold increase in the risk of developing bacteraemia compared with patients with gingivitis (Daly et al., 2001). Other authors, however, found no statistical differences in the prevalence or magnitude of post-scaling bacteraemia between patients with chronic periodontitis and those with aggressive periodontitis (Forner et al., 2008; Lafaurie et al., 2007). In children, the percentages of bacteraemia following scaling and rubber-cup cleaning were not affected by the plaque or gingival indices. Nevertheless, it seems that the presence of periodontal disease does condition the development of bacteraemia when performing periodontal treatment.

With regard to the influence of other factors, Reinhardt et al. showed that the use of sterile water *versus* non-sterile water during scaling with ultrasound did not affect the prevalence or intensity of post-manipulation bacteraemia (Reinhardt et al., 1982). Lofthus et al. detected no significant differences in the prevalence of post-irrigation bacteraemia when chlorhexidine or sterile water was used as the irrigating solution (Lofthus et al., 1991).

## 5.4 Bacteraemia following everyday oral activities

### 5.4.1 Prevalence

Everyday oral activities such as toothbrushing, dental flossing, use of water irrigation devices or chewing can provoke bacteraemia, possibly because these activities produce

small movements of the tooth within the socket, causing intermittent positive and negative pressures that favour the movement of microorganisms into the bloodstream (Roberts, 1999). Specifically, it is estimated that the prevalence of bacteraemia attributable to toothbrushing is of 0% to 62% (median of the majority of series published to date, 22%), the risk with the use of irrigation devices is of 0% to 50% (median of the majority of series published to date, 13%) and the lowest risk is with chewing (median of the majority of series published to date, 3%) (Table 3) (Diz et al., 2011).

EVERYDAY ORAL ACTIVITIES	PREVALENCE OF BACTERAEMIA Median <sup>1</sup> (range)
Toothbrushing	22% (0%-62%)
Supragingival irrigation	13% (0%-50%)
Flossing	19% (0%-41%)
Chewing	3% (0%-17%)

<sup>1</sup>Median of the majority of series published to date.

Table 3. Prevalence of bacteraemia following everyday oral activities

Studies on bacteraemia following everyday oral activities in both adults and children have focused principally on bacteraemia after toothbrushing (Diz et al., 2011). Madsen demonstrated that both toothbrushing and the use of toothpicks produced bacteraemia in 36% of patients with gingival and periodontal alterations (Madsen, 1974). Schlein et al. determined the percentage of positive blood cultures five minutes after completing toothbrushing and found that 25% of subjects had post-activity bacteraemia (Schlein et al., 1991). Roberts et al. and Lucas et al. demonstrated in various studies in children that almost 40% of subjects developed bacteraemia secondary to toothbrushing (Roberts et al., 1997; Lucas et al., 2008), while others authors detected prevalences of up to 62% (Bhanji et al., 2002). In contrast, in recent studies such as those published by Hartzell et al. and Jones et al., the rate of bacteraemia following toothbrushing was zero (Hartzell et al., 2005; Jones et al., 2010). However, it is important to note that the study group in the series published by Jones et al. was formed of mechanically ventilated adults, of whom 87% were receiving empirical antibiotic therapy, which could have affected the results (Jones et al., 2010).

Although some authors were unable to show that supragingival irrigation with water produced a bacteraemic episode (Romans & App, 1971; Tamimi et al, 1969), Felix et al. found that half of the patients with periodontitis who performed this procedure for one minute presented positive post-manipulation blood cultures (Felix et al., 1971). Berger et al. investigated the prevalence of bacteraemia secondary to the use of an oral irrigator for one minute in subjects with no gingival or periodontal disease and, of the 30 individuals evaluated, eight (27%) had positive blood cultures at one minute after completing the irrigation compared to none after simple toothbrushing (Berger et al., 1974). Ramadan et al. found that 18% of patients with advanced periodontitis yielded positive blood cultures after

the use of dental floss or Stim-U-Dents, while Crasta et al. recently reported that 40% of subjects presented positive blood cultures after flossing (Crasta et al., 2009; Ramadan et al., 1975).

Although Cobe demonstrated in 1954 that chewing a hard sweet led to bacteraemia in 17% of patients (Cobe, 1954), Degling did not detect positive blood cultures in any patients with fixed orthodontic appliances after chewing gum for five minutes (Degling, 1972). Similarly, Murphy et al. recently showed that chewing did not cause bacteraemia in patients with chronic periodontitis or plaque-induced gingivitis and that this activity may not be a risk factor for IE (Murphy et al., 2006). Schlegel et al. performed an interesting experiment on dogs in which dental implants had been placed nine months earlier; those authors looked for the presence of bacteraemia after inoculating a suspension of *Staphylococcus aureus* into the peri-implant sulcus and allowing the animals to eat for five minutes. They did not detect any positive blood cultures. Together with the histological findings, this allowed the authors to suggest that the epithelium and connective tissue surrounding the implants acted as a barrier as if it were a “physiological pocket” (Schlegel et al., 1978).

Various authors have compared the prevalence of bacteraemia following everyday oral activities, mainly toothbrushing, with that detected after performing certain dental treatments (Forner et al., 2006; Kinane et al., 2005; Lockhart et al., 2008; Lucas & Roberts, 2000). Lineberger & De Marco analysed the frequency of bacteraemia secondary to the use of dental floss and of a gingival stimulator, finding that between 20% and 30% of patients had positive post-manipulation blood cultures, compared to 50% of patients undergoing periodontal surgery (Lineberger & De Marco, 1973). Lockhart et al. detected a significantly lower number of positive cultures in patients performing toothbrushing than in those undergoing dental extractions (19% and 58%, respectively) (Lockhart et al., 2008). Forner et al. studied the prevalence of positive blood cultures after toothbrushing, chewing and scaling, detecting a significantly lower percentage of bacteraemia after toothbrushing (1.6%) and chewing (6.6%) than after scaling (35%) (Forner et al., 2006). In the series by Kinane et al., the prevalences of bacteraemia after the different activities were the following: toothbrushing, 8%; periodontal probing, 18%; and ultrasonic scaling, 18% (Kinane et al., 2005). In contrast, Lucas & Roberts found no significant differences in the prevalence of positive blood cultures between three groups (toothbrushing, 39%; professional cleaning with a rubber cup, 25%; and scaling, 40%) (Lucas & Roberts, 2000).

#### 5.4.2 Duration

Approximately one third of the publications on bacteraemia following everyday oral activities have evaluated the duration of bacteraemia. It has been found that the prevalence of bacteraemia was 0% to 20% in the first 15 minutes after the activity, 0% to 1% at 20 to 40 minutes and of 2% at one hour (Diz et al., 2011). It may therefore be said that bacteraemia following everyday oral activities does not usually persist for more than 15 minutes and that the duration is shorter than is observed after performing dental extractions.

#### 5.4.3 Intensity and bacterial diversity

Bacteraemia following everyday oral activities is generally of low intensity (median of the series published to date, 0.97 CFU/ml; range; 0.01-32 CFU/ml), although its magnitude is

significantly higher than the baseline bacteraemia observed in the same series (median of the series published to date, 0.02 CFU/ml; range, 0.01-0.05 CFU/ml). In the study by Forner et al., the intensity of bacteraemia following everyday oral activities (toothbrushing and chewing) was significantly lower than those authors detected after scaling (0.11 CFU/ml and 0.19 CFU/ml *versus* 0.78 CFU/ml) (Forner et al., 2006). In contrast, the results published by Lucas & Roberts revealed that the intensity of bacteraemia was higher after toothbrushing ( $32.2 \pm 231$  CFU/ml) than after professional cleaning with a rubber cup or scaling ( $15.9 \pm 83.5$  CFU/ml and  $2.2 \pm 13.2$  CFU/ml, respectively) (Lucas & Roberts, 2000). Nevertheless, analysis of the intensity of bacteraemia following everyday oral activities must take into account the constraints of microbiological quantification techniques, given the indirect information provided by conventional culture and the limitations of sensitivity of quantitative-PCR when dealing with a very small bacterial inoculum (Lockhart et al., 2008).

In the literature reviewed, the most frequently isolated bacteria in positive post-toothbrushing blood cultures were *Streptococcus* spp. (45%) followed by obligate anaerobes (19%) and *Staphylococcus* spp. (15%). Lockhart et al., applying a 16S ribosomal RNA sequencing method for bacterial identification, observed that 48% of positive cultures in the toothbrushing group were viridans group streptococci (Lockhart et al., 2008).

#### 5.4.4 Contributing factors

Toothbrushing is the activity of everyday living for which there is most evidence regarding the influence of different factors that may contribute to the prevalence of bacteraemia. Lockhart et al. demonstrated that older age was a predictive factor for developing bacteraemia after toothbrushing (Lockhart et al., 2009). There is also a widely held view that the probability of developing bacteraemia after toothbrushing using an electric toothbrush could be higher than after using a manual toothbrush (Bhanji et al., 2002; Misra et al., 2007).

Lockhart et al. found no significant relationship between the prevalence of bacteraemia after toothbrushing and any measures of caries (presence and depth of caries, presence and size of apical lucency) (Lockhart et al., 2009). In a number of papers on bacteraemia following toothbrushing, various authors found no statistically significant relationship between the state of oral hygiene or the gingival or periodontal status and the prevalence of bacteraemia (Hartzell et al., 2005; Kinane et al., 2005; Madsen, 1974; Schlein et al., 1991; Sconyers et al., 1973). However, in patients with moderate and high plaque indices ( $PI \geq 1.51$ ) and gingival indices ( $GI \geq 1.51$ ), Silver et al. detected a prevalence of bacteraemia of 60% and 62%, respectively, after toothbrushing compared to 35% and 25%, respectively, in patients with low PI and GI (scores of 0-1.50). Those authors also demonstrated that positive post-toothbrushing blood cultures with isolation of more than three different bacterial species were significantly more common in patients with a GI equal to or greater than 1.51 than in those with a GI of 0 to 1.50 (28% *versus* 2%) (Silver et al., 1977). Lockhart et al., analysing the influence of a number of clinical parameters, found that a PI equal to or greater than 2 (OR, 3.78), a calculus index (CI) equal to or greater than 2 (OR, 4.43) and the type of bleeding (generalised bleeding) after the activity (OR, 7.96) had a significant effect on the prevalence and duration of post-toothbrushing bacteraemia (Lockhart et al., 2009). One of the authors of the present chapter (Tomás et al., 2011) performed a meta-analysis in order to clarify the influence of oral hygiene and gingival and periodontal status on the development of

bacteraemia from everyday oral activities. The results obtained in that meta-analysis showed a significant influence of the plaque and gingival indices (0-1.50 *versus*  $\geq 1.51$ ) on the prevalence of bacteraemia following toothbrushing.

With respect to other everyday oral activities, Murphy et al. stated that differing consistencies of the various chewing mediums might contribute to the differences in the reported prevalence of bacteraemia following chewing (Murphy et al., 2006). Cobe showed that chewing hard candy provoked a higher percentage of bacteraemia than did chewing gum (17.4% *versus* 0%) (Cobe, 1954). Few published studies have looked at the influence of oral hygiene and gingival and periodontal status on the prevalence of bacteraemia after performing dental flossing or chewing. In those studies, there was no statistically significant association between the state of oral hygiene or gingival or periodontal status and the prevalence of bacteraemia (Crasta et al., 2006; Fine et al., 2010; Forner et al., 2006; Murphy et al., 2006; Robinson et al., 1950).

### 5.5 “Cumulative exposure”

Although the potential clinical impact of these episodes of low-level bacteraemia caused by everyday oral activities is unknown, its significance is based on the so-called “cumulative exposure” (Guntheroth, 1984; Roberts, 1999). In 1984, Guntheroth estimated the cumulative exposure to bacteraemia over a period of one month after a tooth extraction and compared this to the results obtained after toothbrushing, during chewing and “in situations of oral sepsis”. For this purpose, he multiplied the duration of bacteraemia, expressed in minutes per day, by its prevalence in each situation and calculated that in one month, the cumulative exposure to bacteraemia secondary to two extractions was of only six minutes, whereas this reached 120 minutes after toothbrushing, 510 minutes with chewing and 4,740 minutes with “physiological bacteraemia due to oral sepsis” (Guntheroth, 1984).

In 1999, Roberts repeated the estimation of cumulative exposure to bacteraemia applying a similar methodology to that used by Guntheroth but with certain modifications: to the frequency of positive post-dental-manipulation blood cultures and the duration of the episodes (assuming a mean time of 15 minutes), as applied by Guntheroth, he added the size of the bacterial inoculum and estimated the number of dentogingival procedures that a patient with cardiac pathology would undergo in a period of one year. Roberts calculated the index of cumulative exposure as an expression of the “relative risk” of developing bacteraemia after a certain dental procedure by comparing the results with those obtained after a standard manipulation (extraction of a deciduous molar). In that study, certain conservative dental procedures, such as the placement of a rubber dam, led to a risk of cumulative exposure to bacteraemia 2,110,341 times higher than the extraction of a deciduous molar, and toothbrushing (twice a day) carried a risk 154,219 times higher than the dental extraction. He also attributed a high risk of cumulative exposure to bacteraemia of oral origin to the activities of everyday living in patients with and without oral infection (7,691,707 and 5,640,585 times higher, respectively, than a deciduous tooth extraction) (Roberts, 1999).

Three years later, the Roberts’ research group estimated the cumulative exposure to bacteraemia (expressed as the number of CFU/ml/min/year) secondary to various dental procedures in a group of 136 children with cardiac pathology, differentiating between

dental manipulations in which the administration of antibiotic prophylaxis was indicated and those in which it was not. According to those authors, the placement of a rubber dam caused the highest value of cumulative exposure (8,849,000 CFU/ml/min/year) and the extraction of a deciduous tooth the lowest (0.059 CFU/ml/min/year). Dental examination produced a cumulative exposure of 1,999 CFU/ml/min/year and rubber-cup dental polishing with prophylactic paste an exposure of 16,410 CFU/ml/min/year (Al-Karaawi et al., 2001).

Despite the above, experts on this subject such as Delahaye & De Gevigney suggested that caution should be observed in the interpretation of this “theoretical analysis”, as factors such as the duration of the bacteraemia could vary between patients. According to those authors, a prospective study must be designed in order to analyse all the components of cumulative exposure to bacteraemia individually. The concept of “cumulative exposure” has generated significant controversy in the scientific community (Delahaye & De Gevigney, 2001).

## **6. Current perspective on the prevention of infective endocarditis of oral origin**

The American Heart Association (AHA) published the first protocol for the prevention of IE associated with dental procedures in 1955 (AHA, 1955). Since that time, many expert committees in different countries have drawn up distinct prophylactic regimens, many of which have subsequently been revised and modified based on different types of studies, including those on the prevalence of bacteraemia secondary to dental procedures.

In the latest guidelines published by the British Society for Antimicrobial Chemotherapy, the AHA, the National Institute for Health and Clinical Excellence (NICE) of the United Kingdom, and the European Society of Cardiology (Gould et al., 2006; Habib et al., 2009; Wilson et al., 2007; National Institute for Health and Clinical Excellence [NICE], 2008), the emphasis for the cause of IE has shifted from procedure-related bacteraemia to cumulative bacteraemia due to everyday oral activities. NICE considered that it was “biologically implausible” that a dental procedure could lead to a greater risk of IE than regular toothbrushing (NICE, 2008). Some of those expert committee guidelines concurred with the premise: “Maintenance of optimal oral hygiene and periodontal health may reduce the incidence of bacteraemia following everyday oral activities and is more important than prophylactic antibiotics for a dental procedure to reduce the risk of IE” (NICE, 2008; Wilson et al. 2007). 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” (NICE, 2008).

## **7. Conclusions**

Apart from its possible implication in the onset of episodes of IE, there has been increasing interest in bacteraemia of oral origin in the past two decades due to the major role it is considered to play in the progression of atherosclerosis and consequently in the occurrence of chronic diseases.

It is imperative that molecular sequence-based approaches be validated and used in prospective trials to achieve a better understanding of the bacterial characteristics associated with bacteraemia of oral origin.

Dental extraction is the procedure that carries the highest risk of bacteraemia in terms of prevalence, duration and magnitude. There is no conclusive evidence on the contributing factors that predispose to the development of bacteraemia in patients undergoing dental procedures, although it is likely that gingival and periodontal health is relevant to the onset of bacteraemia when performing periodontal interventions.

Activities of everyday living, such as chewing and toothbrushing, can also cause bacteraemia and their clinical importance is based on the concept of “cumulative exposure to bacteraemia”. A meta-analysis showed that elevated plaque accumulation and gingival inflammation scores significantly increase the prevalence of bacteraemia following toothbrushing.

Scientific evidence in the field of oral bacteraemia has greatly influenced clinical practice guidelines on prophylaxis against IE of oral origin.

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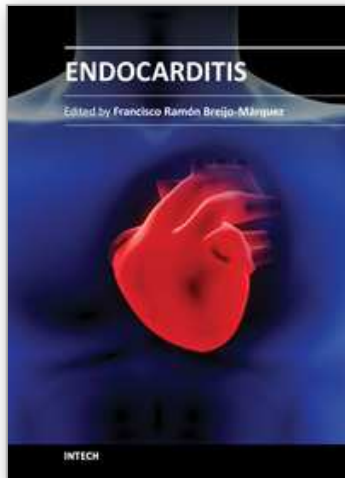
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## **Endocarditis**

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Endocarditis is a disease that occurs as a result of the inflammation of the endocardium. It is an inflammatory process located in the inner lining of the cardiac chambers and native or prosthetic valves. It is characterized by colonization or invasion of the heart valve vegetations composed of platelets forming, fibrin and microcolonies of microorganisms, and occasionally of inflammatory cells. Other structures may also be affected, such as the interventricular septum, chordae tendineae, the mural endocardium or even intra-cardiac implants. The book covers, with scientific rigour, the most prevalent causes and current treatments of endocarditis, as well as the cases when the organs remote from the heart are affected by this disease.

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